Plaintiffs rely not on the face of the contract but on the alleged circumstances surrounding the Monsanto-Southwall Agreement. Plaintiffs argue that the Southwall Agreement and the 1994 Crown Amendment were "intertwined", and that the contracting parties knew, recognized and intended that plaintiff fabricate the prelaminates called for in the Southwall Agreement. To the contrary, the circumstances surrounding the 1994 Crown Amendment and the Southwall Agreement are compelling evidence that Crown was not an intended third party beneficiary of the Southwall Agreement. The 1994 Crown Agreement included carefully crafted restrictions on Crown's right to use Monsanto technology. It defies common sense that Monsanto and Southwall intentionally rendered those restrictions meaningless by providing Crown the unrestricted right to use the same technology as a third party beneficiary of the Southwall Agreement.

***5** Plaintiffs argue that Crown must have been an intended beneficiary because it was the only company capable of offering Southwall the necessary encapsulation service. Acknowledging that plaintiff must be used or will be used for its encapsulation service is not the same as intending to benefit Crown with the promised performance under the contract. Plaintiff Crown is merely an incidental beneficiary. *See* Restatement (Second) of Contracts § 302(2). The Restatement emphasizes this:

> *e. Incidental beneficiaries.* Performance of a contract will often benefit a third person. But unless the third person is an intended beneficiary, as here defined, no duty to him is created.
>
> 17. B contracts with A to buy a new car manufactured by C. C is an incidental beneficiary, even the promise can only be performed if money is paid to C.

Restatement (Second) of Contracts § 302 cmt. e, illus. 17. In both the illustration and the present case, the contracting parties understood that a third-party would be involved and would derive some benefit from their agreement. But in both agreements there was no indication that they intended to give the benefit of their performance to that third-party. Here, the benefit to the third-party upon performance is clear. However, more than the contracting parties' mere acknowledgment of a third-party benefit is required to be an intended beneficiary.

New York law requires that to enforce a contract as a third-party beneficiary that third-party must be an intended beneficiary of the performance under the contract. Nothing appears on the face of the Southwall Agreement that would indicate that plaintiff Crown was such an intended beneficiary. While that alone is sufficient under New York law, the circumstances surrounding the Agreement do not support a conclusion of intent either. Plaintiffs can not show that Southwall or defendant intended the contract to benefit Crown or to permit it to enforce contractual rights.

WFDL

Plaintiffs seek to invoke the aegis of the Wisconsin Fair Dealership Law, alleging that defendant's revocation of its waiver of the Crown Agreement's Paragraph 13 constituted a termination that violated the WFDL's good cause and notice provisions. *See* Wis. Stat. §§ 135.03 & 135.04. To be eligible for the protections of the WFDL a plaintiff must first establish that it is a "dealer" within the meaning of the WFDL. It is with this first step that plaintiffs' WFDL claim falters.

The WFDL defines a "dealer" as a "grantee of a dealership situated in this state." Wis. Stat. § 135.02(2). The Wisconsin Supreme Court recently examined what it means to be "situated in this state." *Baldewein Co. v. Tri-Clover, Inc.*, 606 N.W.2d 145 (Wis.2000). In *Baldewein,* the Supreme Court established guidelines for determining whether a dealership was "situated in this state", including a non-exclusive nine factor test. 606 N.W.2d at 151-53.

Although recognizing that in-state sales are an important factor, the Supreme Court rejected a singular focus on the putative dealer's in-state sales. The Supreme Court adopted instead a dual focus:

> ***6** [The inquiry] must involve an analysis of the totality of the dealership investment that is specialized to the marketing of the grantor's products in this state; in other words, the amount of money and other resources the dealer has sunk into the development of the Wisconsin market, in addition to the amount of sales the dealer derives from this state.
>
> *Baldewein,* 606 N.W.2d at 151-52.

Under this general formulation it is apparent that Crown has no dealership "situated in this state". It is undisputed that plaintiff Crown has no customers in Wisconsin. Consequently, it derives no revenue from the Wisconsin market. Moreover, there is no evidence that Crown has expended a single dollar to develop or cultivate a market in Wisconsin. Having no market in Wisconsin and not having attempted to develop one, plaintiff Crown cannot be deemed to be "situated" in Wisconsin under the broad principles announced in *Baldewein.*

Nevertheless, the Supreme Court in *Baldewein* continued to elucidate a more specific nine factor test in analyzing whether a dealership is "situated" in Wisconsin. The court announced that:

> [T]o determine whether a dealership is "situated in this state" under the WFDL, courts should examine the following factors: 1) percent of total sales in Wisconsin (and/or percent of total revenue derived from Wisconsin); 2) how long the parties have dealt with each other in Wisconsin; 3) the extent and nature of the obligations imposed on the dealer regarding operations in Wisconsin; 4) the extent and nature of the grant of territory in this state; 5) the extent and nature of the use of the grantor's proprietary marks in this state; 6) the extent and nature of the dealer's financial investment in inventory, facilities, and good will of the dealership in this state; 7) the personnel devoted to the Wisconsin market; 8) the level of advertising and/or promotional expenditures in Wisconsin; 9) the extent and nature of any supplementary services provided in Wisconsin. We do not intend this list to be all-inclusive. The inquiry should focus on the nature and extent of the dealership's development of, investment in and reliance upon the Wisconsin market.
>
> *Baldewein,* 606 N.W.2d at 152-53.

Plaintiffs attempt to apply these nine factors in a vacuum-ignoring the Supreme Court's admonition that the factors must be analyzed with an eye towards the dealer's relationship with the Wisconsin market. Taken in the proper context the factors show that plaintiff Crown has no dealership "situated in the state".

First, plaintiff Crown makes no sales within the state. Plaintiff's customers are all out-of-state or overseas. Plaintiffs' formalistic argument that sales to out-of-state customers delivered FOB Crown's Sun Prairie, Wisconsin plant should be counted as in-state sales must be rejected. This same argument was rejected when the Wisconsin Supreme Court stated that where title and risk passes is irrelevant under the WFDL. *Baldewein,* 606 N.W.2d at 153. Sales revenues are not derived from the Wisconsin market merely because the out-of-state customers took possession of goods within the state.

***7** No other factor favors plaintiffs. Although Crown and defendant had a commercial relationship spanning twelve years, that relationship is unrelated to the Wisconsin market; defendant imposes no obligations on Crown's operations affecting the Wisconsin market. Defendant has not granted Crown a Wisconsin territory and has not granted it commercial use of marks within Wisconsin. Plaintiff Crown has made no financial investments to reach the Wisconsin market, has no personnel devoted to it and engages in no advertising or promotion within it. No supplementary services are provided by plaintiff Crown within the Wisconsin market.

Plaintiff Crown's only connection with Wisconsin is its location, which is irrelevant in the "situated in the state" analysis. *Baldewein,* 606 N.W.2d at 153. The WFDL focuses on protecting investments in dealerships serving the Wisconsin market, not in businesses merely located in the state. Because plaintiff Crown can not show investment in the Wisconsin market nor revenue derived from it, Crown cannot be deemed to be a dealer with a dealership "situated" in Wisconsin. Accordingly, it can not invoke the protective measures in the WFDL.

Covenant Not to Compete

Defendant moves for summary judgment on plaintiffs' third claim which seeks a declaratory judgment that Paragraph 13 of the Crown Agreement is invalid and unenforceable.

Plaintiff characterizes Paragraph 13 as a covenant not to compete. It reads:

> 13. SECRECY PROVISIONS. [Crown] shall treat and maintain, and cause its employees and agents to treat and maintain, as Monsanto's confidential property, and not use or disclose to others or man-

> ufacture a solor [sic] Saflex type product during the term of this Agreement and for fifteen (15) years thereafter, except as is necessary to perform the work hereunder ... any information ... regarding Monsanto's products, plans, programs, plants, processes, costs, equipment, operations or customers which may be heretofore or hereafter disclosed to, or come within the knowledge of, [Crown], its employees or agents in the performance of this Agreement, without in each instance securing the prior written consent of Monsanto.

1988 Crown Agreement ¶ 13. The quoted language imposes two restrictions on plaintiff Crown. First, it must treat as confidential specific information held by Monsanto and disclosed to Crown during the performance of the contract. Exceptions to this requirement are set forth later in Paragraph 13. Second, Crown must refrain from manufacturing a solar "Saflex type product" for anyone except Monsanto during the term of the Agreement and for fifteen years thereafter.

The parties agree that Missouri law governs the Crown Agreement. In Missouri, a promise not to compete, standing alone, is illegal and contrary to public policy as a restraint of trade. *Renal Treatment Centers-Missouri, Inc. v. Braxton,* 945 S.W.2d 557, 563 (Mo.Ct.App.E.D.1997) (citing John D. Calamari & Joseph Perillo, *Contracts,* Specific Performance §§ 16-19 (1977)). However, such an agreement as part of a larger legitimate transaction-making it an ancillary restraint-may be valid if it is reasonable in duration and scope. *Id.* Agreements with such ancillary restraints have been recognized between employer and employees, buyers and sellers of businesses and partners of a partnership. *Id.* (citing Restatement (Second) of Contracts § 188 (1979)). However, this list is not exclusive. The Restatement recognizes this principle is applicable in other contexts where the "a valid transaction or relationship gives the promisee a legitimate interest sufficient to sustain a promise not to compete." *Id.* (quoting Restatement (Second) of Contracts § 188 cmt. e (1979)).

***8** Although no Missouri state court has reached the issue, the law of covenants not to compete is not designed to reach restrictions such as the first one imposed by Paragraph 13. This is a confidentiality provision. Plaintiff Crown may not use or disclose certain information described by the paragraph as confidential. Such an agreement cannot be characterized as a covenant not to compete nor as an unreasonable restraint of trade. Other state courts that have addressed this issue have stated that a contract is not a restraint of trade if it does not seek to prevent a party from engaging in similar business in competition with the promisee, but instead seeks to prevent the disclosure or use of confidential information. *State Farm Mut. Auto Ins. Co. v. Dempster,* 344 P.2d 821, 826 (Cal.App.1959); *Hayes-Albion v. Kuberski,* 364 N.W.2d 609, 613 (Mich.1984); *Glucol Mfg. Co. v. Schulist,* 214 N.W. 152 (Mich.1927); *ChemiMetals Processing, Inc. v. McEneny,* 476 S.E.2d 374, 376 (N.C.Ct.App.1996). The District Court for the Eastern District of Missouri has noted the difference between covenants not to compete and confidentiality agreements: "A person bound to a covenant not to compete is restricted in his choice of occupation while an individual bound to a confidentiality agreement is merely prevented from disclosing certain information constituting 'trade secrets'." *Coulter Corp. v. Leinert,* 869 F.Supp. 732, 734 (E.D.Mo.1994).

Barring a dramatic departure by the Missouri Supreme Court from the substance of the decisions of other states it is apparent that Missouri law would not subject confidentiality agreements to the same standards as applied to covenants not to compete. Plaintiffs cite no authority for such a departure. Accordingly, the Court finds that plaintiffs' challenge to the validity of Paragraph 13 of the Crown Agreement fails to the extent it requires plaintiff Crown not to use or disclose information designated as confidential.

However, Paragraph 13 also forbids plaintiff Crown from producing a solar "Saflex type product" during the term of the Agreement and for fifteen years thereafter. Despite the absence of Missouri case law applying the law of non-compete covenants to contractual arrangements between corporations, the clause constitutes a promise to refrain from competition which could not otherwise be valid unless it was a restraint ancillary to a legitimate contract. *See Renal Treatment Centers,* 945 S.W.2d at 563; *see also* Restatement (Second) of Contracts §§ 187 & 188 (1979).

Covenants against competition, when properly identified as an ancillary restraint, must serve a proper interest of the promisee and must be reasonably limited in time and place to protect those interests. *Osage Glass, Inc. v. Donovan,* 693 S.W.2d 71, 74 (Mo.

banc.1985); *see also* Restatement (Second) of Contracts § 188 (1979). The promisees' interests protectable by such covenants are their interests in trade secrets and customer contacts. *See Superior Gearbox Corp. v. Edwards*, 869 S.W.2d 239, 247-48 (Mo.Ct.App.1993).

***9** Here, Paragraph 13 and its promise not to compete is ancillary to the legitimate obligations in the Crown Agreement. Defendant has produced no evidence as to its interest in protecting confidential information and customer contacts nor as to the reasonableness of the non-compete clause in protecting those interests. It is unknown whether plaintiff could produce a competing solar "Saflex type product" without using or disclosing Monsanto Information and thereby violating the confidentiality portion of Paragraph 13. Likewise it is not even clear what constitutes a solar "Saflex type product". The confidentiality provision in Paragraph 13 is designed to protect defendant's trade secrets and customer contacts. Consequently, an important factual issue exists as to what extent a non-compete provision is reasonably necessary to protect those same trade secrets and customer contacts. This issue-the reasonableness of the non-compete provision-precludes defendant's motion for summary judgment as to the validity of the non-compete provision in Paragraph 13.

The '511 Patent-Anticipation and Obviousness

Plaintiffs move for summary judgment that the '511 patent is anticipated by U.S. Patent No. 4,017,661 to Gillery (the '661 patent), and is obvious under the '661 patent and other prior art. Defendant moves for summary judgment that the '511 patent is neither anticipated nor obvious.

A claim is anticipated when all the elements and limitations of the claim are found within a single prior art reference. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed.Cir.1991). There must be no difference between the reference and the patented invention as viewed by one of ordinary skill in the art. *Id.* In order to prevail on its anticipation defense defendant must also overcome the presumption that the patent examiner properly applied the prior art in issuing the patent and prove invalidity by clear and convincing evidence. *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359-60 (Fed.Cir.1984).

There is no question that the '661 patent is prior art, having been identified as such in the specification of the '511 patent at col. 1, lines 44 and 58. Accordingly, the relevant inquiry is whether each element and limitation of the challenged claims is found in the '661 patent. There is considerable dispute between the parties concerning whether the patent examiner considered the '661 patent and the resulting impact on the relevant burden of proof. As subsequent analysis reveals, the '661 patent does not anticipate the '511 patent or render it obvious and this conclusion would be the same regardless of whether it was considered by the examiner. Accordingly, the Court does not reach that issue.

The '661 patent, as well numerous other prior art inventions, disclose the first three elements of claim one. It was well known in the prior art to create a solar control film by coating a transparent plastic carrier surface with a multilayer solar control film and bonding it to a energy absorbing plastic safety layer. This is apparent from column 1 of the '511 specifications wherein it is recognized that these elements were well known in the art. The '511 patent further acknowledges that the general optical design of metallic interference coatings was known. Column 5, lines 30-56. Certainly the '661 patent includes these elements.

***10** The only real issue is whether the limitation "wherein said solar control film contributes no more than about 2% visible reflectance, based on total visible incident radiation" is found in the '661 patent. Plaintiffs concede that the '661 patent does not explicitly disclose this limitation but contend that the disclosure is inherent in the '661 teachings.

> To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from given set of circumstances is not sufficient.

In re Robertson, 169 F.3d 743, 745 (Fed.Cir.1999) (citations omitted).

The disclosure of the '661 patent surely does not meet this standard for the 2% visible reflectance lim-

itation. The '661 patent reveals nothing about the desirablility of reducing solar control film reflectance to 2% or less. The two examples in the preferred embodiment suggest that the thickness of the silver layer in the coating stack should be 150 and 160 Angstroms-a thickness which is recognized by the '661 patent itself to produce about 14% reflectance. This reflectance is consistent with the disclosure of the '511 patent at column 13, table 2 and its related text. If none of the disclosed preferred embodiments of the '661 invention meet the 2% limitation, it can hardly be inherent in the disclosure.

While it is possible to produce a solar film assembly incorporating the elements of claim 1 of the '661 patent which also satisfies the elements and limitations of claim 1 of the '511 patent, a 2% reflectance is certainly not the necessary result of following the teachings of the '661 patent. The 2% limitation is not inherent in the '661 patent. Plaintiffs have also suggested that UK Patent Application GB 2 057 355, (the "GB '355 patent") which describes a solar control stack similar to that of the '661 patent, anticipates the '511 patent. There is no additional disclosure in the GB '355 patent which would alter the preceding analysis. Claim 1 of the '511 patent is not anticipated by either patent. Because claim 1 is the only independent claim of the '511 patent, it follows that none of the other dependent claims can be anticipated.

Relying primarily on the same prior art, plaintiffs argue that if the '511 patent is not anticipated it is at least rendered obvious under 35 U.S.C. § 103 because "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time of the invention to a person having ordinary skill in the art." In order to prevail defendant must demonstrate obviousness by clear and convincing evidence. *Loctite Corp. v. Ultraseal, Ltd.*, 781 F.2d 861, 872 (Fed.Cir.1985). The ultimate issue of obviousness has been termed an issue of law. However, its determination is dependent on a series of factual issues as set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Those inquiries are as follows: (1) determining the scope and content of prior art; (2) comparing the differences between the prior art and the claims at issue; (3) determining the level of ordinary skill in the art; and (4) considering objective evidence of obviousness or nonobviousness. *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870 (Fed.Cir.1993). When a defendant argues that a combination of prior art references renders the patented invention obvious, the defendant has the burden to establish some motivation in the prior art for one of ordinary skill in the art to make the combination. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed.Cir.1998).

***11** It was known to those skilled in the art and disclosed in the prior art to make a solar control film by coating PET with a multilayer reflective coating consisting of a metallic layer between two dielectric layers. It was also known and disclosed to design the film so as to maximize the reflection of infrared radiation and the transmission of visible light, and to include a metal layer in the stack with conductivity appropriate for use in electrical resistance defrosting of the window. However, no prior art identified by the plaintiffs discloses that reflectance below 2% will mask wrinkles or even discloses a solar film with reflectance below that threshold.

Perhaps more importantly, prior to the '511 patent there was no teaching in the prior art which provided motivation to reduce the solar film reflectivity contribution below 2% because there was no disclosure of the impact of such a reduction on obscuring wrinkles. Although the prior art generally sought to reduce visible light reflectivity and thereby enhance visible light transmission, it also recognized that superior infrared reflectivity was generally sacrificed by a very thin metal layer, GB '355 patent lines 5-44, as was the conductivity and continuity of the metal layer for defrosting purposes, '661 patent at col. 4, lines 25-38. Furthermore, the existing art made it clear that the required level of visible light transmission for a windshield application (between 70 and 80 percent) could readily be achieved in a composition where the solar film contributed considerably more than 2% visible light reflectivity. Accordingly, the prior art (including the '661 patent) taught that the proper compromise to achieve the conflicting goals of infrared reflectance, visible light transmission and conductivity was a solar film with a visible light reflectivity greater than 2%.

The contribution of the '551 patent of both the desirability of reducing the visible light reflectivity contribution of the solar film below 2% to mask wrinkles and the means to accomplish that goal while maintaining acceptable infrared reflectance and electrical properties was a nonobvious contribution to the

art.

The '258 Patent-Anticipation and Obviousness

Plaintiffs rely primarily upon a patent they identify as JP 59-223256A (the JP '256 patent) in support of their argument that the '258 patent is anticipated or obvious. Defendant initially objects on the basis that there is no foundation for the translation offered by plaintiffs and that they have identified the wrong patent in their submissions. Specifically, exhibit I to the Ranney affidavit referenced by plaintiffs, does not appear to be the document referred to in plaintiffs' brief. The Court does not address these preliminary arguments because assuming the document is correctly translated and identified it does not anticipate or render obvious the '258 patent.

The critical elements of the '258 patent are the final element of each independent claim which requires that the PVB layers of the patented laminate before bonding are "characterized by a wave index value, WI, of less than 15,000 square micrometers." This element is neither disclosed not suggested by the JP '256 patent. The disclosure of JP '256 recognizes that PVB with a surface roughened for deairing produced wrinkles in the laminate after bonding. It suggests avoiding this problem by laminating smooth extruded PVB and embossing it after lamination with a prescribed roughening pattern. It teaches nothing about the characteristics of roughened PVB which causes wrinkling and suggests that PVB with a roughened surface before bonding will always produce wrinkles in a finished laminate.

***12** The invention of the '258 patent is that pre-roughened PVB, whether extruded or embossed, can be incorporated in a laminate without wrinkling provided it falls within the wave index parameters prescribed and defined by the '258 specification. That element is clearly not disclosed or inherent in the JP '256 patent.

Plaintiffs also argue that if the JP '256 patent does not anticipate the '258 patent it renders it obvious when combined with the teachings of European Patent Application 0 185 863 (EP '863 Patent) which teaches a method for roughening PVB. To the contrary, the JP '256 patent teaches not to use a pre-roughened PVB sheet because such a procedure will result in reflective distortion. Furthermore, neither patent teaches the means to measure waviness or the threshold of waviness in PVB sheeting which will produce a distortion free laminate after bonding. Plaintiffs have not produced evidence to demonstrate that it would have been obvious to one of ordinary skill in the art to practice the invention of the '258 patent based on prior art at the time. Defendant is entitled to summary judgment on the claim.

Invalidity for Failure to Name Inventor

Plaintiff Krone claims that he was improperly excluded as a named inventor on both the '511 and '258 patents and therefore seeks to have them declared invalid or corrected to reflect that he is an inventor pursuant to 35 U.S.C. § 256. Defendant moves for summary judgment asserting that the undisputed facts establish that Krone was not an inventor.

Section 256 provides that the non-joinder of a joint inventor does not invalidate a patent if the omitted inventor was omitted by error without deceptive intention on his part. It further provides that the court may order correction of the inventors named on the patent if appropriate. There is no suggestion by either party that Krone was omitted from the patent through any deceptive intention. Accordingly, there is no basis to invalidate the patent and the sole issue is whether the present facts viewed most favorably to plaintiff Krone could permit a finding that he should be added to the patent as a joint inventor.

The undisputed facts establish that Krone is not an inventor within the meaning of the patent statute. In order to be found a co-inventor plaintiff must demonstrate by clear and convincing evidence that he contributed to the conception of at least one claim in of the patent. *Ethicon, Inc. v. United States Surgical Corp.*, 135 F.3d 1456, 1460-61 (Fed.Cir.1998). Unless there is a dispute of underlying facts, inventorship is a question of law. *Id.* One does not qualify as a joint inventor by assisting the actual inventor after conception of the invention, even if the specification discloses the means to practice the invention in the preferred embodiment. *Id.*

Plaintiff Krone developed a machine for laminating PET and PVB. Neither the '511 nor the '258 patent makes any claim relating to a laminating machine, even though it is clear that such a machine will be necessary to practice the invention of either patent. Under these circumstances it is impossible to conclude that Krone conceived of any aspect of the inventions.

He admittedly did not make any contribution to the inventive concept of the '511 patent that a solar control film which contributes no more than 2% reflectance will mask wrinkles. He had no input into the design of the solar stack to achieve this result. Similarly, he did not conceive of the concepts of waviness or a waviness index and did not contribute to any experiments which led to the invention that PVB which met the low waviness standard could produce a distortion free laminate. Although he certainly contributed to the joint venture between the parties by the contribution of his mechanical modifications to laminating machinery, that contribution is simply not a part of the claims which are the inventions of the patents in suit.

ORDER

***13** IT IS ORDERED that plaintiffs' motion for summary judgment is DENIED;

IT IS FURTHER ORDERED that defendant's motion for summary judgment is DENIED concerning the enforceablility of the restrictive covenant at paragraph 13 of the Crown Agreement and is in all other respects GRANTED.

W.D.Wis.,2000.
Crown Operations Intern., Ltd. v. Solutia, Inc.
Not Reported in F.Supp.2d, 2000 WL 33906466 (W.D.Wis.)

END OF DOCUMENT

Date of Printing: Feb 14, 2013

KEYCITE

Crown Operations Intern., Ltd. v. Solutia, Inc., 2000 WL 33906466 (W.D.Wis., Aug 22, 2000) (NO. 99-C-0802-S)

History

Direct History

1 COMPOSITE SOLAR/SAFETY FILM AND LAMINATED WINDOW ASSEMBLY MADE THEREFROM, US PAT 4973511, 1990 WL 895830 (U.S. PTO Utility Nov 27, 1990)

Ruled Valid by

=> 2 **Crown Operations Intern., Ltd. v. Solutia, Inc.,** 2000 WL 33906466 (W.D.Wis. Aug 22, 2000) (NO. 99-C-0802-S)

AND Ruled Valid by

3 Crown Operations Intern. Ltd. v. Solutia, Inc., 2000 WL 33799740 (W.D.Wis. Aug 30, 2000) (NO. 99-C-0802-S)

Decision Affirmed in Part, Reversed in Part by

4 Crown Operations Intern., Ltd. v. Solutia Inc., 289 F.3d 1367, 62 U.S.P.Q.2d 1917 (Fed.Cir.(Wis.) May 13, 2002) (NO. 01-1144), rehearing denied (Jun 10, 2002) (BNA Version)

5 COMPOSITE SOLAR/SAFETY FILM AND LAMINATED WINDOW ASSEMBLY MADE THEREFROM, US PAT 4973511, 1990 WL 895830 (U.S. PTO Utility Nov 27, 1990)

Ruled Valid by

6 Crown Operations Intern., Ltd. v. Solutia Inc., 289 F.3d 1367, 62 U.S.P.Q.2d 1917 (Fed.Cir.(Wis.) May 13, 2002) (NO. 01-1144), rehearing denied (Jun 10, 2002) (BNA Version)

7 LAMINATE FOR A SAFETY GLAZING, US PAT 5091258, 1992 WL 1041346 (U.S. PTO Utility Feb 25, 1992)

Ruled Valid by

=> 8 **Crown Operations Intern., Ltd. v. Solutia, Inc.,** 2000 WL 33906466 (W.D.Wis. Aug 22, 2000) (NO. 99-C-0802-S)

AND Ruled Valid by

9 Crown Operations Intern. Ltd. v. Solutia, Inc., 2000 WL 33799740 (W.D.Wis. Aug 30, 2000) (NO. 99-C-0802-S)

Decision Affirmed in Part, Reversed in Part by

10 Crown Operations Intern., Ltd. v. Solutia Inc., 289 F.3d 1367, 62 U.S.P.Q.2d 1917 (Fed.Cir.(Wis.) May 13, 2002) (NO. 01-1144), rehearing denied (Jun 10, 2002) (BNA Version)

Court Documents

Appellate Court Documents (U.S.A.)

C.A.Fed. Appellate Petitions, Motions and Filings

11 CROWN OPERATIONS INTERNATIONAL, LTD. and Marshall H. Krone, Plaintiffs-Appellants, v. SOLUTIA INC., Defendant-Cross Appellant., 2002 WL 32749297 (Appellate Petition, Motion and Filing) (C.A.Fed. May 28, 2002) **Petition of Plaintiffs-Appellants Crown Operations International, Ltd. and Marshall H. Krone for Panel Rehearing** (NO. 01-1144)

C.A.Fed. Appellate Briefs

12 CROWN OPERATIONS INTERNATIONAL, LTD. and Marshall H. Krone, Plaintiffs-Appellants, v. SOLUTIA INC., Defendant-Cross Appellant., 2001 WL 34373090 (Appellate Brief) (C.A.Fed. Mar. 8, 2001) **Brief of Plaintiffs-Appellants Crown Operations International, Ltd. and Marshall H. Krone** (NO. -1156, 01-1144)

13 CROWN OPERATIONS INTERNATIONAL, LTD. and Marshall H. Krone, Plaintiffs-Appellants, v. SOLUTIA INC., Defendant-Cross Appellant., 2001 WL 36088576 (Appellate Brief) (C.A.Fed. Mar. 8, 2001) **Brief of Plaintiffs-Appellants Crown Operations International, Ltd. and Marshall H. Krone** (NO. 01-1144, 01-1156)

14 CROWN OPERATIONS INTERNATIONAL, LTD. and Marshall H. Krone, Plaintiff-Appellants, v. SOLUTIA INC., Defendant-Appellee., 2001 WL 34373088 (Appellate Brief) (C.A.Fed. Apr. 20, 2001) **Brief of Appellee Solutia Inc.** (NO. -1156, 01-1144)

15 CROWN OPERATIONS INTERNATIONAL; LTD. and Marshall H. Krone, Plaintiff-Appellants, v. SOLUTIA INC., Defendant-Appellee., 2001 WL 36088574 (Appellate Brief) (C.A.Fed. Apr. 20, 2001) **Brief of Appellee Solutia Inc.** (NO. 01-1144)

16 CROWN OPERATIONS INTERNATIONAL, LTD. and Marshall H. Krone, Plaintiffs-Appellants, v. SOLUTIA INC., Defendant-Cross Appellant., 2001 WL 34373089 (Appellate Brief) (C.A.Fed. May 4, 2001) **Reply Brief of Plaintiffs-Appellants Crown Operations International, Ltd. and Marshall H. Krone** (NO. 01-1144)

17 CROWN OPERATIONS INTERNATIONAL, LTD. and Marshall H. Krone, Plaintiffs-Appellants, v. SOLUTIA INC., Defendant-Cross Appellant., 2001 WL 36088575 (Appellate Brief) (C.A.Fed. May 4, 2001) **Reply Brief of Plaintiffs-Appellants Crown Operations International, Ltd. and Marshall H. Krone** (NO. 01-1144)

Trial Court Documents (U.S.A.)

W.D.Wis. Trial Pleadings

18 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA INC., a Delaware corporation, Defendant/Counterclaim Plaintiff, v. Crown Operations International, Ltd., a Wisconsin corporation, and Marshall H. Krone, Counterclaim Defendants., 2000 WL 35635270 (Trial Pleading) (W.D.Wis. Jun. 27, 2000) **Solutia Inc.'s Answer to Plaintiffs' Amended Complaint, Affirmative Defenses and Counterclaims** (NO. 99C802S)

W.D.Wis. Expert Testimony

19 CROWN OPERATIONS INTERNATIONAL, v. SOLUTIA, INC., 2000 WL 34606405 (Expert Report and Affidavit) (W.D.Wis. Apr. 14, 2000) **Expert Report of Max G. Lagally** (NO. 99-CV-802-S)

20 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA, INC., a Delaware corporation, Defendant/Counterclaim Plaintiff. v. Crown Operations International, Ltd., a Wisconsin corporation, and Marshall H. Krone, Counterclaim Defendants., 2000 WL 34606402 (Expert Deposition) (W.D.Wis. Jun. 27, 2000) **Videotape Deposition of: Max G. Lagally, Ph.D.** (NO. 99C802S)

21 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA INC., a Delaware corporation, Defendant., 2000 WL 34606404 (Expert Deposition) (W.D.Wis. Aug. 10, 2000) **Deposition of Professor Frederick J. McGarry** (NO. 99-C-802-S)

22 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA, INC., a Delaware corporation, Defendant/Counterclaim Plaintiff, v. Crown Operations International, Ltd., a Wisconsin corporation, and Marshall H. Krone, Counterclaim Defendants., 2000 WL 34606403 (Expert Deposition) (W.D.Wis. Aug. 14, 2000) **Deposition of Harry F. Manbeck, Jr.** (NO. 99C8025)

W.D.Wis. Trial Motions, Memoranda And Affidavits

23 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA, INC., a Delaware corporation, Defendant/Counterclaim Plaintiff, v. Crown Operations International, Ltd., a Wisconsin corporation, and Marshall H. Krone, Counterclaim Defendants., 1999 WL 34871236 (Trial Motion, Memorandum and Affidavit) (W.D.Wis. 1999) **Solutia's Memorandum in Opposition to Plaintiffs' Motion for Reconsideration** (NO. 99C802S)

24 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA INC., a Delaware corporation, Defendant/Counterclaim Plaintiff, v. Crown Operations International, Ltd., a Wisconsin corporation, and Marshall H. Krone, Counterclaim Defendants., 2000 WL 35635271 (Trial Motion, Memorandum and Affidavit) (W.D.Wis. Jun. 14, 2000) **Brief in Support of Solutia Inc.'s Motion for Summary Judgment on Plaintiffs' Fourth and Fifth Causes of Action (Patent Counts)** (NO. 99C802S)

25 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA INC., a Delaware corporation, Defendant., 2000 WL 35635272 (Trial Motion, Memorandum and Affidavit) (W.D.Wis. Jun. 15, 2000) **Plaintiffs' Memorandum in Support of Motion for Partial Summary Judgment** (NO. 99-C-802-S)

26 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA INC., a Delaware corporation, Defendant., 2000 WL 35635274 (Trial Motion, Memorandum and Affidavit) (W.D.Wis. Aug. 7, 2000) **Plaintiffs' Memorandum in Oppo-**

sition to Solutia's Summary Judgment Motion on Counts VI, VII and VIII of Plaintiff's Amended Complaint (NO. 99-C-802-S)

27 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA INC., a Delaware corporation, Defendant., 2000 WL 35635273 (Trial Motion, Memorandum and Affidavit) (W.D.Wis. Aug. 31, 2000) **Plaintiffs' Memorandum in Support of Motion for Reconsideration** (NO. 99-C-802-S)

W.D.Wis. Expert Resumes

28 Mark E. Hoffman, CPA, curriculum vitae filed in Crown Operations International v. Solutia, Inc, 1999 WL 34999843 (Court-filed Expert Resume) (W.D.Wis. 1999) **Expert Resume of Mark E. Hoffman, CPA** (NO. 99-C-802-S)

29 Harry F. Manbeck, Jr., curriculum vitae filed in Grown Secretions international v. Solution, Inc., 2000 WL 35923647 (Court-filed Expert Resume) (W.D.Wis. Jul. 6, 2000) **Expert Resume of Harry F. Manbeck, Jr.** (NO. 99-C-802-S)

Dockets (U.S.A.)

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30 CROWN OPERATIONS v. SOLUTIA INC, NO. 01-1144 (Docket) (C.A.Fed. Jan. 2, 2001)

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31 CROWN OPERATIONS INTERNATIONAL, LTD. v. SOLUTIA, INC., NO. 3:99C0802S (Docket) (W.D.Wis. May 17, 2002)

32 CROWN OPERATIONS INTERNATIONAL, LTD. v. SOLUTIA, INC., NO. 3:99CV00802 (Docket) (W.D.Wis. May 17, 2002)

Expert Court Documents (U.S.A.)

C.A.Fed. Appellate Briefs

33 CROWN OPERATIONS INTERNATIONAL, LTD. and Marshall H. Krone, Plaintiffs-Appellants, v. SOLUTIA INC., Defendant-Cross Appellant., 2001 WL 34373090 (Appellate Brief) (C.A.Fed. Mar. 8, 2001) **Brief of Plaintiffs-Appellants Crown Operations International, Ltd. and Marshall H. Krone** (NO. -1156, 01-1144)

34 CROWN OPERATIONS INTERNATIONAL, LTD. and Marshall H. Krone, Plaintiff-Appellants, v. SOLUTIA INC., Defendant-Appellee., 2001 WL 34373088 (Appellate Brief) (C.A.Fed. Apr. 20, 2001) **Brief of Appellee Solutia Inc.** (NO. -1156, 01-1144)

35 CROWN OPERATIONS INTERNATIONAL, LTD. and Marshall H. Krone, Plaintiffs-Appellants, v. SOLUTIA INC., Defendant-Cross Appellant., 2001 WL 34373089 (Appellate Brief) (C.A.Fed. May 4, 2001) **Reply Brief of Plaintiffs-Appellants Crown Operations International, Ltd. and Mar-**

shall H. Krone (NO. 01-1144)

W.D.Wis. Expert Testimony

36 CROWN OPERATIONS INTERNATIONAL, v. SOLUTIA, INC., 2000 WL 34606405 (Expert Report and Affidavit) (W.D.Wis. Apr. 14, 2000) **Expert Report of Max G. Lagally** (NO. 99-CV-802-S)

37 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA, INC., a Delaware corporation, Defendant/Counterclaim Plaintiff. v. Crown Operations International, Ltd., a Wisconsin corporation, and Marshall H. Krone, Counterclaim Defendants., 2000 WL 34606402 (Expert Deposition) (W.D.Wis. Jun. 27, 2000) **Videotape Deposition of: Max G. Lagally, Ph.D.** (NO. 99C802S)

38 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA INC., a Delaware corporation, Defendant., 2000 WL 34606404 (Expert Deposition) (W.D.Wis. Aug. 10, 2000) **Deposition of Professor Frederick J. McGarry** (NO. 99-C-802-S)

39 CROWN OPERATIONS INTERNATIONAL, LTD., a Wisconsin corporation, and Marshall H. Krone, Plaintiffs, v. SOLUTIA, INC., a Delaware corporation, Defendant/Counterclaim Plaintiff, v. Crown Operations International, Ltd., a Wisconsin corporation, and Marshall H. Krone, Counterclaim Defendants., 2000 WL 34606403 (Expert Deposition) (W.D.Wis. Aug. 14, 2000) **Deposition of Harry F. Manbeck, Jr.** (NO. 99C8025)

W.D.Wis. Expert Resumes

40 Mark E. Hoffman, CPA, curriculum vitae filed in Crown Operations International v. Solutia, Inc, 1999 WL 34999843 (Court-filed Expert Resume) (W.D.Wis. 1999) **Expert Resume of Mark E. Hoffman, CPA** (NO. 99-C-802-S)

41 Harry F. Manbeck, Jr., curriculum vitae filed in Grown Secretions international v. Solution, Inc., 2000 WL 35923647 (Court-filed Expert Resume) (W.D.Wis. Jul. 6, 2000) **Expert Resume of Harry F. Manbeck, Jr.** (NO. 99-C-802-S)

EXHIBIT H

2 of 13 DOCUMENTS

BRISTOL-MYERS SQUIBB COMPANY, Plaintiff-Appellant, v. BEN VENUE LABORATORIES, INC., BEDFORD LABORATORIES, and BOEHRINGER INGELHEIM CORPORATION, Defendants-Appellees, and IMMUNEX CORPORATION (ANDA now owned by Baker Norton Pharmaceuticals, Inc.), IVAX CORPORATION, and ZENITH GOLDLINE PHARMACEUTICALS, INC., Defendants-Appellees, and MARSAM PHARMACEUTICALS, INC. and SCHEIN PHARMACEUTICAL, INC., Defendants-Appellees, and MYLAN PHARMACEUTICALS, INC., Defendant-Appellee.

00-1304

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

246 F.3d 1368*; *2001 U.S. App. LEXIS 7262*; *58 U.S.P.Q.2D (BNA) 1508

April 20, 2001, Decided

SUBSEQUENT HISTORY: [**1] Rehearing and Rehearing En Banc Denied June 13, 2001, Reported at: *2001 U.S. App. LEXIS 14223*.
Rehearing, en banc, denied by *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 2001 U.S. App. LEXIS 14223 (Fed. Cir., June 13, 2001)*

PRIOR HISTORY: Appealed from: United States District Court for the District of New Jersey. Judge William H. Walls.
Bristol-Myers Squibb Co. v. Boehringer Ingelheim Corp., 86 F. Supp. 2d 433, 2000 U.S. Dist. LEXIS 2153 (D.N.J., 2000)
Bristol-Myers Squibb Co. v. Boehringer Ingelheim Corp., 86 F. Supp. 2d 433, 2000 U.S. Dist. LEXIS 2151 (D.N.J., 2000)
Bristol-Myers Squibb Co. v. Immunex Corp., 86 F. Supp. 2d 447, 2000 U.S. Dist. LEXIS 2150 (D.N.J., 2000)

DISPOSITION: AFFIRMED-IN-PART, VACATED-IN-PART, and REMANDED.

COUNSEL: Robert L. Baechtold, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for plaintiff-appellant. With him on the brief were Nicholas M. Cannella, Bruce C. Haas, Jennifer A. Reda, and F. Christopher Mizzo. Of counsel on the brief were Evan R. Chesler, and Richard J. Stark, Cravath, Swaine & Moore, of New York, New York. Also of counsel on the brief was William J. O'Shaughnessy, McCarter & English, of Newark, New Jersey.

Martin B. Pavane, Cohen, Pontani, Lieberman & Pavane, of New York, New York, argued for defendants-appellees Ben Venue Laboratories, Inc. et al. With him on the brief were William A. Alper, and Mindy H. Chettih. Of counsel on the brief was Robert P. Raymond, Boehringer Ingelheim Corporation, of Ridgefield, Connecticut. Of counsel were Alfred H. Hemingway, Jr., and Yunling Ren.

William L. Mentlik, Lerner, David, Littenberg, Krumholz & Mentlik, LLP, of Westfield, New Jersey, argued for defendants-appellees Immunex Corporation, et al. With him on the brief were Arnold H. Krumholz, Roy H. Wepner, [**2] and Michael H. Teschner. Of counsel on the brief was Jay B. Shapiro, Stearns Weaver Miller

Weissler Alhadeff & Sitterson, P.A., of Miami, Florida. Also of counsel on the brief were Gerson A. Zweifach, and Sharon L. Davis, Williams & Connolly LLP, of Washington, DC.

E. Anthony Figg, Rothwell, Figg, Ernst & Manbeck P.C., of Washington, DC, for defendant-appellee Mylan Pharmaceuticals, Inc. With him on the brief were Steven Lieberman, and Glenn E. Karta. Of counsel on the brief was Charles Guttman, Proskauer Rose LLP, of New York, New York, for defendant-appellee Marsam Pharmaceutical, Inc., et al. Of counsel was Frank Holahan, Harwood & Lloyd, LLC, of Hackensack, New Jersey.

JUDGES: Before LOURIE, GAJARSA, and DYK, Circuit Judges.

OPINION BY: LOURIE

OPINION

[*1371] LOURIE, *Circuit Judge*.

Bristol-Myers Squibb Company appeals from the decision of the United States District Court for the District of New Jersey granting the motion by Ben Venue Laboratories, Inc., Bedford Laboratories, Boehringer Ingelheim Corporation, Immunex Corporation, IVAX Corporation, Zenith Goldline Pharmaceuticals, Inc., Marsam Pharmaceuticals, Inc., Schein Pharmaceutical, Inc., and Mylan Pharmaceuticals, Inc. (collectively, [**3] "the defendants") for summary judgment that claims 1-3 and 6 of *U.S. Patent 5,641,803* and claims 1, 2, 5, 6, 8 and 9 of *U.S. Patent 5,670,537* are invalid for anticipation. *Bristol-Myers Squibb Co. v. Boehringer Ingelheim Corp., 86 F. Supp. 2d 433 (D.N.J. 2000)* ("*Bristol II*").

Because the district court did not err in holding claims 1-3 and 6 of the *'803 patent* and claims 1, 2, 5 and 8 of the *'537 patent* invalid, we affirm the court's judgment as to those claims. The district court erred in holding claims 6 and 9 of the *'537 patent* invalid, however. We therefore vacate the court's grant of summary judgment with respect to those two claims.

BACKGROUND

Bristol-Myers Squibb Co. ("Bristol") is the assignee of the *'803* and *'537 patents*, which relate to a three-hour administration of the antitumor drug paclitaxel. [1] The patents derive from the same parent application and share the same specification. Claim 1 of the *'803 patent* reads as follows:

> 1. A method *for reducing hematologic toxicity* in a cancer patient undergoing taxol treatment comprising parenterally administering to said patient *an antineoplastically effective amount* of *about 135-175 mg/m2* [**4] *taxol over a period of about three hours.*

'803 patent, col. 16, ll. 13-18 (emphasis added). The *'537 patent* is also directed to three-hour paclitaxel administration and additionally requires premedication, as shown in representative claims 1 and 5 below:

> 1. A method for treating a patient suffering from a taxol-sensitive tumor comprising
>
> (i) premedicating said patient with a medicament that reduces or eliminates hypersensitivity reactions, and
>
> (ii) parenterally administering to said patient about 135-175 mg/m2 taxol over about three hours.

[*1372]

> 5. A method for treating a cancer patient *to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity*, said method comprising:
>
> (i) premedicating said patient with a medicament that reduces or eliminates hypersensitivity reactions; and
>
> (ii) parenterally administering to said patient about 135-175

> mg/m2 taxol over about 3 hours.

'537 patent, col. 15, ll. 45-51; col. 16, ll. 21-27 (emphasis added).

> 1 Paclitaxel is the generic name of the anticancer agent derived from the Pacific Yew tree. Taxol (R) is the registered trademark for Bristol's anticancer drug, which includes paclitaxel as its active ingredient.

[**5] Claims 2 and 8 of the *'537 patent* differ from claims 1 and 5, respectively, only in the dosage amount, which is "about 135 mg/m2 taxol." *Id.* at col. 16, ll. 5-6; ll. 41-42. Claims 6 and 9 of the *'537 patent* are directed to the same particular premedicants; claim 6 depends from claim 5 and claim 9 depends from claim 8. Claim 6 is reproduced below as representative of claims 6 and 9:

> 6. The method of claim 5 wherein the step of premedicating said patient comprises the administration of a medicament selected from the group consisting of *steroids, antihistamines, H[2] receptor antagonists*, and combinations thereof.

'537 patent, col. 16, ll. 28-32 (emphasis added).

The defendants filed Abbreviated New Drug Applications ("ANDAs") seeking approval to market paclitaxel prior to the patents' expiration, alleging that the patents were invalid over, *inter alia*, an article by Kris in which Kris treated patients with three-hour infusions of paclitaxel within the claimed dosage ranges but observed no antitumor response. Mark G. Kris, et al., *Phase I Trial of Taxol Given as a 3-Hour Infusion Every 21 Days*, 70 Cancer Treatment Reports 605-07 (1986) ("*Kris*"). [**6] Patients treated with more than 190 mg/m2 of paclitaxel, an amount greater than the claimed range of 135-175 mg/m2, showed treatment-limiting hypersensitivity reactions. In his concluding remarks, Kris commented:

> Hypersensitivity reactions constitute a severe and unpredictable treatment-limiting toxicity for the present cremophor-containing formulation of taxol given on this schedule. Further studies are needed to see if *pretreatment regimens*, alternative schedules . . . or a reformulated preparation will permit the safe administration of this compound.

Id. at 607. (emphasis added). Kris did not employ the suggested pretreatment regimens in that study.

Bristol sued for infringement based on the defendants' ANDAs under *35 U.S.C.A. § 271(e)(2) (West Supp. 2000)*; the defendants moved for summary judgment that the patents were invalid for anticipation under *35 U.S.C. § 102(b) (1994)* and obviousness under *35 U.S.C. § 103 (Supp. IV 1998)*.

Following a *Markman* hearing, the district court construed the claims. *Bristol-Myers Squibb Co. v. Immunex Corp., 86 F. Supp. 2d 447 (D.N.J. 2000)* [**7] ("*Bristol I*"). The court first determined that the preamble expression in claim 5 of the *'537 patent*, "[a] method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity," merely stated the intended use or purpose of the invention and did not limit the scope of the claim. *Id. at 451*. The court then held that the expression in the '803 claims, "an antineoplastically [2] effective amount," was inseparable from the specific concentrations [*1373] described in the claims and only stated the purpose of the invention comprising the stated method steps. *Id. at 454*. Finally, the court held that the expression "reducing hematologic toxicity" meant a reduction in toxicity relative to that normally experienced in a twenty-four-hour paclitaxel infusion, which was the standard infusion time prior to Bristol's development of the three-hour infusion time. *Id. at 455-456*.

> 2 An "antineoplastic drug" is an agent "that is antagonistic to the growth of a neoplasm," which is a tumor. *McGraw-Hill Dictionary of Scientific and Technical Terms* 103, 1332 (5th ed. 1994).

[**8] In *Bristol II*, the court granted the defendants' motion for summary judgment that the claims at issue were invalid, holding that Kris anticipated most of the claims in the *'803* and *'537 patents*. *Bristol II, 86 F. Supp. 2d at 442, 444*. The court found that Kris disclosed all of the necessary steps to administer paclitaxel according to the claims, including dosage levels, duration of infusion, and premedication. *Id. at 441*. Although Kris did not actually premedicate the patients, the court determined

"that one skilled in the art would have known exactly what Kris's premedication 'suggestion' entailed and would have not have had to engage in further experimentation to gain possession of the patented invention." *Id.* The court relied on Bristol's statement during prosecution that the invention was drawn to "a novel method for administering taxol to patients that have been pretreated with conventional medication for minimizing hypersensitivity reactions" for its determination that Kris's suggestion of premedication would have enabled someone of skill in the art to pretreat patients according to the claims. *Id.*

Although the court did not consider [**9] the preamble language of reducing toxicity levels and tumor regression to be limiting, the court determined that even if these claim terms were limiting, the claims would have been inherently anticipated because reducing toxicity and tumor regression were necessary consequences of practicing the method steps of Kris. *Id.* at 442. However, the court denied the defendants' motion for summary judgment that the claims were obvious over Kris and other references because it found a genuine factual dispute as to whether Kris would have led a person of ordinary skill in the art to have had a reasonable expectation of success from following his treatment regimens. Bristol then disclaimed claims 4 and 5 of the *'803 patent* and claims 3, 4, 7, and 10 of the *'537 patent* in a stipulation under *Fed. R. Civ. P. 54(b)* to obtain a final judgment. Bristol appeals from the court's claim construction and invalidity judgment. We have jurisdiction of this appeal pursuant to *28 U.S.C. § 1295(a)(1) (1994).*

DISCUSSION

Claim construction is an issue of law, *Markman v. Westview Instruments, Inc., 52 F.3d 967, 970-71, 34 U.S.P.Q.2D (BNA) 1321, 1322 (Fed. Cir. 1995)* [**10] (en banc), *aff'd, 517 U.S. 370, 134 L. Ed. 2d 577, 116 S. Ct. 1384 (1996)*, that we review *de novo*, *Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456, 46 U.S.P.Q.2D (BNA) 1169, 1172 (Fed. Cir. 1998)* (en banc). If the body of the claim sets out the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." [*1374] *Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 U.S.P.Q.2D (BNA) 1161, 1166 (Fed. Cir. 1999).*

Summary judgment is appropriate when there is no genuine issue of material fact and the moving party is entitled to judgment as a matter of law. *Fed. R. Civ. P. 56(c)*; *Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 247-48, 91 L. Ed. 2d 202, 106 S. Ct. 2505 (1986).* On motion for summary judgment, the court views the evidence and any disputed factual issues in the light most favorable to the party opposing the motion. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 587, 89 L. Ed. 2d 538, 106 S. Ct. 1348 (1986).* [**11] A patent is presumed to be valid, *35 U.S.C. § 282 (1994)*, and this presumption can only be overcome by clear and convincing evidence to the contrary. *See, e.g., WMS Gaming Inc. v. Int'l Game Techs., 184 F.3d 1339, 1355, 51 U.S.P.Q.2D (BNA) 1385, 1396-97 (Fed. Cir. 1999).* "[A] claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference." *Celeritas Techs. Ltd. v. Rockwell Int'l Corp., 150 F.3d 1354, 1360, 47 U.S.P.Q.2D (BNA) 1516, 1522 (Fed. Cir. 1998).* To anticipate, the reference must also enable one of skill in the art to make and use the claimed invention. *In re Donohue, 766 F.2d 531, 533, 226 U.S.P.Q. (BNA) 619, 621 (Fed. Cir. 1985).*

A. *Claim Construction*

Bristol argues that the district court erred by not giving effect to the preamble "for reducing hematologic toxicity" and the expression "an antineoplastically effective amount" in the '803 claims. In particular, Bristol asserts that "an antineoplastically effective amount" is limiting because it was added by amendment to distinguish over Kris, who observed no antitumor efficacy. Similarly, Bristol argues that [**12] the court improperly read out the phrase "[a] method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity" from claims 5, 6, 8, and 9 of the *'537 patent*, asserting that this expression is the only difference between claims 1 and 5 and therefore must be given effect under the doctrine of claim differentiation. Finally, Bristol argues that these expressions are limitations because they distinguish the new use of the process over the prior art, which did not show usefulness for treating cancer in three-hour paclitaxel infusions.

The defendants respond that the expressions "reduced hematologic toxicity" and "antineoplastically effective amount" in the *'803 patent* claims merely state

the intended result of those claims and are non-limiting. Furthermore, the defendants point out that "antineoplastically effective amount" was not required by the examiner to distinguish over the prior art because Bristol voluntarily added the phrase to the claims after the examiner had found them allowable. The defendants also assert that the preamble language of the '537 claims, "to effect regression of a taxol-sensitive [**13] tumor, said method being associated with reduced hematologic toxicity," only states an intended result of that claimed method. Moreover, the defendants assert that the doctrine of claim differentiation does not apply to distinguish the scope of claim 5, which recites that expression, from claim 1, which does not, because both claims are independent. The defendants also argue that Bristol's claim construction arguments violate the rule of consistency, which requires courts to construe claims consistently for both validity and infringement. Finally, the defendants respond to Bristol's argument that the asserted claim limitations [*1375] are necessary to distinguish over the prior art on the basis of the discovery of the new "usefulness" of three-hour paclitaxel infusions, arguing that the prior art was directed to that same use -- treating cancer -- and that Bristol's sole contribution was in recognizing a new result of that same use, *i.e.*, that it worked to treat cancer.

We first address the preamble language of the claims in the *'803 patent*, "for reducing hematologic toxicity." We discern no error in the district court's interpretation of that language as non-limiting, and merely expressing [**14] a purpose of reducing hematologic toxicity relative to the toxicity experienced by a patient undergoing a twenty-four-hour infusion. The steps of the three-hour infusion method are performed in the same way regardless whether or not the patient experiences a reduction in hematologic toxicity, and the language of the claim itself strongly suggests the independence of the preamble from the body of the claim. *See*, *e.g.*, *In re Hirao, 535 F.2d 67, 70, 190 U.S.P.Q. (BNA) 15, 16-17 (CCPA 1976)* (holding that the preamble was non-limiting because it merely recited the purpose of the process, which was fully set forth in the body of the claim). Furthermore, this is not a case in which a new use of a process should be considered to be a limitation because that new use distinguishes the process over the prior art, as we will discuss *infra*. We therefore affirm the district court's construction of this expression as non-limiting.

We reach the same conclusion with respect to the expression "an antineoplastically effective amount," also in the '803 claims. That expression of intended result essentially duplicates the dosage amounts recited in the claims that are also described [**15] in the specification as "antineoplastically effective." *'803 patent*, col. 5, ll. 40-44 ("It has also been surprisingly discovered that lower taxol dosages, such as about 135 mg/m2 can be administered via infusions lasting about 3-hours to about 28-hours, and still be antineoplastically effective."). The express dosage amounts are material claim limitations; the statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim.

We also agree with the defendants that the amendment adding "antineoplastically effective amount" was voluntarily made after the examiner had already indicated to Bristol that the claims were allowable. *See* Supplemental Response for Application No. 08/544,594 (Jan. 10, 1997). These unsolicited assertions of patentability made during prosecution do not create a material claim limitation where we have determined that the language does not create one. Indeed, for purposes of infringement, Bristol apparently does not see this expression as requiring efficacy; Bristol stated its view in response to requests for admission that the claims of each patent would be infringed without a showing of an objective [**16] response in every patient. Bristol cannot have an expression be limiting in this context and non-limiting in another. *W.L. Gore & Assocs., Inc. v. Garlock, Inc., 842 F.2d 1275, 1279, 6 U.S.P.Q.2D (BNA) 1277, 1280-81 (Fed. Cir. 1988)* ("Having construed the claims one way for determining their validity, it is axiomatic that the claims must be construed in the same way for infringement."). We therefore affirm the district court's interpretation of "antineoplastically effective amount" as non-limiting.

We next construe the expression "[a] method for treating a cancer patient [*1376] to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity" in the preambles of claims 5 and 8 of the *'537 patent*. Again, we agree with the defendants that this language is only a statement of purpose and intended result. The expression does not result in a manipulative difference in the steps of the claim. Moreover, Bristol would have us construe the claims as limited to those instances of practicing the claimed method that achieve the stated result for purposes

of validity, but as encompassing all instances of carrying out the physical steps for purposes [**17] of infringement. Again, Bristol cannot have it both ways. *W.L. Gore, 842 F.2d at 1279, 6 U.S.P.Q.2D (BNA) at 1280-81.*

We are also unpersuaded by Bristol's argument that this expression must be given effect under the doctrine of claim differentiation to distinguish between claims 1 and 5 and claims 2 and 8. The doctrine only creates a presumption that each claim in a patent has a different scope; it is not a "hard and fast" rule of construction. *Comark Communications, Inc. v. Harris Corp., 156 F.3d 1182, 1186, 48 U.S.P.Q.2D (BNA) 1001, 1005 (Fed. Cir. 1998).* We decline to blindly apply the doctrine in this case to supplant other canons of claim construction that compel our conclusion that independent claims 1 and 5 have identical scope and that independent claims 2 and 8 have identical scope. We therefore affirm the district court's interpretation of claims 5 and 8 as limited only to the actual steps of those claims, without regard to the result of performing the claimed steps.

Finally, we address Bristol's argument that new uses of old processes are patentable, that we should treat the expressions of efficacy as limitations because they distinguish the new use of the [**18] process over the prior art, and that claims should be read to preserve their validity. Bristol is correct that new uses of known processes may be patentable. *See 35 U.S.C. § 101 (1994)* ("Whoever invents or discovers any new and useful process . . . may obtain a patent therefor."); *35 U.S.C. § 100(b) (1994)* ("The term 'process' means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material."). However, the claimed process here is not directed to a new use; it is the same use, and it consists of the same steps as described by Kris. Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent. *In re May, 574 F.2d 1082, 1090, 197 U.S.P.Q. (BNA) 601, 607 (CCPA 1978)*; *Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 633, 2 U.S.P.Q.2D (BNA) 1051, 1054 (Fed. Cir. 1987)* (holding claimed process for making fertilizer anticipated by a disclosure of the same process for making fertilizer even though prior art did not disclose the "inventive concept"); *cf. Mehl/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1366, 52 U.S.P.Q.2D (BNA) 1303, 1306-1307 (Fed. Cir. 1999)* [**19] (finding anticipation of a method of hair depilation by an article teaching a method of skin treatment but recognizing the disruption of hair follicles).

In *May*, one of our predecessor courts held that claims to the method of effecting analgesic activity without producing physical dependency by administering a genus of non-addictive analgesic compounds were anticipated by a disclosure of a species of that genus that was used as an analgesic. *In re May, 574 F.2d at 1090, 197 U.S.P.Q. (BNA) at 607.* Although the prior disclosure was silent as to the addictiveness of the prior art compound, May's appealed claims [*1377] merely recited a newly discovered result -- non-addictiveness -- of a known method directed to the same use, *i.e.*, treating pain with an analgesic. *Id.* The court therefore held that those claims were anticipated by the prior disclosure. *Id.* Similarly, Bristol has done no more than claim a result (efficacy) of three-hour paclitaxel infusions in cancer patients. As in *May*, the purpose -- treating cancer -- is no different from the purpose disclosed by Kris. Although in suitable cases we will construe claims so as to preserve their validity, *Wang Labs., Inc. v. Am. Online, Inc., 197 F.3d 1377, 1383, 53 U.S.P.Q.2D (BNA) 1161, 1165 (Fed. Cir. 1999),* [**20] the expressions "reduced hematologic toxicity," "antineoplastically effective amount," and "[a] method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity" do not impart patentability to Bristol's claims because, as we hold here, they do not distinguish those claims over the prior art. We therefore affirm the district court's conclusion that these expressions of intended efficacy and reduced toxicity are non-limiting.

B. *Anticipation*

Bristol argues that Kris cannot anticipate the claims because Kris is a failed experiment and therefore that it does not describe the claimed invention for purposes of *35 U.S.C. § 102(b).* Although acknowledging that we have found anticipation by references that disparage the claims at issue, Bristol asserts that the Supreme Court held in *United States v. Adams, 383 U.S. 39, 148 U.S.P.Q. (BNA) 479, 15 L. Ed. 2d 572, 86 S. Ct. 708 (1966)*, that a reference that failed to achieve its intended result cannot anticipate. Bristol also argues that Kris does not enable premedication and that the court erred in relying on statements [**21] made by Bristol during prosecution because these statements were made eight years after Kris was published and cannot demonstrate

the enablement of that earlier reference. Finally, Bristol argues that Kris does not anticipate claims 6 and 9 of the *'537 patent* because Kris does not disclose the particular premedicants recited in those claims.

The defendants respond that a negative reference that discloses each limitation of a claimed invention describes that invention for purposes of *35 U.S.C. § 102(b)* even if it disparages that invention. The defendants distinguish *United States v. Adams*, arguing that the allegedly anticipatory disclosure in that case was different from the claimed invention as well as inoperative. The defendants take issue with Bristol's characterization of Kris as a "failed experiment," stating that Kris was only a Phase I trial under Food and Drug Administration ("FDA") procedures in which searching for efficacy was not his goal. The defendants also assert that Kris enabled the pretreatment limitations of the *'537 patent* and that the court properly relied on extrinsic evidence, such as Bristol's statements made during prosecution. The [**22] defendants cite several additional references that demonstrate the enablement of Kris's suggestion to premedicate. Finally, the defendants argue that claims 6 and 9 are anticipated by Kris's suggestion to premedicate because they recite only drugs commonly used for premedication, and that the claims alternatively would have been obvious under *35 U.S.C. § 103*.

1. *'803 Patent*

We conclude that the district court did not err in granting summary judgment of invalidity on the basis of anticipation of claims 1-3 and 6 of the *'803* [*1378] *patent*. Kris administered three-hour infusions of 135 mg/m2 paclitaxel to three patients and 160 mg/m2 to four patients. *Kris* at 606. Kris therefore performed all of the claimed steps at dosage levels that anticipate those in the claims. Although Kris did not observe any anticancer effects, we have already determined that the claims only require the administration of specific amounts of paclitaxel and not the achievement of a particular result.

We are not persuaded by Bristol's argument that Kris cannot anticipate under the rationale of *United States v. Adams* because it is a failed experiment. In *Adams*, the Court stated that [**23] "an inoperable invention or one which fails to achieve its intended result does not negative novelty." *Adams, 383 U.S. at 50, 148 U.S.P.Q. (BNA) at 483*. In that case, however, the alleged anticipatory disclosure used a different electrolyte and cathode than what was claimed. *Id.* Thus, the Court found no anticipation because the asserted reference, while also lacking operability, simply did not anticipate. In *Celeritas*, we stated that "[a] reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis." *Celeritas, 150 F.3d at 1361, 47 U.S.P.Q.2D (BNA) at 1522*. Kris performed all the steps of the '803 claims at issue. No particular result is required by those claims as we have construed them. Moreover, Kris's failure to observe an antitumor response does not mean that the protocol he used would never result in an antitumor response, especially in the context of a small group of patients in a Phase I study in which the focus is safety, not efficacy. Bristol's own expert, Dr. O'Connell, testified that "anyone [**24] who is experienced in oncology and read a Phase I trial would . . . only learn what drugs may become available in the future from further study and learn something about the toxicities to be expected but nothing about the efficacy." Kris simply performed the claimed method on patients who did not show any antitumor effect. Kris's performance of these same steps today would literally infringe the '803 claims; it is axiomatic that that which would literally infringe if later anticipates if earlier. *Lewmar Marine, Inc. v. Barient, Inc., 827 F.2d 744, 747, 3 U.S.P.Q.2D (BNA) 1766, 1768 (Fed. Cir. 1987)*. Moreover, Kris enabled the performance of those steps even though he did not achieve a favorable outcome, which was not a requirement of the claim. We therefore conclude that the district court did not err in holding that Kris anticipates claims 1-3 and 6 of the *'803 patent*.

2. *'537 Patent*

We also conclude that the district court did not err in granting summary judgment of invalidity on the basis of anticipation of claims 1, 2, 5 and 8 of the *'537 patent*, which are similar to the '803 claims but include the additional limitation of "premedicating said patient with a medicament [**25] that reduces or eliminates hypersensitivity reaction." Bristol correctly asserts that Kris's suggestion of premedication is primarily directed to patients receiving higher doses who experienced hypersensitivity reactions, and that Kris did not actually employ premedication. Nevertheless, Kris did not confine his pretreatment suggestion only to patients given higher doses; rather, he stated that "hypersensitivity reactions constitute a severe and unpredictable treatment-limiting

toxicity for the present cremophor-containing formulation of taxol given [*1379] on this schedule," referring to the dosage schedule of his entire study. *Kris* at 607. He then stated that "further studies are needed to see if pretreatment regimens . . . will permit the safe administration of this compound." *Id.* Furthermore, although he did not actually premedicate the patients himself, anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art. *Donohue, 766 F.2d at 533, 226 U.S.P.Q. (BNA) at 533* ("It is not, however, necessary that an invention disclosed in a publication shall have actually [**26] been made in order to satisfy the enablement requirement.").

Enablement of an anticipatory reference may be demonstrated by a later reference. In *Donohue*, we accepted the use of a later reference, Lincoln, to show enablement of an earlier anticipatory reference, Nomura. *Id. at 532, 226 U.S.P.Q. (BNA) at 620.* Although anticipation requires a showing of each limitation of a claim in a single reference, we looked to Lincoln and another reference only "to show that the claimed subject matter, as disclosed in Nomura, was in the public's possession." *Id. at 534, 226 U.S.P.Q. (BNA) at 622.* Our predecessor court held in *In re Samour* that additional references may be relied on for anticipation under *35 U.S.C. § 102(b)* "solely as evidence that, more than one year prior to appellant's filing date, a method of preparing the claimed subject matter . . . would have been known by, or would have been obvious to, one of ordinary skill in the art." *Samour, 571 F.2d 559, 562, 197 U.S.P.Q. (BNA) 1, 4 (CCPA 1978).* Furthermore, that court held that additional references used solely to show enablement of an anticipatory reference need not antedate that [**27] reference, but must show that the claimed subject matter was in possession of the public more than one year prior to the applicant's filing date. *Id. at 563, 197 U.S.P.Q. (BNA) at 4.* We therefore may look to any references that establish that Kris's suggestion of pretreatment would have been enabling to one of skill in the art more than one year prior to Bristol's earliest filing date of August 3, 1992.

The district court relied on Bristol's "admission" made during prosecution that the claimed invention was drawn to "a novel method for administering taxol to patients that have been pretreated with conventional medication for minimizing hypersensitivity reactions" for its conclusion that premedication was conventional, and thus Kris would have enabled someone to premedicate patients. *Bristol II, 86 F. Supp. 2d at 441.* Bristol's 1995 statement to the examiner, although perhaps characterizing the state of the art of premedication prior to filing, does not necessarily characterize the state of the art more than one year prior to filing. We therefore decline to rely on these statements as establishing enablement.

Nevertheless, the defendants assert that several [**28] additional references show enablement of Kris for pretreatment prior to August 3, 1991, the critical date for purposes of anticipation. For example, Weiss et al., *Hypersensitivity Reactions from Taxol*, J. Clinical Oncology, Vol. 8, No. 7, 1263-68 (July 1990), discloses pretreating patients before giving them paclitaxel. Similarly, Rowinsky et al., *Taxol: A Novel Investigational Antimicrotubule Agent*, J. Nat'l Cancer Institute, Vol. 82, No. 15, 1247-1259 (1990), reports giving prophylactic "anti-allergic" regimens consisting of steroids and H[2]-histamine antagonists before six-hour paclitaxel infusions to patients. We agree with the defendants that [*1380] these references and others demonstrate that Kris's pretreatment suggestion was enabling more than one year before Bristol filed its original application. We therefore hold that the district court did not err in concluding that claims 1, 2, 5, and 8 of the *'537 patent* are anticipated by Kris.

Bristol has asserted that its inventors achieved success, where Kris had assertedly failed, and that the patent system is supposed to encourage and reward success. Moreover, Bristol and its inventors persevered despite the discouraging tone [**29] of Kris's paper. We appreciate the point. However, one cannot obtain a valid patent on a known use of a known process that has been described in the literature more than one year prior to the date of one's invention. Such processes are old, regardless of the relative success of the prior and later participants. We are not in a position to evaluate what other incentives and rewards Bristol and its inventors may have been subject to and benefited from. We can only apply the law to the facts in light of the decision of the district court. We are pleased that Bristol and its inventors persevered, but can only affirm the district court's decision of invalidity.

We do agree with Bristol, however, that the district court erred by granting summary judgment of

anticipation of claims 6 and 9 of the *'537 patent*. Kris discloses only the use of premedicants generally, not the specific classes of premedicants in those claims: steroids, antihistamines, and H[2]-receptor antagonists. Anticipation requires a showing that each limitation of a claim is found in a single reference, *Donohue, 766 F.2d at 534, 226 U.S.P.Q. (BNA) at 621*. Nevertheless, the disclosure of a small genus may anticipate [**30] the species of that genus even if the species are not themselves recited. *In re Petering, 49 C.C.P.A. 993, 301 F.2d 676, 682, 133 U.S.P.Q. (BNA) 275, 280 (CCPA 1962)*.

The record in this case does not establish whether the general class of premedicants that are suitable to prophylactically treat hypersensitivity reactions before administration of a cancer drug such as paclitaxel is small enough such that Kris's disclosure of premedicants effectively described the specific classes of premedicants in claims 6 and 9. The district court relied on Bristol's statement during prosecution concerning pretreatment as "conventional medication for minimizing hypersensitivity reactions" in its determination that Kris's general disclosure of premedicants anticipated the specific ones recited in claims 6 and 9. *Bristol II, 86 F. Supp. 2d at 442 n.3*. We are not persuaded that these statements, presumably relating to the state of the art around the time of filing, establish that suitable premedicants consisted of only a few classes of compounds such that a person of skill in the art would have been in possession of those classes as of the date of Kris for purposes of anticipation [**31] under *§ 102(b)*. On summary judgment, we must draw all inferences in favor of the non-movant, Bristol. We therefore vacate the district court's grant of summary judgment with respect to claims 6 and 9. On remand, the district court should determine whether, perhaps even as a matter of law upon a sufficient record, there were so few suitable classes of premedicants that Kris's general suggestion to premedicate would have been understood by one of skill in the art as a suggestion to premedicate with steroids, antihistamines, and H[2]-receptor antagonists, as in claims 6 and 9 of the *'537 patent*.

Finally, we decline the invitation by the defendants to hold these claims invalid in [*1381] the alternative as obvious over Kris in combination with other references. The district court held that there were disputed factual issues as to whether one of ordinary skill in the art would have had a reasonable expectation of success based on Kris's disclosure, and we will not disturb this holding in light of Kris's discouraging conclusions about the three-hour paclitaxel schedule he disclosed.

CONCLUSION

Because the district court did not err in determining that claims 1-3 and 6 of the *'803 patent* and [**32] claims 1, 2, 5, and 8 of the *'537 patent* are invalid for anticipation, we affirm the court's grant of summary judgment as to those claims. However, we vacate its grant of summary judgment with respect to claims 6 and 9 of the *'537 patent*. We therefore

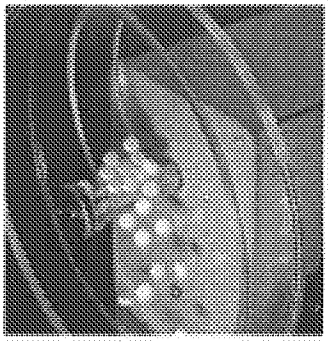
AFFIRM-IN-PART, VACATE-IN-PART, and REMAND.

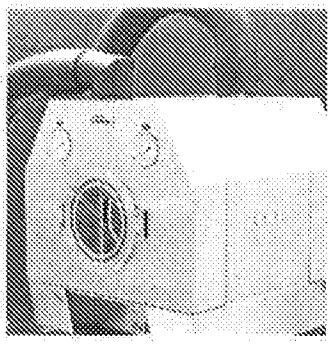
EXHIBIT I

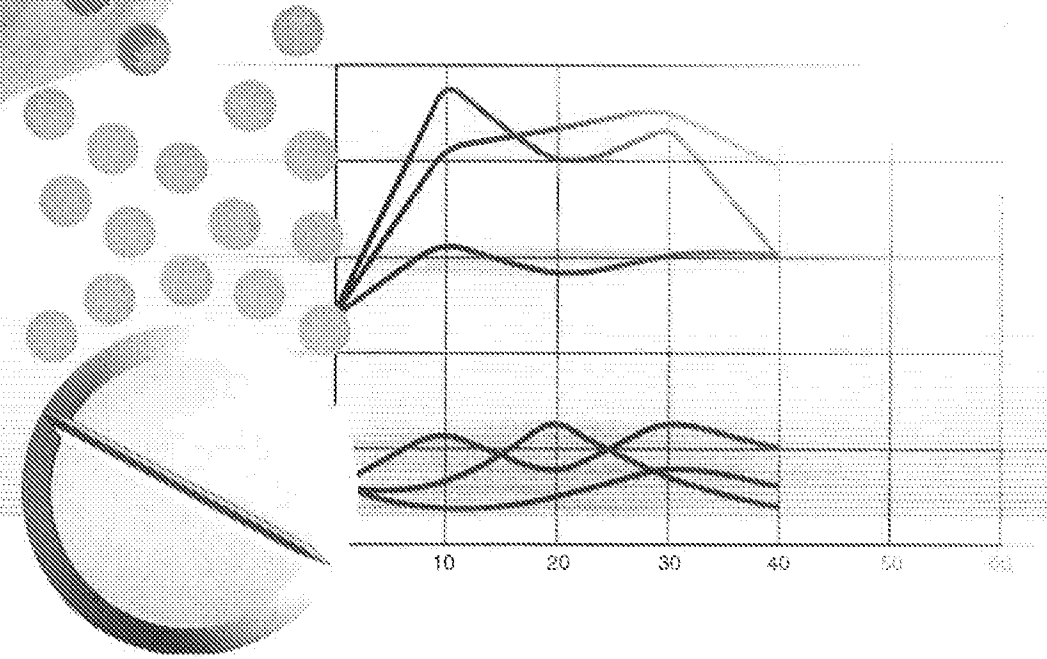
METHOCEL Cellulose Ethers

in Aqueous Systems

for Tablet Coating







Meet All Coating Quality Specifications, Improve Other Tablet Properties, and Maximize Production Speed

METHOCEL* Premium cellulose ethers produce tough, printable, economical, and highly consistent tablet coatings whether they are aqueous, hydroalcoholic, or solvent-based. Coatings are micro-thin, noncaloric, nonnutritive, nonallergenic, and more resistant to microorganism growth than those formulated with natural gums, sugar, and most other cellulosics.

Beyond producing coatings of the highest quality, METHOCEL products can improve other tablet physical properties and allow the coating process to be performed with optimum speed and efficiency.

This brochure explains the use of METHOCEL products in tablet coating systems in more detail. It also offers discussions of a general nature on the formulation and application of coatings in an effort to speed your development work. We hope you find it useful in anticipating and avoiding some of the common obstacles encountered during formulation and production.

*Trademark of The Dow Chemical Company

A Review of the Principle Advantages of METHOCEL in Tablet Coatings

Given the wide variety of routes available to a tablet coating of acceptable quality, why has the family of METHOCEL Premium products become the starting point for so many different applications?

Formulation Versatility and the Ability To "Fine Tune"

One reason for the popularity of METHOCEL is simply that these products have been used successfully in tablet coatings for over 25 years. Their performance is well documented and there is a large body of data to reference and rely upon. This speeds development and reduces its expense.

Also important is that with seven separate products and the ability to blend different grades, this polymer family produces an extremely wide range of required viscosities, solids content, and film properties. As a result, the decision to begin formulating a coating system with METHOCEL is not only rewarded with a coating that's acceptable, but one that has been optimized by several measures.

Improve Product Appearance, Help Assure Consumer Acceptance

First of all, coatings based on METHOCEL Premium cellulose ethers improve product appearance. They produce a glossy, quality finish that eliminates dusting. Films of METHOCEL make clear, sharp coatings that are nonionic and compatible with FD&C dyes, lakes, and pigments. They are excellent surfaces for printing, while clearly enhancing and displaying scoring, logos, and other distinguishing features of a tablet's surface.

Plus, although aqueous polymer films do not deliver the extraordinary high gloss of a sugar coating, tablet appearance is maintained at high levels with METHOCEL by careful process adjustments. Plasticizer selection, application rates, polymer concentration, and application of a second coat to specifically enhance sheen allow an even higher tablet gloss.

Coatings of METHOCEL also offer excellent barrier properties, limiting the migration of water and oxygen to protect sensitive cores. Properly done, an aqueous coating of METHOCEL can be applied to multi-vitamin tablets, for example, without causing the cores to discolor or break down. Further evidence to support the excellent barrier properties of these films can be seen in their use as coatings for food products, such as nuts. Films of METHOCEL effectively improve shelf life of nutmeats.

Of course a primary objective with coatings is to ease swallowing. Clear coatings of METHOCEL begin to hydrate in the mouth, then become slick to allow a tablet to slide easily down the throat. Studies with simulated esophageal passages have documented improved swallowing ease with tablets bearing a coating with METHOCEL as compared with uncoated tablets.

In short, with METHOCEL Premium products you easily achieve a quality image that promotes consumer acceptance.

Improve Tablet Physical Properties

Beyond providing the easy-to-swallow, micro-thin coatings consumers demand, METHOCEL also improves many other product properties. Compared to sugar, METHOCEL is a much better film former. Coatings can double tablet compressive strength and reduce friability while only increasing tablet size by 1-3 mil and product weight by 1-3%. Your products stand up to the rigors of handling and shipping. So the quality appearance achieved at the plant is maintained right to the consumer's home.

Another advantage with METHOCEL Premium products is the availability of low pH grades (pH 4 to 5) to inhibit bacterial growth yet maintain their viscosity under normal storage conditions. This feature, along with the fact that METHOCEL is compatible with a wide variety of preservatives and alone is relatively resistant to bacterial degradation, makes it easy to meet shelf life requirements.

Production Speed and Simplicity

Coatings made with METHOCEL can minimize coating cycle time too. They allow the use of high productivity spray application equipment. And spraying and drying can be done in a single pan. (Also consider that the low viscosity of METHOCEL E5 Premium LV permits high solids in the coating solution so less water must be removed.)

By permitting the use of automated equipment, coatings based on METHOCEL can contribute to lower labor costs in two ways. First, since the same procedures are used with each product there's less need for involvement by highly skilled and experienced personnel. Coating is no longer an "art form" but rather a highly controlled process. Second, fewer total people are involved in the process.

In short, METHOCEL meets all the primary goals for tablet coatings. Plus it improves other tablet properties while making sure production speed and economy are maintained.

Technical Assistance Every Step of the Way

A final reason for the popularity of METHOCEL really has little to do with the product family. It involves the years of experience and knowledge we have accumulated and can bring to bear on your specific applications. Some of this information is contained on the pages that follow. But necessarily it is somewhat general in scope. Rest assured, however, that after several decades of involvement with the formulation of coating systems for virtually every pharmaceutical product category, chances are we can help meet your specific application needs quickly, efficiently, and with optimum results. Look to the rest of this brochure for additional evidence to support the conclusion that METHOCEL is worth further investigation.

An Overview of METHOCEL Products For Tablet Coating

METHOCEL Premium products represent the hypromellose[1] product family of the highest quality. Here's why.

- METHOCEL is manufactured according to the stringent requirements of Good Manufacturing Practices (GMPs).
- Dow's manufacturing facilities are registered and regularly inspected by the FDA.
- METHOCEL products are produced from dedicated processes and equipment to assure the highest purity.
- Dow offers a Certificate of Analysis with every shipment so you have documentation of product quality and the consistency of that quality from shipment to shipment.

In short, when hypromellose is the product type of choice, METHOCEL Premium products should be the brand of choice to best ensure the production of consistently high quality products day in and day out.

Available Grades

In tablet coating applications, only the Premium (USP, EP, JP) grades of METHOCEL "E" cellulose ethers should be used. These products will meet the requirements of FDA and USP as well as EP, JP if so specified. See Table 1.

Product Description of METHOCEL Premium Products	
Physical form	free-flowing white/off-white powder
Particle size	100% pass through 30 mesh screen; 99% pass through 40 mesh screen
Packaging	available in 50-lb multi-wall bags or 50-kg fiber drums

[1]Previously referred to as hydroxypropyl methylcellulose or HPMC.

TABLE 1: Properties of Select Premium METHOCEL E Cellulose Ethers[1]
(Not to be considered sales specifications)

Product Description[2]	METHOCEL E3 Premium LV	METHOCEL E5[3] Premium LV	METHOCEL E6 Premium LV	METHOCEL E15 Premium LV	METHOCEL E50 Premium LV	METHOCEL A15 Premium LV	METHOCEL K3 Premium LV
Methoxyl, %	28-30	28-30	28-30	28-30	28-30	27.5-31.5	19-24
Hydroxypropyl, %	7-12	7-12	7-12	7-12	7-12	0	7-12
Moisture, % as packaged, max	3.0	3.0	3.0	3.0	3.0	3.0	5.0
Ash, max %	3.0	3.0	3.0	3.0	1.5	1.5	3.0
Sodium chloride, max %	1.0	1.0	1.0	1.0	0.5	1.0	1.0
Arsenic, as As, max	3 ppm	3 ppm	3 ppm	3 ppm	3 ppm	3 ppm	3 ppm
Heavy metals, as Pb, max	10 ppm	10 ppm	10 ppm	10 ppm	10 ppm	10 ppm	10 ppm
Viscosity[4], 2.0% in water, mPa•s	2.4-3.6	4-6	5-7	12-16	40-60	12-18	2.4-3.6 cps

[1] Also available in European Pharmacopoeia, EP, and Japanese Pharmacopoeia, JP grades.
[2] Meets all requirements in USP XXI monograph for hypromellose.
[3] Also available as METHOCEL E5 Premium LV low pH.
[4] Millipascal-seconds, mPa•s, is equivalent to cP (centipoise).
All solution viscosities are measured with Ubbelohde viscometers at a 2% concentration in water at 20°C (68°F).

A Brief Review of the Coating Process

The following review of the process involved with aqueous polymeric film coatings is offered for those not intimately involved in the manufacturing process. As a result it is purposely basic and is not intended for the very experienced reader.

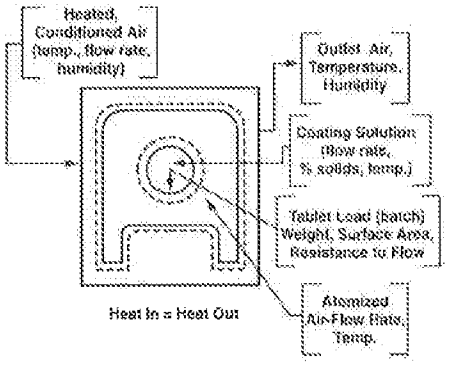
A Matter of Equilibrium

The use of polymer film coatings has often been attempted for the first time with a sense of concern by the formulator. Will the coating have the proper characteristics? Will it coat easily? Will the product still be stable and acceptable? Particularly when formulating aqueous coatings, many are concerned that the stability of water-sensitive drugs will be affected. As a result, many turn to organic solvent coating systems. Today, however, aqueous film coatings are being used more often on a wide range of pharmaceutical products, many of which were considered to be very sensitive to water.

To use aqueous coatings on different drug substrates, you simply need to understand the coating process. It is most easily viewed as a simple, black box thermodynamic model as shown in Figure 1.

First, consider the amount of fluid being applied to the tablet surface as the hydraulic load. One can calculate the need for the amount of incoming air, the temperature of the air, and the humidity of the air required to evaporate the incoming water. The goal is to enable the coating equipment to evaporate the water at the same rate as it is being put into the process.

Figure 1: "Black Box" Model



$(C_p, air)(AFR)(\Delta T) = (212°F\text{-}T_{in})(C_p, sol)+(Water\ vol)(H_{vap})$

C_p, air — heat capacity of air
AFR — air flow rate
ΔT — difference between inlet and outlet air temperature
T_{in} — initial temperature of coating solution
Cp, sol — heat capacity of solution
H_{vap} — heat of vaporization

Too high a temperature can cause spray drying of the coating solution or instability of the drug due to high tablet core temperatures.

In conclusion, it is simply necessary to monitor the amount of liquid being applied to the coating surface, the ability of the air to evaporate the material under the fixed conditions of air flow rates, humidity, air temperature, and the tablet surface area. (A more complete thermodynamic model is discussed in an article published by *Pharmaceutical Technology* entitled "A Thermodynamic Model for Aqueous Film Coating," April 1987, by Glen C. Ebey.)

Whether you complete a thorough thermodynamic analysis of the process or simply monitor important parameters like exhaust air temperature and the various fluid and air flow rates, aqueous coating can be done with relative ease.

With this in mind let's review the individual factors which must be controlled by the formulator to assure the quality of the coating.

The Coating Solutions

Regardless of the delivery system, the coating solution must be formulated to have a sprayable solution viscosity. Generally this means a viscosity of the coating solution in the range of 150-400 mPa•s, although higher viscosities may be possible under certain equipment conditions. Formulations may contain optional surfactants, plasticizers, or pigments. It should be noted, however, that these additional excipients can affect the viscosity of the coating solution. Yet the major factor controlling the formulation is the viscosity of the polymer grade being used and the concentration of polymer in the solution.

A variety of solvents may be used with tablet coating systems of METHOCEL hypromellose. At its inception, organic solvent systems of methylene chloride/alcohol blends were used. This allowed very fast drying at relatively low temperatures or air volumes.

In some cases, hydroalcoholic solvent systems are used where the water content in the solvent mixture may range from 20-80% by weight.

Hypromellose is not soluble in absolute alcohol but may be applied if more than 20% water is included in the alcohol.

The use of alcohol/water solvents also allowed for relatively fast coating but was slower than the methylene chloride/alcohol system.

Finally, in more recent times, aqueous coating has become the preferred choice. This did require increased air handling and heat exchange to facilitate rapid coating. Aqueous systems can be formulated at varying water or solids content depending on the choice of polymer, molecular weight, and the use of pigments. The effect of formulation variables on film properties will be discussed later, but in general the higher the coating solids content the faster the tablet may be coated.

Coating Formulation Guidelines

Typical Formulation Ingredients

Polymer

METHOCEL cellulose ethers are available in a variety of pharmaceutical grades as shown on page 7. Most often, METHOCEL E Premium products, hypromellose 2910 USP grade, are preferred for use in aqueous film coatings. These products tend to have the best clarity, color, and film properties. METHOCEL E products are available in a range of molecular weights. The viscosity of a 2% solution of these products are available as 3, 5, 6, 15, and 50 mPa•s.

METHOCEL K products can also be considered for tablet coating, but they are not highly recommended except when sugar coatings are also involved. See page 23 for further discussion of the use of METHOCEL K products.

In those countries where only methylcellulose is approved as a food coating material, METHOCEL A15 Premium LV can be used for tablet coating. This product also produces a good coating on tablet surfaces with similar properties to the hypromellose product. All METHOCEL Premium products are available in USP, European Pharmacopoeia, and Japanese Pharmacopoeia grades.

Solvent

METHOCEL products can be formulated in organic, hydroalcoholic, and aqueous solvent systems. As mentioned, each solvent system has a specific impact on the coating process. Any of the METHOCEL products may be formulated in these solvent systems. It is recommended, however, that METHOCEL E products be used in organic or hydroalcoholic systems where better polymer compatibility is desired.

The viscosity-concentration relationship for different solvents varies slightly with the choice of solvents. The information given in Figures 2, 3, 4, 5, 6, 7, 8, 9, and 10 may be useful in predicting polymer concentrations necessary to achieve sprayable coating solution viscosities.

Figure 2: Viscosity Concentration Chart for Low Viscosity METHOCEL E Premium Products in Water

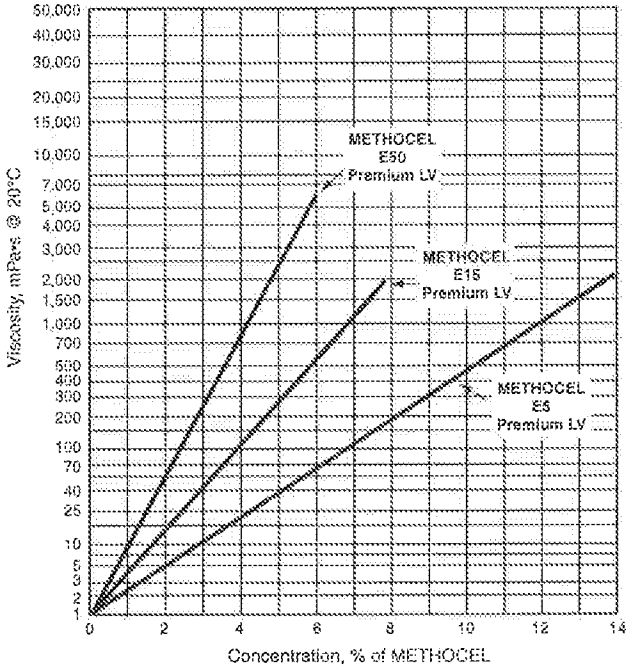


Figure 3: Viscosity Concentration for METHOCEL in an 80:20 Wt/Wt Water-Ethanol Mixture

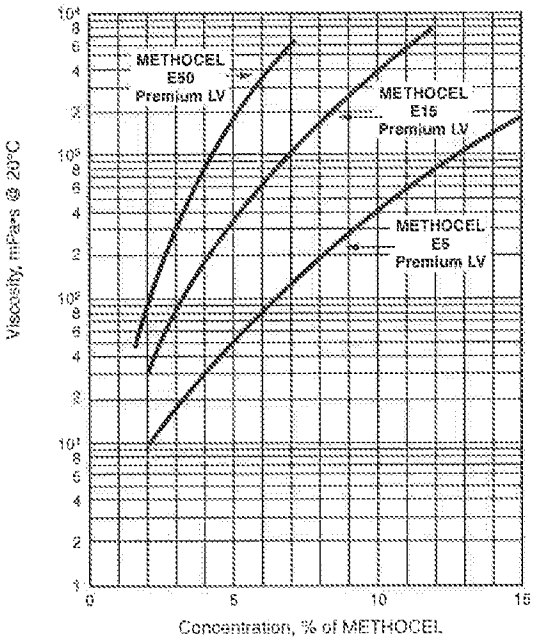


Figure 4: Viscosity Concentration for METHOCEL in a 60:40 Wt/Wt Water-Ethanol Mixture

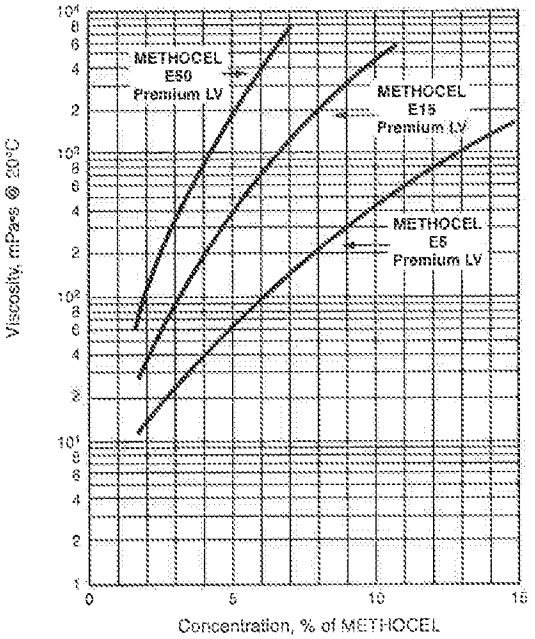


Figure 5: Viscosity Concentration for METHOCEL in a 40:60 Wt/Wt Water-Ethanol Mixture

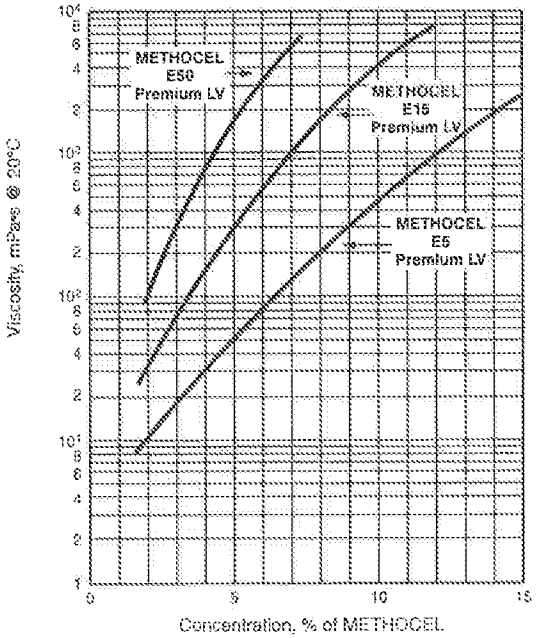


Figure 6: Viscosity Concentration for METHOCEL in a 20:80 Wt/Wt Water-Ethanol Mixture

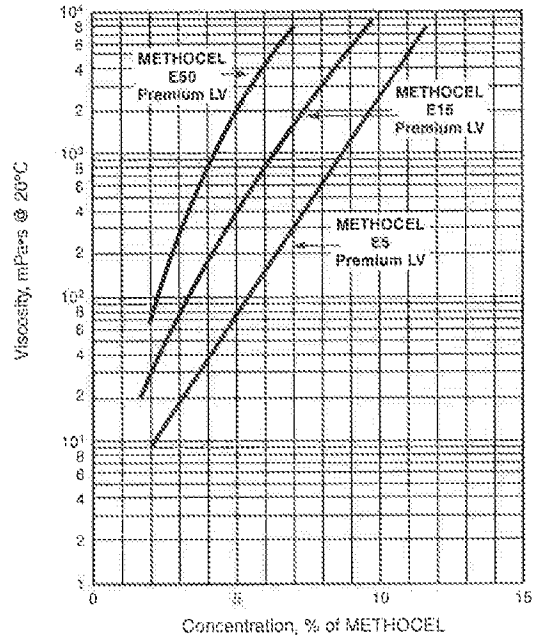


Figure 7: Viscosity Concentration for METHOCEL in a 80:20 Wt/Wt Methylene Chloride-Ethanol Mixture

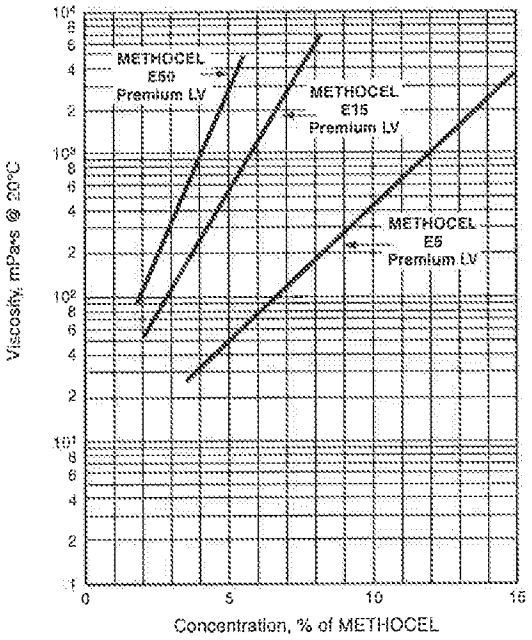
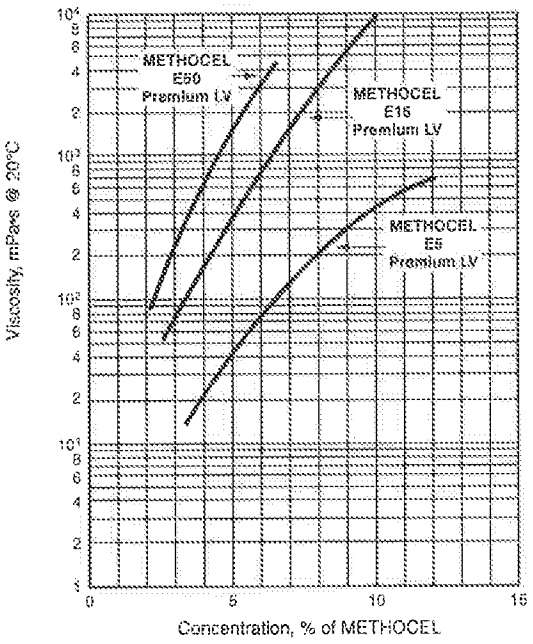


Figure 8: Viscosity Concentration for METHOCEL in a 60:40 Wt/Wt Methylene Chloride-Ethanol Mixture



Plasticizer

The function of a plasticizer in a coating formulation is to soften films or make them less brittle. This is particularly important when using very low molecular weight grades of hypromellose. Generally, water-soluble plasticizers are chosen for use in aqueous systems and solvent-soluble plasticizers are used with organic solvent systems. Using a plasticizer can lead to smoother films, increase adhesion to the tablet surface, reduce logo bridging, and actually reduce cracking or chipping by improving film toughness.

Pigments

Pigments are used to allow coloration of tablets. The use of aluminum lake or iron oxide pigments has essentially replaced the use of soluble dyes. Pigments or pigment dispersions are added to polymer solutions in amounts required to achieve the desired coloring while hiding or masking taste effects. Generally, the level of pigment used will be from 50-200% of the polymer weight in a coating solution.

Figure 9: Viscosity Concentration for METHOCEL in a 40:60 Wt/Wt Methylene Chloride-Ethanol Mixture

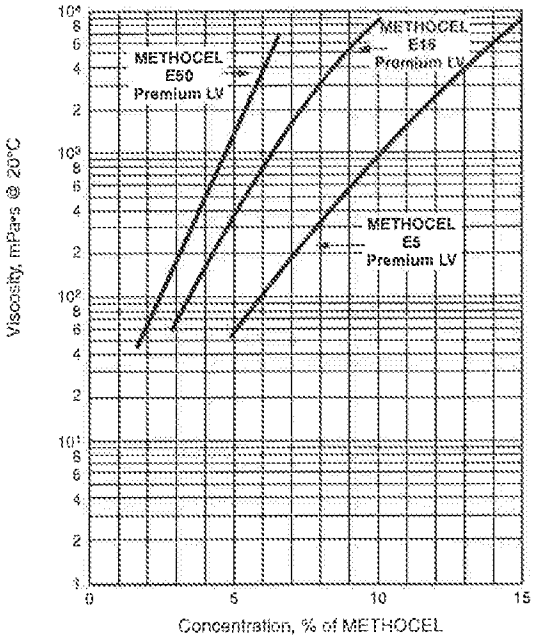
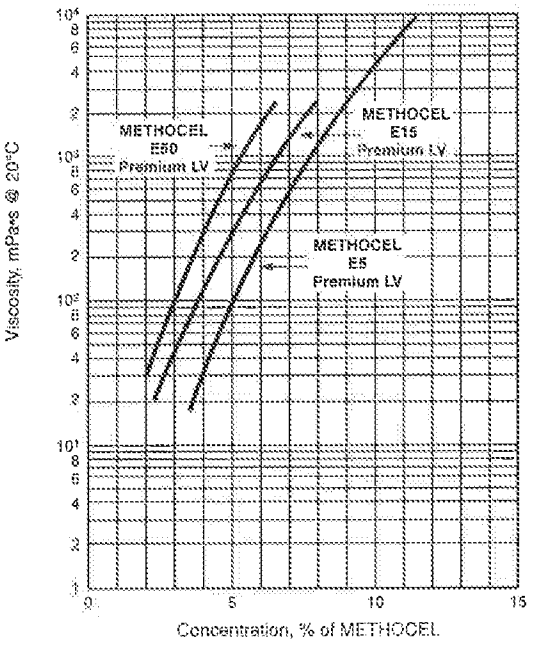


Figure 10: Viscosity Concentration for METHOCEL in a 20:80 Wt/Wt Methylene Chloride-Ethanol Mixture



Surfactants

Surfactants are sometimes used to aid in color dispersion and development of the tablet coating. The use of surfactants may also depress the viscosity of the polymer solution. Reduction of pigment flocculation through the use of surfactants can also improve the coating gloss. We generally do not recommend the use of surfactants except to solve specific performance problems.

Evaluation of Films Containing METHOCEL in Tablet Coating

Many methods have been used and reported on the evaluation of polymer films for tablet coating. Besides actual tablet coating evaluations we have found that the physical evaluation of free films provides useful information. The following data and observations have been made through testing of 1 mil dry films made by casting on glass and drying at 50°C. While there is a substantial amount of data scatter, trends may be clearly seen when formulation parameters were changed. Film testing was done on an Instron, testing in 50% RH at 75°F. Measurement of tensile at break, work to break, elongation at break, and Young's Modulus were recorded and evaluated. We find that toughness is the best predictor of overall film performance as it includes both the film strength and ability to deform without breakage. Young's Modulus has been reported as useful in predicting adhesion. The lower the Young's Modulus the better the film adhesion to tablet substrates.

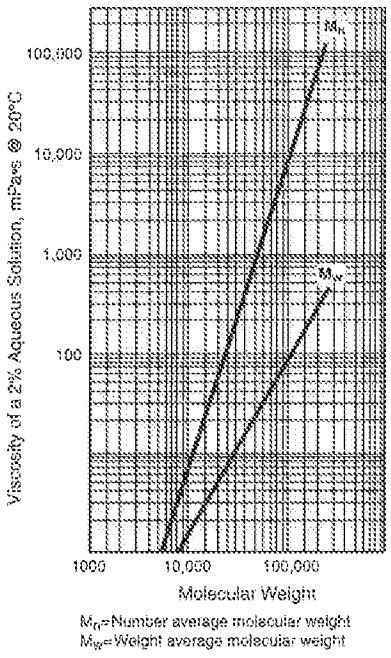
Formulation Factors That Affect Film Properties

Polymer Molecular Weight (Viscosity Grade)

It has often been reported that polymer molecular weight will dramatically affect the strength of films. Since the molecular weight of polymers and the 2% viscosity can be directly correlated we will use viscosity and molecular weight interchangeably. See Figure 11. The names for METHOCEL products specify the 2% aqueous solution viscosity so it is more useful to think of molecular weight in terms of viscosity.

In general, as viscosity decreases the strength of a film will decrease. It will also become more brittle.

Figure 11: Approximate Molecular Weight/ Viscosity Correlation for Hypromellose, 20°C



M_n=Number average molecular weight
M_w=Weight average molecular weight

Figure 12: Film Properties of Low Molecular Weight METHOCEL E Products

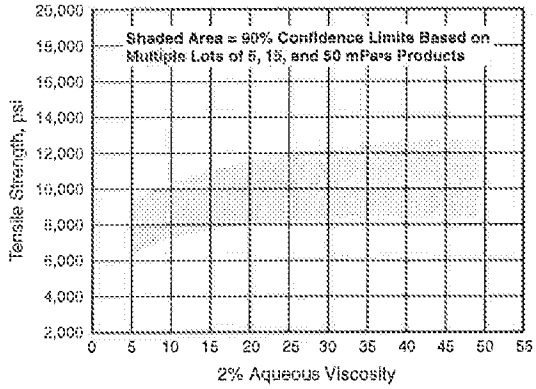


Figure 13: Film Properties of Low Molecular Weight METHOCEL E Products

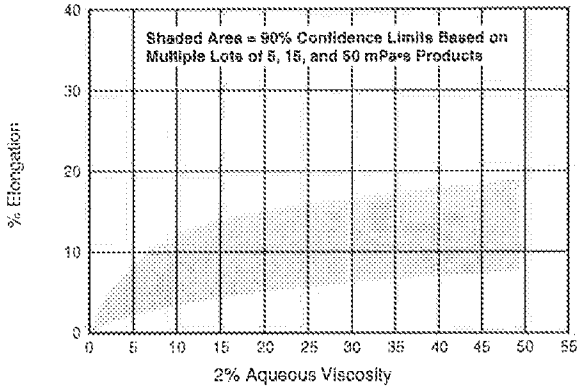


Figure 14: Film Properties of Low Molecular Weight METHOCEL E Products

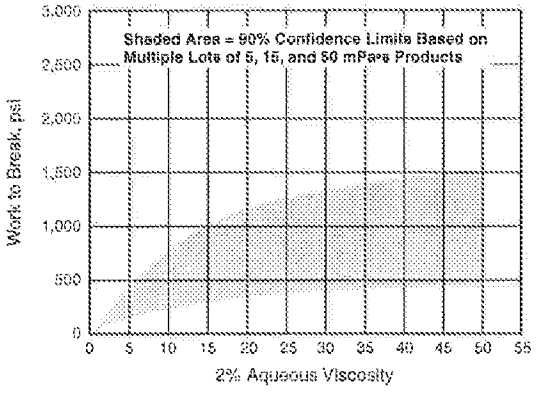


Figure 12 shows how the tensile strength of a film decreases with decreasing viscosity. The shaded area represents the 90% confidence limits for data from many different lots and viscosities. Enough data have been taken to use these results as a standard for comparison of new products or blends. In Figure 13 the increasing brittleness at low viscosity is shown by the reduction in elongation. At 3 mPa•s it becomes very difficult to remove the films from glass plates because of the film brittleness. Figure 14 shows the combined effects of strength loss and brittleness by depicting the reduction in film toughness (work to break) with decreasing molecular weight.

Figure 15: Blending Chart for METHOCEL E5 and E15 Premium LV (USP) (5% concentration in water)

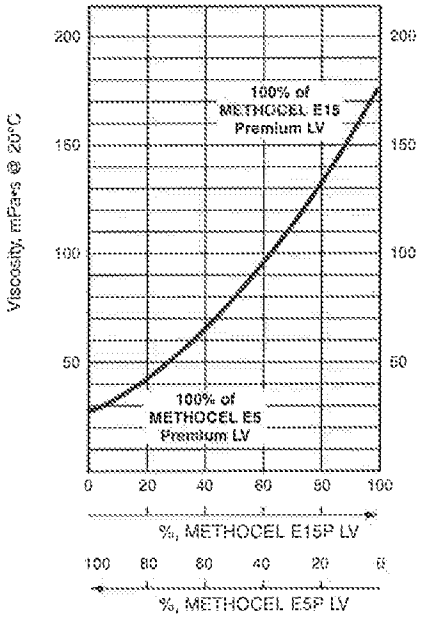
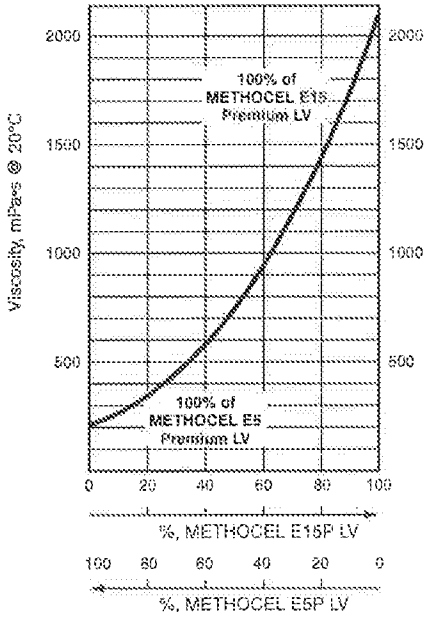


Figure 16: Blending Chart for METHOCEL E5 and E15 Premium LV (USP) (10% Concentration in Water)

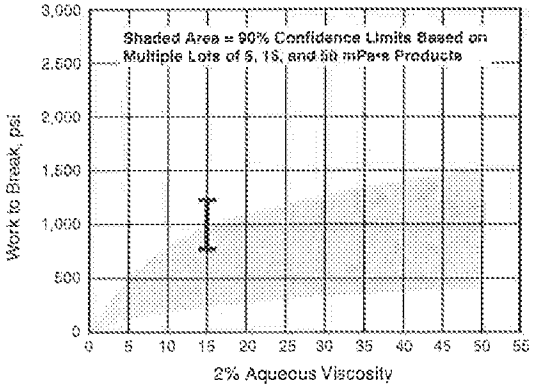


Most companies that coat tablets wish to use the lowest viscosity possible to maximize production efficiency. One can see, however, that there is a trade-off in physical properties with lowering molecular weight. This is why METHOCEL E3P LV is seldom used alone as the coating polymer.

Reduction of film properties usually causes problems like logo bridging or cracking. The level at which this becomes a problem is very dependent on the tablet substrate, geometry, and engraving. For example, one of our customers experienced a 10-fold increase in the incidence of cracking when the polymer viscosity varied from 6 to 5 mPa•s.

Although a wide variety of viscosity grades are available, intermediate viscosity grades may be available on request or can be manufactured through blending (Figures 15 and 16).

Figure 17: Film Properties of Low Molecular Weight METHOCEL E Products (Comparison to E5/E50P LV Blends)



Blending Different Molecular Weight Grades of METHOCEL

Experimentation has shown that wide blends of viscosity grades often give better results than the narrower molecular weight distribution of a manufactured product. For example we have found that a blend of METHOCEL E5P LV and METHOCEL E50P LV to achieve a nominal viscosity of 15 mPa•s generally outperformed the typical METHOCEL E15P LV product (Figure 17). While blending of product viscosities is usually not necessary, improvements in coverage, cracking, or logo bridging may be achieved on difficult tablet substrates.

Effects of Plasticizers

The use of plasticizers with hypromellose film coatings is very common. However, many different types have been reported in use. We chose to evaluate the effect of various plasticizers on film properties of METHOCEL as well as evaluate the optimum plasticizer level.

Since the most common level of plasticizer in use today is about 20% based on polymer solids, we chose to evaluate a variety of plasticizers with hypromellose at that level. A control of METHOCEL E5 Premium LV with no plasticizer was included for reference. As expected, most plasticizers made the films less brittle and increased elongation results. Interestingly, the higher molecular weight polyethylene glycols often used in film coating actually decreased elongation (Figure 18). Other plasticizers like oleic acid, triacetin, and propylene glycol (PG) had little effect.

Figure 18: Effects of Plasticizers on METHOCEL E5 Premium LV Films (Elongation)

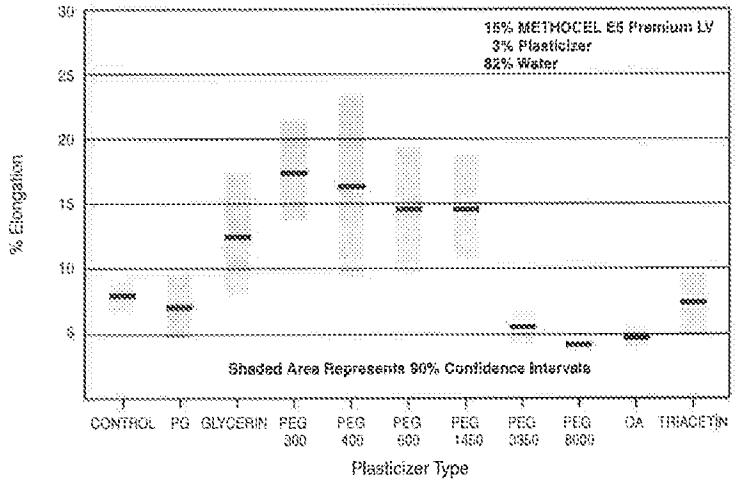


Figure 20: Effects of Plasticizers on METHOCEL E5 Premium LV Films (Toughness)

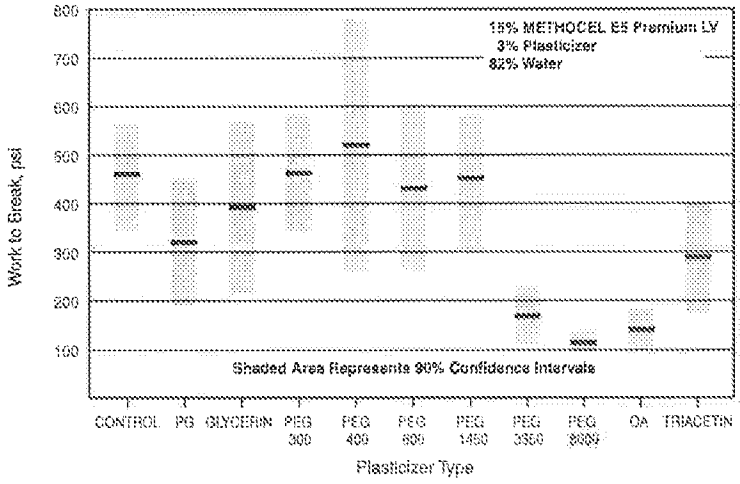


Figure 19: Effects of Plasticizers on METHOCEL E5 Premium LV Films (Tensile Strength)

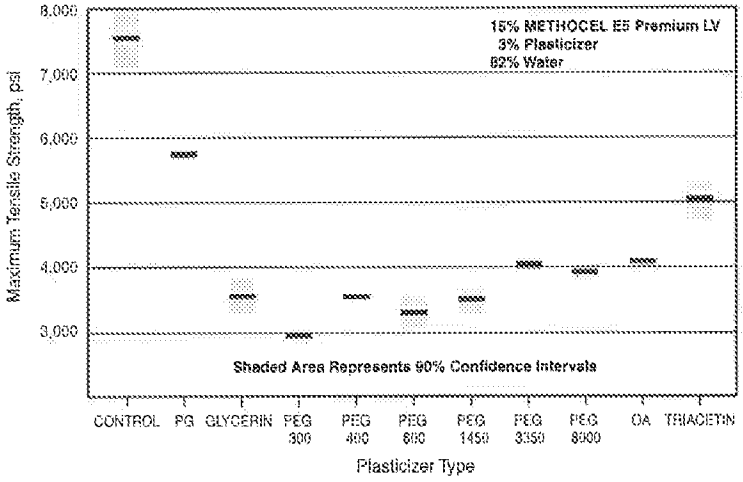
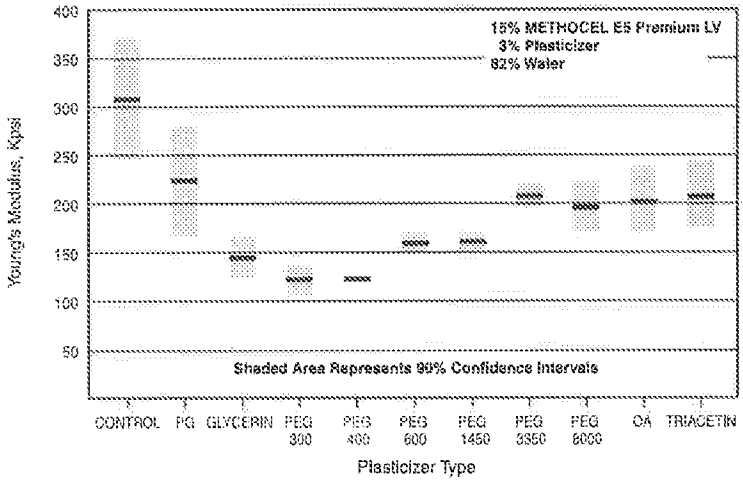


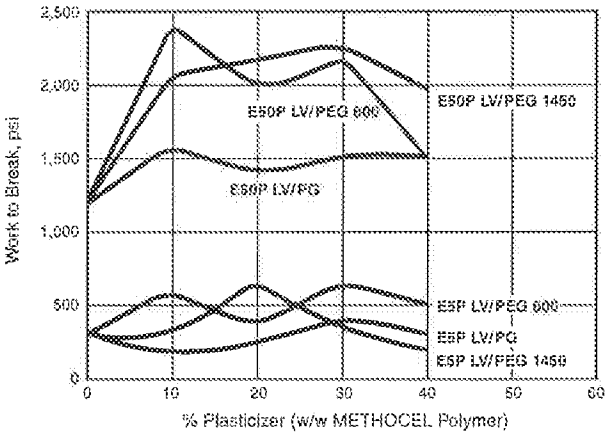
Figure 21: Effects of Plasticizers on METHOCEL E5 Premium LV Films (Young's Modulus)



Again, as expected, the use of plasticizer reduced the tensile strength of all the films (Figure 19). An evaluation of film toughness, however, shows that equivalent to improved performance was seen with the low molecular weight polyethylene glycols from PEG 300 to PEG 1450 (Figure 20). All of the plasticizers tended to reduce the value for Young's Modulus and may indicate an increase in adhesion (Figure 21). Finally, in aqueous systems, it is generally recommended that water-soluble plasticizers be used. In nonaqueous systems, plasticizers like triethylcitrate, triacetin, castor oil, acetylated monoglycerides, and oleic acid may be preferred.

The amount of plasticizer used is very important to film properties. If the film is over-plasticized it will lose toughness or may exceed the capacity of the polymer to hold the plasticizer. For example, increasing the level of propylene glycol in a film of METHOCEL demonstrated that an optimum level is 20-30% based on polymer solids. Levels of propylene glycol greater than this do not significantly degrade film properties, possibly due to compatibility limitations or volatility of the plasticizer. With the less volatile polyethylene glycol PEG 600 and PEG 1450, an optimum is reached at 20-30% plasticizer based on polymer solids. Beyond this optimum a continual decrease in film toughness is experienced. In Figure 22 the optimum film toughness is shown for METHOCEL E50 Premium LV. With the lower molecular weight METHOCEL E5 Premium LV the optimum is more difficult to interpret.

Figure 22: Effects of Plasticizer Concentration on METHOCEL E Premium LV Films (Toughness)



Polymer Blends

It may at times be advantageous to blend polymers of varying types. Hydroxypropyl cellulose (HPC), for example, has been used in film coating. While HPC typically is much more brittle than hypromellose it does have the property of being a better adhesive. Used alone the film may be tacky and cause problems in sticking or picking of tablets. But when used in combination with hypromellose, the HPC product imparts better adhesion. For example, when HPC-EF and HPC-LF were added to METHOCEL E5P LV in increasing concentrations, the films lost strength (Figure 23), toughness (Figure 24), and became brittle (Figure 25). It was noticed, however, that the films adhered very tightly to glass plates. It was theorized and has been shown in practice that the use of HPC in hypromellose films will increase adhesion. This can be predicted from the reduction in Young's Modulus seen in Figure 26. We recommend that if adhesion needs to be increased to solve problems such as logo bridging, that HPC-EF or -LF be used at a maximum of 25% of the total polymer solids. Additional amounts may weaken the films too much to be useful.

Other polymer blends have been used at times by the industry. Blends of methylcellulose and polyvinyl pyrrolidone (PVP) have been used commercially. While PVP has poor film formation properties, it can be used at very high concentrations with very low viscosity in water. This could be a method of increasing polymer concentration without detrimentally raising solution viscosity. Care should be taken, however, to evaluate the properties of the film or coated tablet to ensure successful formulation.

Figure 23: Film Tensile Strength of Blends of METHOCEL E5P LV Hypromellose/Hydroxypropyl Cellulose

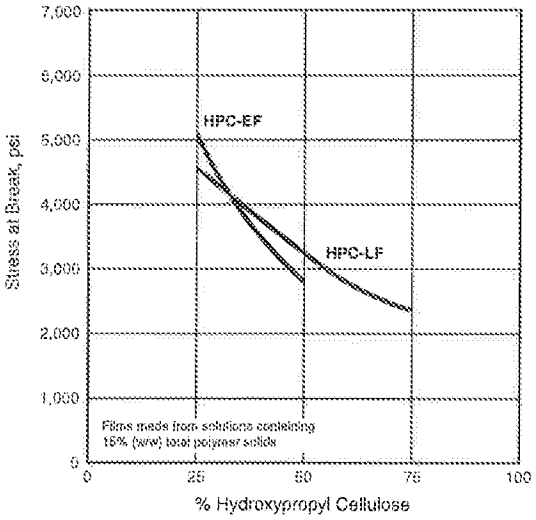


Figure 24: Film Strength of Blends of METHOCEL E5P LV Hypromellose/Hydroxypropyl Cellulose

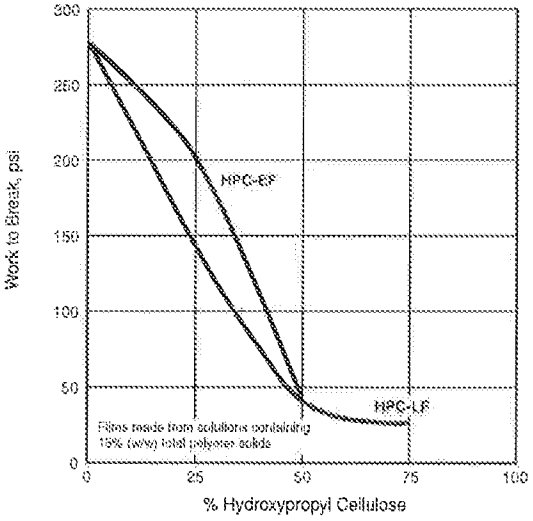


Figure 25: Film Elongation of Blends of METHOCEL E5P LV Hypromellose/Hydroxypropyl Cellulose

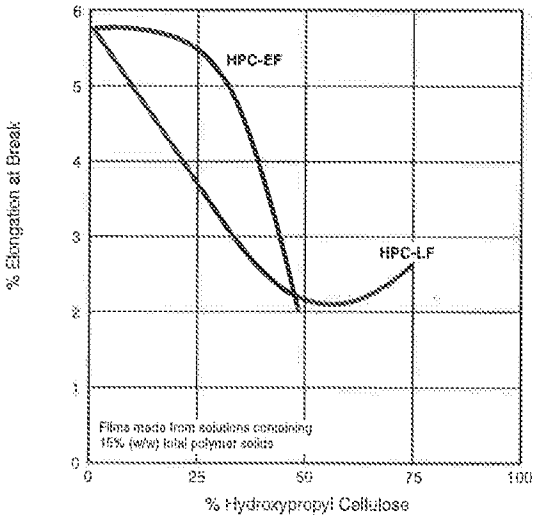
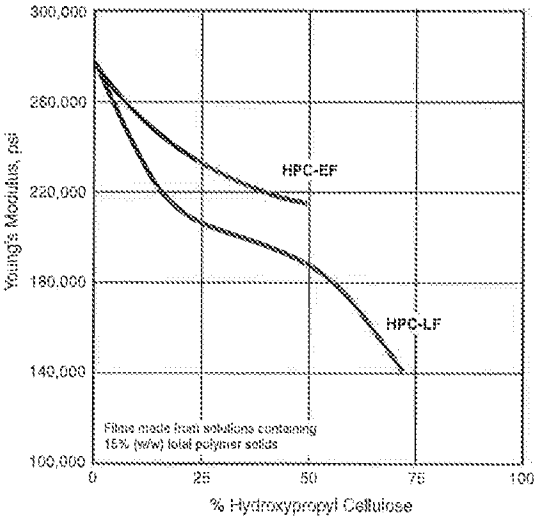


Figure 26: Young's Modulus of Blends of METHOCEL E5P LV Hypromellose/Hydroxypropyl Cellulose



Pigmented Coatings

Very often it is desirable to apply opaque, pigmented coatings. Pigmented coatings can provide additional light stability to dosage forms and help differentiate tablets by color. Most pigments are supplied as color dispersions in alcohol, propylene glycol, or water. Pigments used in tablet coatings generally are either aluminum lakes or iron oxides, with titanium dioxide and talc used in white or pastel colors.

When pigments are used in tablet coatings they have a significant effect on the film properties. As with any plastic, when pigments are added a reduction in flexibility and strength is usually experienced. Additionally, because the pigments are usually dispersed in a plasticizer like propylene glycol, the plasticization effect may be entirely dependent on the ratio of pigment to polymer used in the formulation. In the plasticizer section of this brochure it was shown that additional levels of propylene glycol in an unpigmented film did not necessarily lead to reduced film properties.

To examine the effect of the plasticizer supplied in pigment dispersions, a series of pigmented films was prepared using pigment and METHOCEL E15 Premium LV at a ratio of 1 to 2. A variety of commercial pigments were used and film properties plotted in Figure 27 versus the amount of plasticizer contributed by the pigment dispersion. A control unpigmented METHOCEL E15 Premium LV is plotted as well.

It is clearly seen that the pigmented films exhibit a distinct loss of strength from the unpigmented control. The very high levels of propylene glycol found in some of the pigment dispersions did not detrimentally affect film strength.

Normally, pigmented films are formulated with additional plasticizer even though there may be an excess available from the pigment dispersion. To evaluate the effect of additional plasticizer, an additional 20% polyethylene glycol 600 (PEG 600) was added to the pigmented film coatings. In every case an increase in film properties (Figure 28) was noted with the additional plasticizer. This strongly suggests the use of the optimal 20-30% additional polyethylene glycol plasticizer when formulating pigmented films.

Microbiological Considerations

When working with aqueous solutions, the possibility of microbiological contamination is a valid concern. It has been reported in the literature that many cellulose-based polymers can support microbiological growth. With cellulose ethers the higher the level of chemical substitution, the more resistant to enzymatic breakdown the polymer becomes. METHOCEL E products have a relatively high level of substitution but will support microbiological growth in the very low viscosity grades. It is therefore important to take reasonable care in the preparation of coating solutions to keep all the equipment and excipients clean. Usually GMP standards will suffice. METHOCEL Premium products are supplied to meet USP guidelines for microbiological attributes and are certified to be free of the USP pathogenic organisms. The production process for METHOCEL products is essentially self-sterilizing so no significant contamination of METHOCEL has ever occurred.

It is normally recommended that aqueous solutions be made and used within one week's time. Additional protection can be obtained by the use of preservatives like propylparaben or methylparaben or the addition of alcohol to the solution.

Figure 27: Effect of Various Pigment Dispersions on Film Properties of METHOCEL E15 Premium LV (Tensile Strength)

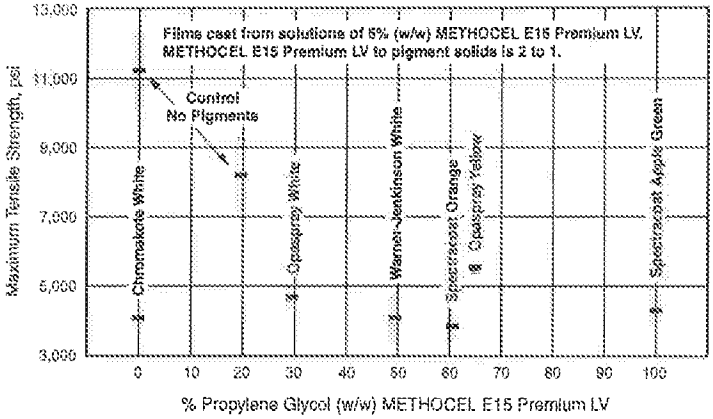
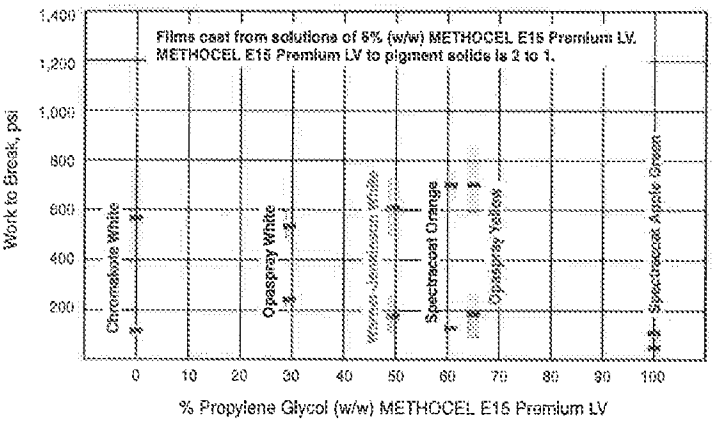


Figure 28: Effect of Adding PEG 600 to Pigmented METHOCEL E15 Premium LV Films (Toughness)



Use of METHOCEL in Sugar Coatings

METHOCEL products have found application in sugar coatings as a seal coating or as a film modifier. As a subcoating, METHOCEL E5 Premium LV or METHOCEL E15 Premium LV can be used with or without plasticizer to place a protective layer over the tablet core. In cases where additional protection from moisture is desired, ETHOCEL* ethylcellulose can be combined with METHOCEL in a co-solvent blend of methylene chloride/alcohol and applied to the tablet cores. At 25% ETHOCEL Standard 10 Premium and 75% METHOCEL E15 Premium LV, little effect is seen on drug dissolution. At higher levels of ethylcellulose (e.g., >75%), a delay in drug diffusion is experienced.

METHOCEL products may be used in sugar coatings to reduce coating brittleness. In cases where hygroscopicity is a problem, we recommend the use of METHOCEL E5 Premium LV or possibly METHOCEL E15 Premium LV for sugar compatibility. Compatibility is tested and it is relevant to fully understand before the addition of sugar. Use of urea and/or some of the simple sugars will also improve polymer compatibility in sugar systems. These hygroscopic polymers may also replace the conventional use of acacia and/or gelatin in sugar coatings.

*Trademark of The Dow Chemical Company

Production Considerations

Preparation of the Coating Solution

Proper preparation of the coating solution is necessary to achieve good coating in a reasonable amount of time. METHOCEL polymers are supplied as a fine powder and will rapidly hydrate in cold water. The hydration is so rapid that without proper agitation, clumps of gels with dry powder inside can form. Once formed, additional agitation and time are needed to completely hydrate all the polymer.

Several methods are useful in aiding the timely preparation of coating solutions.

1. Dispersion in hot water. Since METHOCEL products are not soluble in hot water, lump-free dispersing can be easily accomplished by dispersion in hot water. Temperatures in excess of 80°C are recommended, but even temperatures of 60-80°C will slightly aid the polymer dispersion. The polymer dispersion is then cooled to cause polymer hydration. The cooling may be accomplished externally in jacketed vessels or part of the water may be reserved as cold water and added after polymer dispersion.

2. Blending of ingredients. Another method to minimize polymer agglomeration consists of separating polymer particles by dilution with other coating excipients. Combinations of dry pigments, dry plasticizer, and polymer can often be added directly to process water.

3. Dispersion in a nonsolvent. When formulating hydroalcoholic or organic solvent coatings of METHOCEL, solutions are easily made by dispersing the polymer in alcohol (a non-solvent) and then hydrated by the addition of water. In organic systems METHOCEL can be dispersed in alcohol and then hydrated by the addition of methylene chloride.

4. Direct addition to room temperature water. This method, while the most difficult, is often used in large scale coating operations due to equipment and heat transfer limitations. METHOCEL products may be added directly to process water if a slow controlled addition of the polymer is used in combination with good agitation. Care must be taken to control the agitation level to minimize foaming and allow sufficient time for complete polymer hydration.

A Word about Foaming

Solutions of METHOCEL products have a tendency to foam under agitation because these polymers are surface active. Air entrapped in ingredients or that is introduced by excessive agitation can increase this tendency. However, once foaming had occurred, it can be reduced by defoamers like Dow Corning AF products or by settling over time.

When mixing solutions, the level of agitation should be changed as thickening occurs. Agitation should move the fluid surface in the vessel and start to pull a small vortex. As thickening occurs, the agitator speed will need to be increased to maintain sufficient mixing. Proper blade placement and baffling are necessary so consultation with equipment suppliers is recommended. A quiescent period of 15-45 minutes is usually recommended after mixing to allow most of the entrapped air to move to the surface.

A Word about Filtration

It is often beneficial to subject coating solutions to filtration. This ensures that any lumps or incompletely hydrated polymers are removed. Use of a 60 to 80 mesh screen can normally be accomplished with commercial filtration devices. Gravity flow is possible, but air pressurization is preferred for rapid filtration.

Application Rate

The rate of coating solution delivery is an important process control variable. While fast application of the coating solution is important to minimize batch times it must be remembered there are limitations for each type of equipment and coating solution being utilized. Practical limits can be determined by utilizing the basic thermodynamic relationships and monitoring exhaust air temperature. The flow rate of coating solutions is generally controlled by a positive displacement pump, although other coating systems may rely upon an air pressure pot delivery system. When using positive displacement pumps, viscosity of the coating solution is not a critical factor in the flow rate. However, when using a pressure pot delivery system, the viscosity of the coating solution will affect the delivery rate. It should also be recognized that the temperature of the coating solution will affect viscosity of the coating solution. As with most polymers, when the solution temperature increases (while staying below the thermal gelation temperature) the coating viscosity will decrease. The application of shear to concentrated polymer solutions can also reduce viscosity.

Air Atomization Pressure and Flow Rates

The amount of air being applied and the amount of pressure being utilized to atomize the liquid droplets can determine the efficiency and effectiveness of the coating system. It is important to make the smallest possible droplet size to ensure rapid drying. Air atomization is generally preferred with aqueous systems because it enhances initial liquid evaporation. Small droplets are necessary to achieve a fine, smooth surface on coating tablets. Changes in air flow rates and air atomization pressure can affect delivery rates when using a system other than a positive displacement pump.

Spray Systems

The numbers and types of spray nozzles utilized in any coating pan are of critical importance and information should be obtained from the equipment manufacturer. It is particularly important that nozzles be selected that can achieve a proper pattern for uniform coating of the tablet surfaces. Nozzle fan angles, the number of nozzles, and the distance from the tablet bed must be optimized so uniform side-to-side coating of the tablet bed is achieved without tending to overwet tablets or spray dry the solution. We recommend you seek information from both the equipment manufacturers for nozzles and coating pans for further information.

Coating Equipment

Modern film coating pans are manufactured by a variety of suppliers. Each supplier has its own configuration for the coating operation. Basic differences revolve around movement of air through the tablet bed. Some manufacturers move air upward through the tablet bed while others pass the air downward through the fluid bed. Some pans are fully perforated around the entire circumference while others have areas or regions of perforation. While there are some basic differences between these designs, each has its own beneficial features and can be effectively utilized for aqueous film coating. Some of the typical manufacturers of equipment today are: Driam of West Germany, Thomas Engineering, Vector Corporation, and Key Industries in the U.S.

Fluid bed coating of tablets may also be desirable for certain formulations. A variety of fluid bed coating equipment is manufactured with many application methods such as top spray, bottom spray, side spray, and tangential rotary spray. Fluid bed equipment is available from Glatt Air Techniques, Vector Corporation, and Aeromatic, as well as other companies.

Drying Air

The volume, temperature, and humidity of the drying air are critical in optimization of the coating process. Generally it is desirable to deliver the greatest possible amount of air at the desired 70-90°C temperature without causing over-fluidization of the tablet bed. Often older equipment is limited by air handling capacity or heating capacity. Therefore we recommend measurement of air flow rates and consultation with equipment manufacturers if coating capacity appears limited. Air flow rates should be monitored during the coating process as exhaust air filters can become restricted with over-spray, dust, and tablet particles.

The condition of inlet air also affects the drying capacity. High humidity air dries tablets less effectively than dry air. Thus a process optimized for one day's atmospheric conditions may need daily adjustment if the inlet air is not conditioned and controlled.

Normally, inlet air is controlled to the range of 70--90°C. Higher or lower temperatures may be desired for specific temperature-sensitive products or for fast coating application.

The Tablet Load

The pan loading and tablet dimensions will also affect coating efficiency. Most coating pans must be filled to an operative volume for tablet coating. Too few or too many tablets lead to inconsistent coating quality. Even the shape of tablets will affect the optimal loading and drying efficiency

of the coating operation. Care must be taken in selection of the tablet shape to be coated. Friable tablets or soft tablets may be very difficult to coat. Tablets using a high level of waxy or hydrophobic ingredients may be difficult to coat due to poor adhesion or poor wetting.

Conclusion

Reliable, tough, printable, and economic tablet coatings can be applied quickly and efficiently, meeting USP, EP, JP, and FDA requirements, from aqueous systems based on METHOCEL E Premium products.

Where desired, the carriers for such coatings can be blends of water with alcohol or other solvents ... up to 100% organic solvent if the coater has not yet initiated aqueous coating.

Dow has been making cellulose ethers for pharmaceutical applications since 1938. Years of experience in solving application needs and developing new products that optimize desired performance are available to Dow customers and prospects.

These resources include a comprehensive bibliography of medical articles on the use of METHOCEL products in pharmaceuticals. In addition, Dow maintains several drug master files, a repository of information that you and the FDA can use to gain quick approval of new formulations. Specialized technical services such as individual consultation or problem-solving assistance by experts who specialize in pharmaceutical applications or METHOCEL products are available on request.

For More Information

To request additional information, complete literature, or product samples, you can reach a Dow representative by calling the phone numbers listed on the back cover. Or visit our web site at **www.methocel.com**.

Health Considerations

METHOCEL cellulose ether products resemble naturally occurring plant and seaweed gums in many of their chemical, physical, and functional properties since all these materials possess a basic carbohydrate structure.

Gums have a long history of use in food and pharmaceutical products. METHOCEL cellulose ether products have had extensive evaluation and testing in both acute and long-term feeding studies in a number of species, including humans. Their use as food additives in a wide variety of food items and their broad use in pharmaceutical products attest to the safety of METHOCEL Premium cellulose ether products.

Dow has been making cellulose ethers for pharmaceutical applications since 1938. Years of experience in solving application needs and developing new products that optimize desired performance are available to Dow customers and prospects.

While dusts from METHOCEL products could conceivably cause temporary mechanical irritation to the skin and eyes under extreme conditions, and may be considered as a nuisance when breathed, the products are not expected to present a significant health hazard in handling. Although no special precautions typically need to be observed to handle the products safely, the use of an approved dust respirator in dusty atmospheres is advised.

METHOCEL products are organic polymers that will burn under the right conditions of heat and oxygen supply. Fires can be extinguished by conventional means.

Storage

In storage or use of any dusts or fine powders, good housekeeping is required to prevent dusts in air from reaching possibly explosive levels.

Caution

Under certain conditions, a fine dust of this material in air may cause a dust explosion when exposed to heat, sparks, or open flame. See "METHOCEL Cellulose Ethers Technical Handbook" when handling large quantities. The National Fire Protection Association's NFPA 654, "*Standard for the Prevention of Fire and Dust Explosions in the Chemical, Dye, Pharmaceutical and Plastic Industries*," should also be followed.

With METHOCEL cellulose ether products with particle sizes of 74μ or less (finer than 200 mesh), critical levels are reached at concentrations of 28 gm/m³ (0.03 oz/ft³). The minimum ignition energy to cause a dust explosion is in the range of 28 mJ. Static of a human body has about 25 mJ.

It is also highly desirable to control dusts in order to prevent accidents caused by slippery floors and equipment.

As a USP grade item, Premium METHOCEL cellulose ethers should not be stored next to peroxides or other oxidizing agents, poisons, pesticides, or ill-smelling articles.

Accidental Spills

To prevent employee falls and accidents, floor spills of dry powder should be thoroughly vacuumed or swept up. Any slight residual product on the walls or floor can then be flushed with water into a sewer. If the spill is a viscous solution it should be further diluted with water before disposal.

Disposal

Dow studies show that METHOCEL cellulose ether products do not biodegrade (that is, they show no 5-, 10-, or 20-day BODs) in aquatic environments. They should therefore present no ecological hazard to aquatic life.

Since METHOCEL cellulose ether products and their formulations present no significant ecological problems they can be disposed of by industrial incineration or in an approved landfill, providing all federal, state, and local regulations are observed. Dow recommends that the material be buried in an approved landfill; incineration should be done under carefully controlled conditions to avoid possibility of dust explosion.

Customer Notice

Dow encourages its customers to review their applications of Dow products from the standpoint of human health and environmental quality. To help ensure that Dow products are not used in ways for which they are not intended or tested, Dow personnel will assist customers in dealing with ecological and product safety considerations. Your Dow sales representative can arrange the proper contacts.

For more information, complete literature, and product samples, you can reach a Dow representative at the following numbers:

From the United States and Canada: .....call 1-800-447-4369
.....fax 1-989-832-1465

In Europe: .....toll-free +800 3 694 6367[1]
.....call +32 3 450 2240
.....fax +32 3 450 2815

From Latin America and Other Global Areas: .....call 1-989-832-1560
.....fax 1-989-832-1465

[1]Toll free from Austria (00), Belgium (00), Denmark (00), Finland (990), France (00), Germany (00), Hungary (00), Ireland (00), Italy (00), The Netherlands (00), Norway (00), Portugal (00), Spain (00), Sweden (00), Switzerland (00), and the United Kingdom (00).

Or you can contact us on the Internet at **www.methocel.com**

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EXHIBIT J

⟨905⟩ UNIFORMITY OF DOSAGE UNITS

Change to read:

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and the *Japanese Pharmacopoeia*. Portions of the general chapter text that are national *USP* text, and are not part of the harmonized text, are marked with symbols (✦✦) to specify this fact.

✦NOTE—In this chapter, *unit* and *dosage unit* are synonymous.✦

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit. The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for external, cutaneous administration.

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified elsewhere in this Pharmacopeia.

The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or ✦*Weight*✦*Variation* (see *Table 1*). The test for *Content Uniformity* of preparations presented in dosage units is based on the assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases.

The test for ✦*Weight*✦*Variation* is applicable for the following dosage forms:

(W1)	Solutions enclosed in unit-dose containers and into soft capsules;
(W2)	Solids (including powders, granules, and sterile solids) that are packaged in single-unit containers and contain no active or inactive added substances;
(W3)	Solids (including sterile solids) that are packaged in single-unit containers, with or without active or inactive added substances, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation; and
(W4)	Hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting the requirements for *Content Uniformity*.

The test for *Content Uniformity* is required for all dosage forms not meeting the above conditions for the ✦*Weight*✦ *Variation* test.■1 ■2S (USP34)

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			≥25 mg and ≥25%	**<25 mg or <25%**
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Solutions in unit-dose containers ✦and into soft capsules✦			WV	WV
Others			CU	CU

Change to read:

CONTENT UNIFORMITY

Select not fewer than 30 units, and proceed as follows for the dosage form designated.

Where different procedures are used for assay of the preparation and for the *Content Uniformity* test, it may be necessary to establish a correction factor to be applied to the results of the latter.

Solid Dosage Forms—Assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (see *Table 2*).

Liquid ■or Semi-Solid■2S (USP34) Dosage Forms—■Assay 10 units individually using an appropriate analytical method.■2S (USP34) Carry out the assay on the amount of well-mixed material that is removed from an individual container

■1 ✦European Pharmacopoeia and Japanese Pharmacopoeia text not accepted by the United States Pharmacopeia: Alternatively, products listed in item (4) above that do not meet the 25 mg/25% threshold limit may be tested for uniformity of dosage units by Mass Variation instead of the Content Uniformity test if the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%, based on process validation data and development data, and if there has been regulatory approval of such a change. The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in *Table 2*.✦■2S (USP34)

in conditions of normal use, and express the results as delivered dose. Calculate the acceptance value (see *Table 2*).

Calculation of Acceptance Value—Calculate the acceptance value by the formula:

$$\left|M - \bar{X}\right| + ks$$

in which the terms are as defined in *Table 2*.

Table 2

Variable	Definition	Conditions	Value
$\bar{X}$	Mean of individual contents (χ_1, χ_2, … , χ_n), expressed as a percentage of the label claim		
χ_1, χ_2, … , χ_n	Individual contents of the units tested, expressed as a percentage of the label claim		
n	Sample size (number of units in a sample)		
k	Acceptability constant	If n = 10, then k =	2.4
		If n = 30, then k =	2.0
s	Sample standard deviation		$\left[\frac{\sum_{i=1}^{n}(\chi_i - \bar{X})^2}{n-1}\right]^{\frac{1}{2}}$
RSD	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$100s/\bar{X}$
M (case 1) to be applied when T ≤101.5	Reference value	If 98.5% ≤$\bar{X}$ ≤101.5%, then	M = $\bar{X}$ (AV = ks)
		If $\bar{X}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\bar{X}$ + ks)
		If $\bar{X}$ >101.5%, then	M = 101.5% (AV = $\bar{X}$ – 101.5 + ks)
M (case 2) to be applied when T >101.5	Reference value	If 98.5 ≤$\bar{X}$ ≤T, then	M = $\bar{X}$ (AV = ks)
		If $\bar{X}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\bar{X}$ + ks)
		If $\bar{X}$ >T, then	M = T% (AV = $\bar{X}$ – T + ks)
Acceptance value (AV)			general formula: $\left\|M - \bar{X}\right\| + ks$ (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance value		L1 = 15.0 unless otherwise specified

Table 2 *(Continued)*

Variable	Definition	Conditions	Value
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	On the low side, no dosage unit result can be less than [1–(0.01)(L2)]M, while on the high side no dosage unit result can be greater than [1 + (0.01)(L2)]M. (This is based on an L2 value of 25.0.)	L2 = 25.0 unless otherwise specified
T	Target content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. ■Unless otherwise stated, T is 100.0 per cent, or T is the manufacturer's approved target content per dosage unit.■*2S (USP34)*		

✦WEIGHT✦ VARIATION

Carry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method. This value is result A, expressed as percent of label claim (see *Calculation of Acceptance Value*). Assume that the concentration (weight of drug substance per weight of dosage unit) is uniform. Select not fewer than 30 dosage units, and proceed as follows for the dosage form designated.

Uncoated or Film-Coated Tablets—Accurately weigh 10 tablets individually. Calculate the content, expressed as % of label claim, of each tablet from the ✦weight✦ of the individual tablet and the result of the *Assay*. Calculate the acceptance value.

Hard Capsules—Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net ✦weight✦ of its contents by subtracting the ✦weight✦ of the shell from the respective gross ✦weight✦. Calculate the drug substance content of each capsule from the ✦net weight✦ of the individual capsule ✦content✦ and the result of the *Assay*. Calculate the acceptance value.

Soft Capsules—Accurately weigh 10 intact capsules individually to obtain their gross ✦weights✦, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the drug substance content in each capsule from the ✦weight✦ of product removed from the individual capsules and the result of the assay. Calculate the acceptance value.

Solid Dosage Forms Other Than Tablets and Capsules—Proceed as directed for *Hard Capsules*, treating each unit as described therein. Calculate the acceptance value.

Liquid Dosage Forms—Accurately weigh the amount of liquid that is removed from each of 10 individual containers in conditions of normal use. If necessary, compute the equivalent volume after determining the density. Calculate the drug substance content in each container from the mass of product removed from the individual containers and the result of the assay. Calculate the acceptance value.

Calculation of Acceptance Value—Calculate the acceptance value as shown in *Content Uniformity*, except that the individual contents of the units are replaced with the individual estimated contents defined below.

$\chi_1, \chi_2, \dots, \chi_n$	=	individual estimated contents of the units tested, where $\chi_i = w_i \times A/\overline{W}$
$w_1, w_2, \dots, w_n$	=	individual ✦weights✦ of the units tested
A	=	content of drug substance (% of label claim) obtained using an appropriate analytical method
$\overline{W}$	=	mean of individual ✦weights✦ $(w_1, w_2, \dots, w_n)$

Change to read:

CRITERIA

Apply the following criteria, unless otherwise specified.

Solid, ■Semi-Solid,■*2S (USP34)* and Liquid Dosage Forms—The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L1%. If the acceptance value is > L1%, test the next 20 units, and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is ≤ L1%, and no individual content of ✦any✦ dosage unit is less than [1 – (0.01)(L2)]M nor more than [1 + (0.01)(L2)]M ✦as specified✦ in the *Calculation of Acceptance Value* under *Content Uniformity* or under ✦*Weight✦ Variation*. Unless otherwise specified, L1 is 15.0 and L2 is 25.0.

EXHIBIT K

U.S. PHARMACOPEIAL CONVENTION

USP–NF General Chapter <905> Uniformity of Dosage Units

Type of Posting Explanatory Note
Posting Date20–Apr–2007

This explanatory note is intended to clarify the steps taken by USP to address issues regarding the harmonization of <905> Uniformity of Dosage Units. It includes current chapter revision status, background information, testing requirements, statistical basis, information about the upcoming revision, and frequently asked questions.

Status of General Chapter <905>

As of January 1, 2007, the updated, harmonized revision of General Chapter <905> published as an Interim Revision Announcement in Pharmacopeial Forum 32(6) [November–December 2006] is official. This version also is published in the 1st Supplement to USP 30–NF 25.

Revision History and Rationale

The ICH Steering Committee considers international harmonization of about 10 specific compendial test chapters as critical to attaining full utility of the ICH Q6A guideline. ICH Q6A recommended the harmonization of certain tests for dosage forms, including General Chapter <905>.

- USP published a revised, harmonized General Chapter <905> on pages 2505–2510 of USP 28–NF 23 with an implementation date of April 1, 2006. This chapter contains the global harmonized text approved by the Pharmacopeial Discussion Group (PDG) as well as USP–specific national text. The PDG consists of USP, the Japanese Pharmacopeia, and the European Pharmacopeia.
- In Pharmacopeial Forum 31(6) [November–December 2005], USP postponed the implementation date of the revised, harmonized General Chapter <905> to January 1, 2007, to allow USP to consider comments received on Weight Variation as a test alternative in certain cases.
- In USP 29–NF 24, both the official and the revised, harmonized versions of <905> appeared. The revised, harmonized version (pages 2760–2765) was to become official on January 1, 2007, but was superseded by the subsequent revision in the Sixth Interim Revision Announcement to USP 29–NF 24 in Pharmacopeial Forum 32(6) [November–December 2006].

Official Harmonized Chapter <905>

The revision of General Chapter <905> that became official on January 1, 2007, was initially proposed in Pharmacopeial Forum 32(4) [July–August 2006] and made official through the Sixth Interim Revision Announcement to USP 29–NF 24 in Pharmacopeial Forum 32(6) [November–December 2006]. The official text includes changes based on the comments received.

Harmonized Chapter Testing Requirements

<905> includes Content Uniformity and Weight Variation procedures and acceptance criteria to evaluate uniformity of dosage units. These apply to both newly registered and existing products.

Content Uniformity is the default test and may be applied in all cases. The test for Weight Variation is applicable for dosage forms specified as W1, W2, W3, and W4.

- The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L1%.
- If the acceptance value is greater than L1%, test the next 20 units and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1% and all individual dosage units fall within the ranges calculated using L2 factor.

Statistical Basis of the New Content Uniformity Criteria

The primary concept underlying the criteria in the revised <905> Uniformity of Dosage Units is that of statistical tolerance intervals. The general idea of tolerance intervals is to use the available data to form an interval that covers a specified proportion of the distribution underlying the data. For content uniformity, this would be the distribution of content and the intent is to form an interval about the label claim within which a specified proportion of units would fall. Technically, an interval (a, b) is a 95% (the "confidence") tolerance interval for 90% of the distribution (the "coverage") if 95% of such intervals with repeated sampling would cover at least 90% of the distribution. The tolerance intervals can be parametric or nonparametric. Parametric intervals are based on an assumed distribution, usually the normal. When assuming the normal distribution, two–sided tolerance intervals are of the form, , where is the average, S the standard deviation, and k depends on the coverage,

confidence, and sample size. (The multiplier, k, becomes smaller as sample size increases, but never to 0. For 95% coverage, for example, it will decrease to 1.96.) This is the form of the criteria used in General Chapter <905>.

The basic tolerance interval has been modified in four ways in constructing the criteria of General Chapter <905>:

1. The tolerance interval is modified to correspond to the standard two-stage testing of content uniformity; i.e., where 10 units are tested and then, if needed, an additional 20 are tested. This requires a k1 after the first stage and then a different k2 after the second stage, if needed, where the sample is larger.
2. The acceptance interval is allowed to be asymmetric with respect to the label claim in those cases where the potency range specified in the monograph is not symmetric. The T of General Chapter <905> is the center of the potency range.
3. A 1.5% interval about the label claim is included so deviations of the mean content from the label claim count only to the extent they are greater than this percentage. This is reflected in the calculation of M.
4. The k's are chosen so that the new procedure has operating characteristics similar to those of the prior General Chapter <905> criteria. Having similar operating characteristics does NOT mean that data that would pass by the prior criteria will pass by the new criteria and similarly for data that would fail. What it means is that is for data drawn from a distribution that is acceptable for content uniformity, the probability of passing is similar with the old and new criteria.

Statistical References

Further information regarding the statistical basis of the chapter is available in the references noted below.

1. Ketori, N, Aoyagi N, Kojima S, A Proposal for Revision of the Content Uniformity Test and Weight Variation Test, PF 23(6), 5325–5333, 1997.
2. Content Uniformity—Evaluation of the USP Pharmacopeial Preview, Members of the Statistics Working Group PhRMA, PF 24(5), 7029–7044, 1998.
3. Content Uniformity—Alternative to the USP Pharmacopeial Preview, Members of the Statistics Working Group PhRMA, PF 25(2), 7939–7946, 1999.
4. Recommendation for a Globally Harmonized Uniformity of Dosage Units Test, Members of the Statistics Working Group PhRMA, PF 25(4), 8609–8624, 1999.
5. Recommendations for a Globally Harmonized Uniformity of Dosage Units Test, Members of the Statistics Working Group PhRMA, PF 25 (4), 8609–8624, 1999.

Calculation Examples

On the following pages are 3 examples involving different outcomes.

Please submit comments or further inquiries on this topic to William Brown, Senior Scientist at web@usp.org or +1-301-816-8380.

Example 1: Pass on First			
95	lower monograph limit		
110	upper monograph limit	**102.5**	T value
15.0	L1 (use 15.0 unless monograph specifies a different value)		
25.0	L2 (use 25.0 unless monograph specifies a different value)		
Step 1 --- content (or weight) of 10 units --- X1, ..., X10			
102.00000	Average of the 10 values expressed as % of the label claim (do not round) --- AVERAGE(X1, ..., X10)		

4.60000	Standard deviation of the 10 values expressed as % of the label claim (do not round) — STDEV(X1, ..., X10)		
102.00000	M value		
11.04000	AV		
Result:	Pass, stop here		
	(USP rounding applied)		
Step 2 — content (or weight) of 20 additional units — X11, –, X30			
	Average of the 30 values expressed as % of the label claim (do not round) — AVERAGE(X1, –, X30)		
	Standard deviation of the 30 values expressed as % of the label claim (do not round) — STDEV(X1, –, X30)		
	Minimum value of the 30, expressed as % of the label claim		
	Maximum value of the 30, expressed as % of the label claim		
	M value		
	AV		
	Minimum allowed value of 30, expressed as % of label claim		
	Maximum allowed value of 30, expressed as % of label claim		
Result:			
	(USP rounding applied)		

Example 2: Fail–Pass		

90	lower monograph limit		
110	upper monograph limit	100.0	T value
15.0	L1 (use 15.0 unless monograph specifies a different value)		
25.0	L2 (use 25.0 unless monograph specifies a different value)		
Step 1 ---- content (or weight) of 10 units ---- X1, ..., X10			
107.00000	Average of the 10 values expressed as % of the label claim (do not round) ---- AVERAGE(X1, ..., X10)		
4.60000	Standard deviation of the 10 values expressed as % of the label claim (do not round) ---- STDEV(X1, ..., X10)		
101.50000	M value		
16.54	AV		
Result:	Does not pass; proceed to step 2		
	(USP rounding applied)		
Step 2 ---content (or weight) of 20 additional units ---- X11, --, X30			
106.50000	Average of the 30 values expressed as % of the label claim (do not round) ---- AVERAGE(X1, --, X30)		
4.60000	Standard deviation of the 30 values expressed as % of the label claim (do not round) ---- STDEV(X1, --, X30)		
78.00000	Minimum value of the 30, expressed as % of the label claim		
118.20000	Maximum value of the 30, expressed as % of the label claim		
101.50000	M value		
14.20000	AV		

76.1	Minimum allowed value of 30, expressed as % of label claim		
126.9	Maximum allowed value of 30, expressed as % of label claim		
Result:	Passes		
	(USP rounding applied)		

Example 3: Fail–Fail			
90	lower monograph limit		
110	upper monograph limit	100	T value
15.0	L1 (use 15.0 unless monograph specifies a different value)		
25.0	L2 (use 25.0 unless monograph specifies a different value)		
Step 1 — content (or weight) of 10 units — X1, ..., X10			
107.00000	Average of the 10 values expressed as % of the label claim (do not round) — AVERAGE(X1, ..., X10)		
4.60000	Standard deviation of the 10 values expressed as % of the label claim (do not round) — STDEV(X1, ..., X10)		
101.50000	M value		
16.54000	AV		
Result:	Does not pass; proceed to step 2		
	(USP rounding applied)		
Step 2 — content (or weight) of 20 additional units — X11, --, X30			

106.50000	Average of the 30 values expressed as % of the label claim (do not round) — AVERAGE(X1, –, X30)		
5.20000	Standard deviation of the 30 values expressed as % of the label claim (do not round) ---- STDEV(X1, –, X30)		
94.70000	Minimum value of the 30, expressed as % of the label claim		
127.10000	Maximum value of the 30, expressed as % of the label claim		
101.50000	M value		
15.40000	AV		
75.1	Minimum allowed value of 30, expressed as % of label claim		
126.9	Maximum allowed value of 30, expressed as % of label claim		
Result:	Fails		
	(USP rounding applied)		

Frequently Asked Questions

Question: What is meant by the term "special procedure" as found under Content Uniformity in the official chapter?

Answer: Typically, the Content Uniformity determination is made on individual dosage units using the procedure found in the Assay. For certain products, a separate procedure is given in the monograph. Where that is the case, the monograph procedure would be considered a special procedure for content uniformity. Theophylline Extended–Release Capsules is an example of a monograph requiring a special procedure for content uniformity.

Question: The harmonized <905> Uniformity of Dosage Units became official on January 1, 2007. Does the harmonized chapter completely replace the current text?

Answer: Yes. As of January 1, 2007, only the revised, harmonized chapter text is official.

Question: I have heard from European colleagues that existing products may be exempt from the requirements of the harmonized chapter and that it will only apply to new formulations. Will the USP allow such grandfathering?

Answer: The harmonized chapter text applies to any monograph, new or existing, that includes a test for Uniformity of Dosage Units.

Question: What is the maximum allowable acceptance value for Content Uniformity testing at level 2, where a total of 30 dosage units have been tested? Our confusion is in the use of the L1 and L2 values (15.0 and 25.0, respectively).

Answer: Content Uniformity testing can be performed in two stages. The first stage has a total of 10 dosage units tested, and an additional 20 dosage units are tested to complete testing at the second stage. L1 is used as the limit for the acceptance value for both stages of test. L2 is used only in the second stage of testing where a total of 30 dosage units have been tested, and it is only used in the calculation of the allowed limits for individual dosage unit content.

Question: Weight Variation is allowed for hard capsules, uncoated tablets, and film–coated tablets containing 25 mg or more of the drug substance comprising 25% or more of the weight of the dosage unit. If a product, such as an uncoated tablet, contains two drug substances but only one of them meets the requirement for weight variation, how can the requirement be met?

Answer: Weight Variation is generally seen as requiring less lab work than the procedure for Content Uniformity. Thus, the allowance to substitute Weight Variation for Content Uniformity may be seen as offering a benefit to manufacturers. In the case of a two-component tablet, the Uniformity of Dosage Units test requirement will be met by the Weight Variation procedure for the component that is present at 25 mg or more and also comprising 25% of the total dosage unit mass. The other component will require the Content Uniformity procedure.

EXHIBIT L

United States Patent [19]

Arter et al.

[11] 4,365,423

[45] Dec. 28, 1982

[54] **METHOD AND APPARATUS FOR DRYING COATED SHEET MATERIAL**

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[73] Assignee: **Eastman Kodak Company**, Rochester, N.Y.

[21] Appl. No.: **247,976**

[22] Filed: **Mar. 27, 1981**

[51] **Int. Cl.**[3] **F26B 3/04**; F26B 13/02

[52] **U.S. Cl.** **34/23**; 34/34; 34/155; 34/231; 34/233; 118/58; 427/372.2

[58] **Field of Search** 34/155, 231, 233, 225, 34/23, 34; 427/372.2, 377; 118/58, 62, 63

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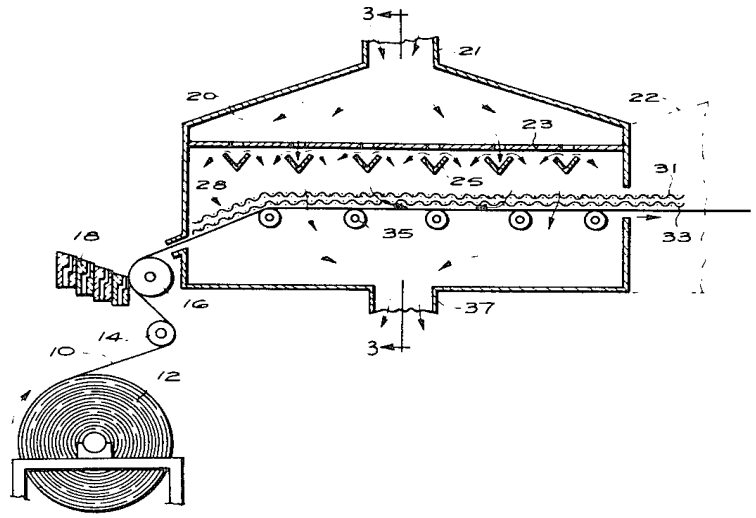
Primary Examiner—Larry I. Schwartz

Attorney, Agent, or Firm—Alfred P. Lorenzo

[57] **ABSTRACT**

In the drying of sheet materials which have been coated with a layer, or with two or more superposed layers, of liquid coating composition, improved drying conditions which result in less formation of mottle are provided by the use of a foraminous shield, such as a screen or perforated plate, located in close proximity to the coated surface. The sheet material, for example a web of paper or polymeric film or a succession of discrete sheets of paper or polymeric film is conveyed through a drying zone, along a predetermined path, while a gaseous drying medium, such as air maintained at an elevated temperature, which serves to promote evaporation of the liquid medium in the coating composition, is directed through the foraminous shield onto the coated surface. The foraminous shield functions to promote uniform heat transfer conditions and restricts the extent to which spent gaseous drying medium, which is discharged from the drying zone, comes into contact with the surface of the coating, thereby minimizing mottle formation. While the foraminous shield is useful in any drying operation in which mottle formation is a problem, it is especially advantageous in the drying of photographic materials, particularly those comprising one or more layers formed from coating compositions that contain volatile organic solvents.

28 Claims, 4 Drawing Figures



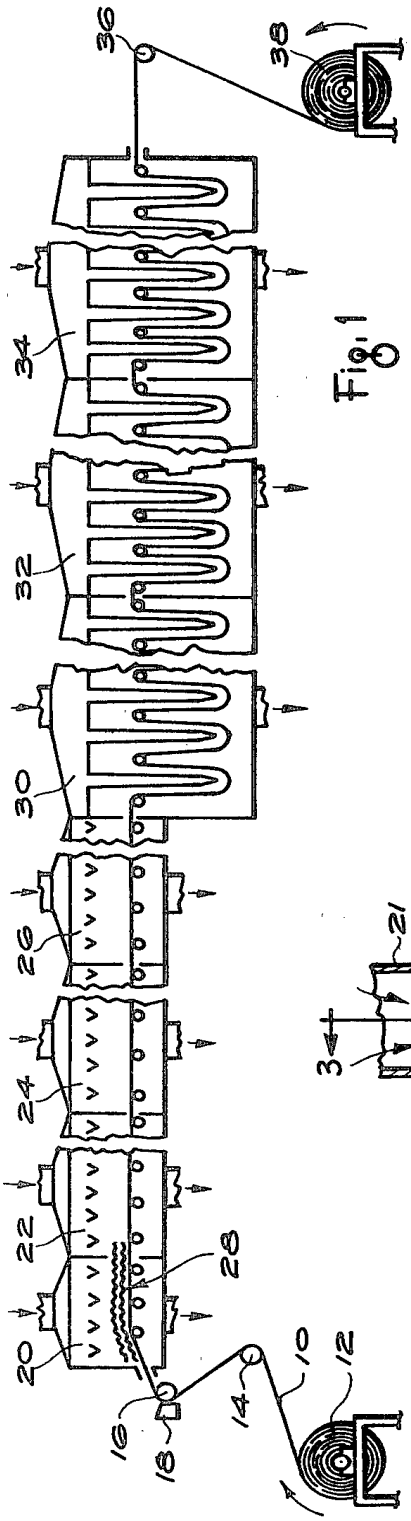


Fig. 1

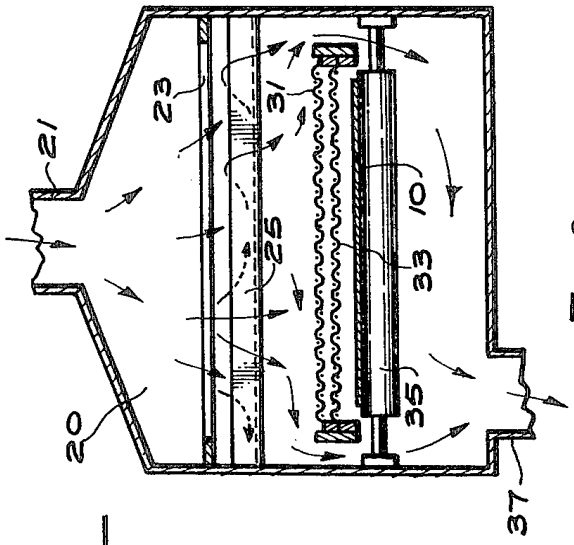


Fig. 3

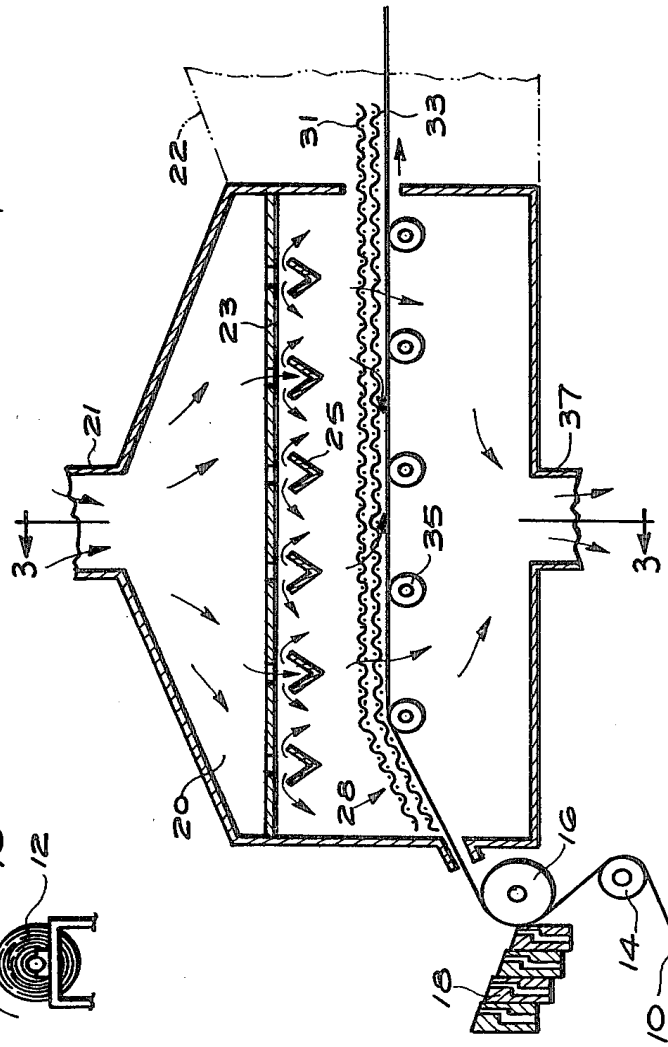
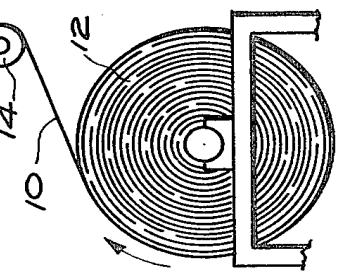


Fig. 2



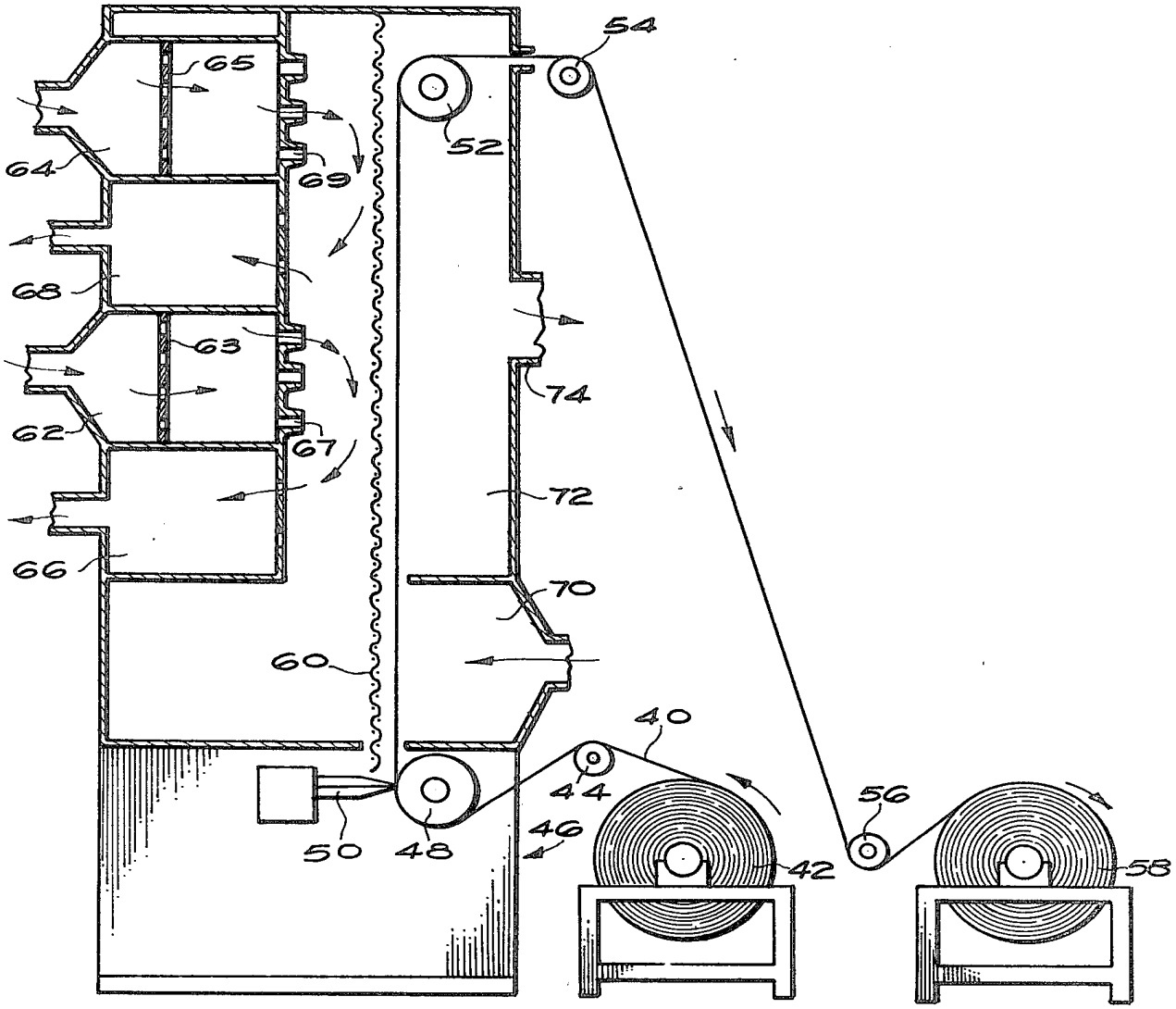


Fig. 4

METHOD AND APPARATUS FOR DRYING COATED SHEET MATERIAL

FIELD OF THE INVENTION

This invention relates in general to the drying of liquid coating compositions that have been coated in the form of a layer, or in the form of two or more superposed layers, on a sheet material; for example, coating compositions that have been coated on web supports in the manufacture of photographic films and papers or in the manufacture of lithographic printing plates. More specifically, this invention relates to an improved method and apparatus for drying coated sheet materials in which the tendency for mottle formation to occur during the drying process is significantly reduced.

BACKGROUND OF THE INVENTION

In the drying of sheet materials that have been coated with a layer of liquid coating composition, it is a common practice to utilize a drying apparatus in which a gaseous drying medium, usually air that has been heated to a suitable elevated temperature, is brought into direct contact with the coated layer in order to bring about evaporation of the liquid medium from the layer. In such driers, the gaseous drying medium is directed in a manner which distributes it uniformly over the surface of the coated layer under carefully controlled conditions that are designed to result in a minimum amount of disturbance of the layer. A common type of drier utilizes a plenum into which the gaseous drying medium is admitted and from which the gaseous drying medium is discharged through a multiplicity of holes, slots or nozzles onto the surface of the layer which is to be dried. In the operation of such driers, the sheet material, which is typically in the form of a web, is continuously conveyed through the drier along a predetermined path at a suitable rate commensurate with the drying load and the operating conditions utilized; while spent gaseous drying medium—that is, gaseous drying medium which has become laden with vapor evaporated from the layer of coating composition—is continuously discharged from the drier. As the web travels through the drier, the gaseous drying medium is directed from the plenum onto the coated surface and the spent medium flows away from the path of travel to be discharged.

A wide variety of different drier designs are known to the art. Thus, for example, the drier can be designed so that the flow of spent gaseous drying medium is essentially transverse to the path of travel of the web, i.e., the spent medium flows over the edges of the web so as to exit from the drier, or so that the flow of spent medium is essentially perpendicular to the path of travel of the web. Also, while it is usually most convenient for the sheet material to be in the form of a web, it can instead be in the form of a succession of discrete sheets conveyed through the drier by suitable means such as an endless belt.

The drying of sheet materials which have been coated with two or more superposed layers is carried out in the same manner as is described above in reference to a single layer coating. To facilitate description, reference is frequently made herein to the coating and drying of a "layer" of coating composition, but it is to be understood, unless the context otherwise requires, that the discussion applies also to the coating and drying of two or more superposed layers. Moreover, the method and apparatus of the present invention find utility not only in manufacturing operations involving wet-on-wet coating techniques, but also in manufacturing operations involving sequential coating and drying steps. As will be readily understood by those skilled in the coating art, wet-on-wet coating techniques include simultaneous multi-layer coating methods, in which two or morre distinct layers are applied to a web support at the same time and the resulting multi-layer composite is dried, and methods in which distinct layers are applied separately, but in close succession and the resulting multi-layer composite is dried, i.e., a first layer is coated on the web and then a second layer is coated over the first layer while it is still in a wet state, and so forth. In contrast, in operations involving sequential coating and drying steps, a first layer is coated and dried, a second layer is coated over the first layer and dried, and so forth.

One of the most common and difficult to avoid problems that is encountered in the drying of coating compositions is the formation of mottle. It is a problem that is encountered under a wide variety of circumstances. For example, mottle, or non-uniform density, is frequently encountered when compositions consisting of solutions of a polymeric resin in an organic solvent are coated in layer form onto sheet materials, such as webs of synthetic organic plastic material. Mottle is an especially severe problem when the coating solvent is a volatile organic solvent but can occur to a significant extent even with aqueous coating compositions or with coating compositions utilizing an organic solvent of low volatility. The mottle is an undesirable defect in some instances because it detracts from the appearance of the finished product and in some instances, such as in the photographic art, it is also undesirable because it adversely affects the functioning of the coated article. Various expedients have been employed heretofore in an effort to eliminate, or at least minimize, the formation of mottle in coated layers. For example, surfactants are often added to the coating compositions as described, for example, in U.S. Pat. No. 3,514,293. These are sometimes effective in reducing mottle, but in many cases the degree to which mottle forms is still excessive in spite of the inclusion of a surfactant in the coating composition. It is believed that there are a variety of factors which can contribute to the formation of mottle and the exact mechanism of its formation is not well understood. Regardless of the specific causes of mottle, its formation in coated layers, as well as the occurrence of other defects such as streaks and lines, is a long standing problem of serious concern in the manufacture of coated materials, and especially in the manufacture of photographic products.

Among the factors which contribute to mottle formation in the drying process are non-uniform drying conditions that commonly exist in driers of the type described hereinabove. Thus, for example, turbulent flow conditions within the gaseous drying medium can result in physical disturbance of the coated layer that manifests itself as mottle in the dried product. Also, non-uniformities with respect to temperature, with respect to heat transfer rates, and with respect to the concentration of vapor in the gaseous drying medium, lead to non-uniform rates of evaporation at different points within the coated layer. The cooling which results from evaporation causes the temperature at the surface of the coated layer to decrease, so that variation in the rate of evaporation leads to the establishment of temperature

differences within the layer. Such temperature differences are believed to function to induce convective flow in the layer which is a significant factor in contributing to the formation of mottle. Particular difficulty in this regard is caused by the flow of the spent gaseous drying medium in direct contact with the surface of the coated layer.

The present invention is directed toward the objective of providing an improved method and apparatus for drying coated sheet materials which reduces or eliminates many of the deficiencies in known drying methods and apparatus that contribute to the formation of mottle.

SUMMARY OF THE INVENTION

In the method of this invention, a coated sheet material is advanced along a predetermined path through a drying zone and a gaseous drying medium is uniformly directed onto the coated surface of the sheet material so as to bring about evaporation of the liquid medium in the coating, with resulting formation of spent gaseous drying medium which flows away from the path of travel for discharge from the drying zone. In order to promote uniform heat transfer conditions and reduce the degree to which flowing spent gaseous drying medium contacts the coated surface, and thereby decrease the extent of mottle formation, a foraminous shield, such as a screen or perforated plate, which is permeable to the gaseous drying medium, is positioned in opposed closely-spaced relationship with the coated surface of the sheet material. The foraminous shield serves to promote flow of the spent gaseous drying medium adjacent the surface of the shield which is remote from the coated surface and to form a quiescent region between the shield and the coated surface which is rich in the vapor of the liquid medium and in which flow of the spent gaseous drying medium is suppressed and uniform heat transfer conditions are promoted.

The foraminous shield is believed to function in several ways to reduce mottle formation. For example, it functions to diffuse currents within the gaseous drying medium and thereby protect the coated layer from turbulence which can cause physical disruption and deformation of the coated layer by impacting thereon. It also suppresses dispersion of the vapor generated by evaporation of the liquid medium to thereby form a "barrier layer" of such vapor between it and the coated surface which helps to promote the maintenance of uniform conditions of temperature and heat transfer. Of particular importance, it suppresses flow of spent gaseous drying medium directly adjacent the coated surface and tends to confine most of such flow to a region on the side of the shield which is remote from the coated surface, to thereby protect the coated layer from the creation of non-uniform conditions which lead to the formation of mottle.

Apparatus for carrying out the method of this invention includes means for advancing the coated sheet material along a predetermined path through a drying zone, such as, for example, drive means and rollers which form a typical web conveyance system, means for uniformly directing a gaseous drying medium onto the coated surface of the sheet material, and a foraminous shield which is positioned in close proximity to the path along which the sheet material travels for performing the functions described hereinabove. In order to provide the uniform flow of gaseous drying medium, for example, warm dry air, the drying apparatus typically includes a plenum which is connected to the gaseous drying medium supply means and functions to provide a controlled uniform flow of the gaseous drying medium through a multiplicity of holes, slots or nozzles. The foraminous shield, for example a screen or perforated plate which is permeable to the gaseous drying medium, is interposed between the plenum and the path in opposing spaced relationship with the wall of the plenum having the multiplicity of holes, slots or nozzles through which the gaseous drying medium flows. The foraminous shield is located in close proximity to the path, so as to form a quiescent region between it and the coated surface in which flow of the spent gaseous drying medium is suppressed and uniform heat transfer conditions are promoted, and is spaced from the opposing wall of the plenum to form a region therebetween in which flow of the spent gaseous drying medium can occur without disturbing the coated surface.

While the foraminous shield that is employed in accordance with this invention can extend over the entire length of the drier, it is not ordinarily necessary for it to do so. It performs its essential function in the initial stage of the drying process and, accordingly, is also effective when used only in the initial portion of the drier. Good results are typically achieved with the foraminous shield extending from the start of the drying zone over a distance equal to about 5 to about 25 percent of the total length of the drying zone. On the other hand, the foraminous shield should preferably be of a width which is substantially commensurate with the width of the coated surface of the sheet material, and most preferably somewhat greater than such width, in order to provide protection for the entire coated surface. Under some conditions, optimum results are achieved when a foraminous shield is also utilized in the coating zone adjacent the inlet to the drier to protect the flow of coating composition from disturbance by ambient air currents during the coating operation. Such use of a foraminous shield is described in copending commonly assigned United States patent application Ser. No. 139,506, "Coating Apparatus Provided With A Protective Shield," by Thomas R. O'Connor, filed Apr. 11, 1980 and issued Sept. 1, 1981, as U.S. Pat. No. 4,287,240, the disclosure of which is incorporated herein by reference. To achieve the maximum benefit, the foraminous shield should substantially enclose the flow of coating composition during the coating operation, should extend over the coated web in the region between the coating hopper and the drier, should extend over the coated web as it passes through the entrance slot into the drier, and should be positioned within the drier in close proximity to the path of the web over a suitable initial portion of the total length of the path.

Since the foraminous shield of this invention tends to suppress the evaporation rate by confining the evaporated vapor, and thereby slows down the driving process, it should preferably not extend into the drier further than is needed to achieve the objective of reducing mottle formation. In this way, the objective of achieving relatively rapid drying in a drier of reasonable length is achieved simultaneously with the objective of solving the mottle problem.

The "drying mottle" with which this invention is concerned is closely related to, but different from, "coating mottle." The formation of coating mottle occurs, as the name indicates, in the coating zone, whereas the formation of drying mottle occurs in the drying

zone. A coating process which is highly effective in alleviating coating mottle is described in Democh, U.S. Pat. No. 4,051,278 issued Sept. 27, 1977. In this process, at least two of (1) the temperature of the atmosphere in the coating zone, (2) the temperature of the coating composition at the point where it is coated on the support, and (3) the temperature of the support at the point where the coating composition is applied thereto, are maintained at a temperature substantially equivalent to the equilibrium surface temperature of the coated layer within the coating zone. The process of the U.S. Pat. No. 4,051,278 is advantageously utilized in combination with the present invention so as to minimize both coating mottle and drying mottle.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic representation of the apparatus of this invention illustrating a preferred embodiment in which the foraminous shield extends over only a small portion of the total length of the drier.

FIG. 2 is a representation to a larger scale of the first section of the drier of FIG. 1 illustrating in more detail the positioning and function of the foraminous shield.

FIG. 3 is a section taken along line 3—3 of FIG. 2.

FIG. 4 illustrates a further alternative embodiment of the invention in which the web travels within the drier along a vertical path rather than the horizontal path illustrated in FIG. 1.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention is described herein with particular reference to the coating and drying of photographic materials. This field of manufacture involves highly exacting specifications so that the occurrence of mottle, streaks, lines, or other defects in the coated layer is of critical concern. However, the invention is in no way limited to use in the manufacture of photographic materials and can be advantageously employed in any process, used in the manufacture of any product, in which a gaseous drying medium is utilized in the drying of a coated layer formed from a mottle-prone coating composition and in which the formation of streaks, lines, or mottle in the coating is of concern. Examples of products to whose manufacture the invention is particularly applicable include photothermographic films, dielectric recording films and lithographic printing plates.

A significant reduction in mottle can be achieved by the method of this invention in the coating and drying of any film-forming material, or mixture of film-forming materials, which can be incorporated in a coating composition which comprises an evaporable liquid medium. It is particularly advantageous in the coating and drying of solutions of polymeric resins in organic solvents because such solvents are often relatively volatile in nature and, in consequence, coatings formed therefrom are prone to mottle formation. Among the numerous examples of film-forming materials with which the invention can be advantageously employed, the following polymers are representative: acetals, acrylics, acetates, cellulosics, fluorocarbons, amides, ethers, carbonates, esters, styrenes, urethanes, sulfones, gelatins, and the like. The polymers can be homopolymers or they can be copolymers formed from two or more monomers. Liquid vehicles for use in the coating composition can be chosen from a wide range of suitable materials. For example, the coating composition can be an aqueous composition or an organic solution comprising an organic solvent. Typical organic solvents include ketones such as acetone or methyl ethyl ketone, hydrocarbons such as benzene or toluene, alcohols such as methanol or isopropanol, halogenated alkanes such as ethylene dichloride or propylene dichloride, esters such as ethyl acetate or butyl acetate, and the like. Combinations of two or more organic solvents can, of course, be utilized as the liquid vehicle or the liquid vehicle can be a mixed agueous-organic system.

The weight percentage of solids in the coating composition can be as high as ninety percent, or more, but will more tyically be in the range of about one to about twenty percent by weight. Optimum viscosity for the coating composition will depend on the type of coating apparatus employed and can be as high as 60,000 centipoise, or more, but will more typically be in the range from about 1 to about 1,000 centipoise. In addition to the film-forming material and the liquid vehicle, the coating composition can contain various optional ingredients such as pigments, surfactants, viscosity modifiers, leveling agents, antifoaming agents, and so forth. The incorporation of surfactants in the coating composition is advantageous in that they serve to reduce the surface tension of the composition and to reduce the rate of change of surface tension as a function of temperature. Accordingly, there is less force causing fluid motion as a result of temperature difference within the coated layer and, in consequence, a reduced tendency to form mottle.

Coating compositions which present particular difficulty because of their pronounced tendency to form mottle are those in which the liquid vehicle is relatively volatile, and it is with these coating compositions that the method and apparatus described herein are most useful. In particular, such compositions are those in which the liquid vehicle is an organic solvent having a boiling point at atmospheric pressure in the range of from about 40° C. to about 85° C.

The object which is coated and dried by the method of this invention can be composed of any material whatever, as long as it is a material which can be coated with a liquid coating composition. It will most typically take the form of a sheet material which is coated as a continuous web in a continuous coating process, but could also be in discrete form such as separate sheets carried through the coating and drying zones by a conveyor belt or similar device. Typical examples of useful sheet materials are polymeric films such as films of polyesters, polyolefins or cellulose esters; metal foils such as aluminum or lead foils, paper, polymer-coated paper such as polyethylene-coated paper; and laminates comprised of various layers of plastics or of plastic and metal foil.

Any suitable type of coating apparatus can be used in the method of this invention. Thus, for example, the coating composition can be coated by dip coating, air knife coating, roll coating, gravure coating, extrusion coating (for example as described in U.S. Pat No. 2,681,294), multilayer bead coating (for example as described in U.S. Pat. No. 2,761,791), curtain coating (for example as described in U.S. Pat. Nos. 3,508,497 and 3,632,374), and so forth. The coating method used can be one in which only a single layer is coated or two or more layers can be coated simultaneously. The coating speed is limited only by the limitations of the particular coating equipment employed and can be as high as 400 meters per minute, or more. Typically, coating speeds of about 10 to about 300 meters per minute would generally be employed in practicing the method described

herein. Wet coverage of the coating composition is also a matter of choice and will depend upon many factors such as the type of coating apparatus employed, the characteristics of the coating composition, and the desired thickness of the coated layer after drying. Typically, wet coverages employed in the method of this invention will be in the range of from about 0.1 to about 1,000 cubic centimeters per square meter of support surface and more usually in the range of from about 5 to about 100 cubic centimeters per square meter. In the interests of decreasing the formation of mottle, it can be advantageous to utilize a high percentage of solids in the coating composition to thereby permit coating at a low wet coverage and with a high viscosity. This tends to immobilize the coating composition and thereby to reduce convective flow and minimize the formation of mottle.

The problem of mottle formation usually becomes increasingly severe as the speed of coating is increased. The reason is that as speed of coating is increased a greater quantity of liquid medium must be removed in the drier per unit of time, and this requires a greater volume of gaseous drying medium. In consequence, the gaseous drying medium must be supplied to the drying zone at a greater volumetric flow rate with resulting increased tendency to disturb the coating and cause mottle. Thus, in some instances, coating speed must be limited to that at which the level of mottle is tolerable. However, with use of the foraminous shield of this invention, it is feasible to substantially reduce the level of mottle while retaining the same coating speed or to substantially increase coating speed without any resulting increase in mottle.

As previously explained, the method and apparatus of this invention are especially useful in drying coating compositions that contain volatile organic solvents. In order to reduce the hazards associated with the drying of such compositions, it is advantageous to introduce drying air into the drier at a very high volumetric flow rate so that the average concentration of solvent in the drier will be maintained at a low level. The need for very high volumetric flow rates results in a requirement for relatively high pressures in the plenum and, as a consequence, the drying air can travel across the surface of the coated layer at relatively high velocities which can seriously disturb the coated layer. Under these circumstances, there is an especially acute need for protecting the coated layer against localized currents and the foraminous shield of this invention is very effective in performing this function. Moreover, since the foraminous shield can be located at a substantial distance from the plenum, a region of relatively large volume can exist therebetween and, accordingly, there is an adequate volume of drying air in this region at all times to keep the concentration of solvent in the air at a level far below that at which hazardous conditions could develop. In addition to facilitating safe operation of driers used to dry coatings containing volatile organic solvents, the method and apparatus of this invention are especially useful in such coating operations because the coatings are particularly prone to streaking and mottle information, and the foraminous shield greatly reduces the tendency for these defects to occur.

In the drying of coating compositions containing volatile organic solvents, the drier is typically operated under negative pressure. In this way, there is an intake of air from the surrounding atmosphere through openings in the drier, such as the web inlet and exit slots, rather than an outflow of solvent laden air from the drier to the surroundings as would occur if the drier were operated under positive pressure. The intake of air at the inlet slot tends to create turbulent conditions adjacent thereto which can be a significant factor in the formation of mottle, but the foraminous shield of this invention is highly effective in protecting the coating from such turbulence.

It is with image-forming compositions that the formation of mottle is usually the greatest problem. Thus, it is in the coating of such compositions that the present invention is usually most valuable.

In the method of this invention, gaseous drying medium passes from the plenum through the foraminous shield to contact the coated layer. At the same time, spent gaseous drying medium, containing vapor generated by evaporation of the liquid medium in the coated layer, passes through the foraminous shield in the opposite direction and flows away from the path of the web to exit from the drier. By keeping the flow of the spent gaseous drying medium substantially out of contact with the surface of the coated layer, such common defects as streaking and mottle formation are greatly reduced. It should be noted that, under typical conditions, only a small fraction of the gaseous drying medium coming from the plenum passes through the foraminous shield, since most of it flows within the region between the foraminous shield and the plenum. Thus, the concentration of solvent in this region is quite low as compared to the much higher concentration in the quiescent region between the coated surface and the foraminous shield.

An important feature of the method and apparatus of this invention is that the foraminous shield structure which is utilized functions to suppress flow of spent gaseous drying medium in contact with the surface of the coated layer while leaving the spent gaseous drying medium free to flow from the drying zone, i.e., the foraminous shield structure does not block exit of the spent gaseous drying medium from the drying zone. Thus, for example, in a typical embodiment of the apparatus, the spent gaseous drying medium is able to flow along the surface of the foraminous shield that is remote from the coated layer and pass over the edges of such surface and thereafter over the edges of the moving web to exit from the drying zone. In this respect, the invention differs in a critical manner from a drier in which the plenum is positioned very close to the surface of the moving web. In such a drier, there is only the narrow zone between the web surface and the plenum where spent drying medium can exhaust, and this narrow zone will have a very high concentration of vapor which could pose considerable hazard when the liquid medium is an organic solvent. In marked contrast, in using the method and apparatus of this invention, there can be a relatively spacious zone between the foraminous shield and the plenum in which spent drying medium can exhaust, and in this zone the concentration of vapor is sufficiently low to present little or no hazard, even with solvents which have a low explosive limit.

Use of the foraminous shield of this invention can result in some degree of suppression of the drying rate. However, this is easily accommodated by extending the length of the drier or by utilizing drying air which impinges on the side of the web opposite the coated layer as well as drying air which impinges on the surface of the coated layer. The warm air which impinges on the side of the web opposite to the coated layer is

effective in introducing heat into the web to thereby promote evaporation of the liquid medium in the coated layer.

While the method of this invention is particularly useful in the coating of compositions containing organic solvents, it can also be advantageously employed in the coating of photographic materials comprising layers formed from aqueous solutions of hydrophilic colloids. Representative examples of such coating compositions are silver halide emulsions in which the hydrophilic colloid is gelatin. Coating compositions employed in the method of this invention can be of various types, such as solutions, dispersions, and suspensions. The invention is useful in the coating and drying of many types of photographic layers in addition to image-forming layes, such as, for example, subbing layers, interlayers, protective overcoat layers, antistatic layers and anti-halation layers.

The path of the sheet material within the drier is a matter of design choice and is dependent upon the particular design of drier that is best suited to accomplish the particular job involved. Generally, the sheet material is conveyed along a horizontal, or substantially horizontal, path. However, under particular conditions, it may be desirable to utilize a design in which the sheet material is conveyed along a path which is inclined from the horizontal or along a path which is vertical. If desired, the drier can utilize a flat-bed design in an initial portion thereof, in which the foraminous shield is utilized, and a festoon design in a subsequent portion.

As previously explained, the foraminous shield can extend throughout the length of the drier, but will most usually be utilized only in the initial portion, such as in a region extending over about 5 to about 25 percent of the total length of the drying zone. The foraminous shield is most effective in the initial stage of the drying process, but is also of some benefit at subsequent stages. Thus, if the design of a particular drier renders it impractical to incorporate the foraminous shield into the drier immediately adjacent to the point of entry of the web, it can be mounted within a region further along the path of travel where it can be conveniently accommodated.

The plenum can be of any design that is useful in providing the uniform distribution of gaseous drying medium that is required in driers of the type described herein. The fresh gaseous drying medium can be supplied to the plenum at a single inlet, but will more usually be supplied at several inlets depending on the length of the drier.

Air that has been heated to a suitable elevated temperature is usually used as the gaseous drying medium. However, inert gases, such as nitrogen gas, can be used in situations where the nature of the coating being dried requires their use.

The particular conditions utilized in the process of this invention will vary greatly, depending on the particular product being manufactured and the selection of optimum conditions for a given product is, in light of the disclosure herein, within the ordinary skill of the art. Factors affecting the process include the design of the foraminous shield, the thickness and composition of the coated layer or plurality of superposed layers, the speed with which the sheet material is conveyed through the drier, the design of the drier, and the volumetric flow rate, temperature, and moisture content at which the air, or other gaseous drying medium, is supplied to the drier. In optimization of the process, a key objective is to provide a uniform rate of heat transfer at all points on the coated surface. Numerous factors affect such rate of heat transfer, including the temperature and humidity of the gaseous medium, the plenum pressure, and the spacing between the plenum and the coated surface.

The shield utilized in the practice of this invention can be constructed of any suitable foraminous material. Examples of useful foraminous materials include metal screening, perforated metal plates, plastic sheeting having a multiplicity of fine holes formed therein, perforated paper, netting such as nylon or other fabric netting stretched taut within a frame, and the like.

The foraminous shield structure of this invention can be made up of a single foraminous element, e.g., a screen or perforated plate, or of a plurality, i.e., two, three or more, of spaced foraminous elements positioned in relation to one another so as to leave a relatively narrow gap therebetween. In other words, the shield structure can be of single-walled construction or of multiple-walled construction, e.g., double-walled or triple-walled.

Factors affecting the performance of the foraminous shield structure of this invention include:

(1) the size of the perforations,
(2) the spacing of the perforations,
(3) the shape of the perforations, e.g., whether they are round, square, oval, etc,
(4) whether the structure is a single-wall or multi-wall structure,
(5) the distance between the walls where it is a multi-wall structure,
(6) whether or not the perforations are aligned when it is a multi-wall structure,
(7) the thickness of the foraminous material,
(8) the edge design of the shield structure,
(9) the distance between the foraminous shield and the adjacent wall of the plenum, and
(10) the distance between the foraminous shield and the coated surface of the sheet material.

All of the above factors are matters of design choice and can be varied widely to achieve optimum results with a particular drying system.

Both the size and spacing of the perforations are very important features in determining the efficiency with which the foraminous shield structures of this invention operate. Very good results are typically obtained with perforations having a size in the range of from about 0.1 to about 5 millimeters, and more preferably in the range of from about 0.25 to about 1.25 millimeters, and with a spacing such that the percentage of open area is in the range of from about 20 to about 65 percent, and more preferably in the range of from about 30 to about 50 percent. (As used herein, size ranges specified for perforation size refer to the diameter of the perforation where it is circular and to the maximum dimension where it is of a shape other than circular. An alternative way of referring to percentage open area is by reference to the "solidity" of the shield, by which is meant the fraction of the total flow area blocked by the shield. For example, a solidity of 0.40 means 40% blocked and 60% open). In contrast with the size and spacing of the perforations, the shape of the perforations is not a particularly important parameter and, generally speaking, the perforations can be of any desired shape.

It is greatly preferred that the foraminous shield structure be a multi-walled structure, i.e., a structure with two, three or more walls. In general, the greater

the number of walls the more efficient the structure. However, under typical conditions, a double-walled shield structure is so efficient that the added cost and complexity of constructing a triple-walled structure would not be justified even though the triple-walled structure would be somewhat more effective. There is usually little to be gained in terms of improved performance by having more than three walls. When two or more walls are used, the distance by which they are spaced from one another is an important design factor. Preferably, the walls are spaced apart a distance in the range of from about 0.1 to about 10 centimeters, and most preferably a distance in the range of from about 0.3 to about 1 centimeters. In multi-wall structures, the degree to which the perforations of one wall align with the perforations of an adjacent wall is also a design factor affecting the overall performance of the shield structure, and it is usually desirable that the perforations be positioned so that they are out of alignment with those of the adjacent wall. Construction of a type in which the spaced walls are parallel to one another is generally satisfactory, but they can also be positioned in non-parallel relationship if desired.

In using multi-wall shield structures, it is sometimes advantageous for the structure to be designed so that the size of the perforations diminishes progressively, with the outermost wall, which is closest to the adjacent plenum wall, having the largest perforations and the innermost wall, which is closest to the surface of the coated layer, having the smallest perforations. For example, a multi-wall shield structure could be comprised of an outermost wall having perforations with a size of 1.5 millimeters, an intermediate wall having perforations with a size of 1 millimeter, and an innermost wall, which would be located closest to the surface of the coated layer, having perforations with a size of 0.5 millimeters.

The thickness of the foraminous material from which the shield is formed is also a significant factor in determining operating effectiveness. Generally speaking, it is desirable that the foraminous material be as thin as is practical since, all other factors being equal, a thin material is more effective than a thick one in reducing turbulence. Good results are typically obtained using foraminous materials with a thickness of less than about 2 millimeters. Thus, whether the shield is constructed from a woven wire screen, in which the thickness is dependent on the diameter of the wire from which the screen is formed, or from a perforated plate material, it is usually advantageous for its thickness to be below the specified value of about 2 millimeters.

The edge design of the foraminous shield can also affect its performance. Thus, for example, it is preferred that the shield extend somewhat beyond the edges of the coated layer to avoid disturbance of the coated layer resulting from "edge-effect" turbulence. As an alternative to extending the shield beyond the edges of the coated layer, it can be angled sharply downward along its edges.

Perhaps the most important of all the design factors relating to the foraminous shield are the distances between the foraminous shield and the adjacent plenum wall and between the foraminous shield and the surface of the coated layer. The optimum distances are determined by many factors, including the pressure at which the drying medium is delivered, the size of the perforations, the number of walls, the percentage of open area, and so forth. Under typical conditions, good results are obtained with a spacing between the foraminous shield and the adjacent plenum wall in the range of from about 5 to about 100 centimeters, and a spacing between the foraminous shield and the surface of the coated layer in the range of from about 1 to about 15 centimeters.

In the apparatus of this invention, the foraminous shield is positioned in close proximity to the surface of the coated layer, but it is often advantageous for it to be relatively widely spaced from the plenum. For example, in those instances in which the vapors generated in the drying process are explosive, it is desirable that the distance between the foraminous shield and the adjacent plenum wall be large relative to the distance between the foraminous shield and the surface of the coated layer, so as to maintain an average vapor concentration which is at a safe low level. Under such circumstances, it is preferred that these distances be in a ratio in the range of from about 2 to 1 to about 20 to 1 and more preferably, in the range of from about 4 to 1 to about 20 to 1.

A particular advantage of the use of a foraminous shield in accordance with this invention is that the air or other gaseous drying medium can be supplied from the plenum at a greater pressure, without detrimentally affecting the coating, than would be feasible without the use of the foraminous shield. The delivery of a greater volumetric flow of air that results from such increased pressure means that the percentage of vapor in the spent air is lower. This is highly advantageous in dealing with potentially hazardous vapors, such as those generated by organic solvents, since it provides a greater margin of safety in keeping well below the explosive limits.

While reference is frequently made herein to a "drying zone," it is to be understood that such zone can, and often will, be comprised of a series of sub-zones, each of which provides different drying conditions. For example, the drying zone may consist of a series of sub-zones utilizing progressively higher temperatures. Such practices are well established, and their purposes clearly understood in the coating and drying arts.

The method and apparatus of this invention are useful in a wide variety of processes. For example, they are useful in the drying of either single-layer or multiple-layer coatings; in the drying of non-settable coatings; in the drying of settable coatings by various processes including those in which a chill-setting zone is used in association with a drying zone; and in either or both of the drying steps of a sequential coating process in which a single or multiple-layer coating is applied over a previously applied and dried single or multiple-layer coating.

Referring now to the drawings, FIG. **1** schematically illustrates a drier equipped with a foraminous shield in accordance with this invention. As shown in FIG. **1**, the sheet material which is coated is a continuous web **10** which is unwound from supply roll **12** and passes around guide roller **14** and then over coating roll **16** where it is coated with a plurality of layers of coating composition by coating hopper **18**. In the coating of compositions containing organic solvents, the coating hopper would typically be enclosed within a chamber in order to keep the solvent from passing into the surrounding environment and to provide effective temperature control during the coating process, but in coating aqueous compositions, such a chamber is generally unnecessary. Immediately after being coated, web **10** passes through a series of drying chambers **20**, **22**, **24**

and 26 in each of which warm dry air is uniformly impinged on the coated layers to effect drying thereof. The chambers 20, 22, 24 and 26 together define a first drying zone, and since this zone can comprise additional similar chambers to provide a sufficiently long path of travel for web 10, the series of chambers is illustrated as being broken at several places. A foraminous shield 28, composed of stainless steel screening mounted in close proximity to the path of web 10 and just above the coated surface thereof, extends throughout chamber 20 and partially into chamber 22. Web 10 moves rapidly through drying chamber 20 with the coated surface thereof spaced from, but in close proximity to, the opposing surface of stationary foraminous shield 28 to thereby create a quiescent zone, i.e., a zone in which there are no turbulent flow conditions, which is rich in the vapor resulting from evaporation of the liquid medium in the coating. After passing through the first drying zone defined by chambers 20, 22, 24 and 26, web 10 passes through a second drying zone defined by chambers 30, 32 and 34. Since the second drying zone can comprise additional similar chambers to extend the path of travel of web 10, this series of chambers is also illustrated as being broken at several places. The first drying zone functions to carry out the major portion of the drying of the coated layers, while the second drying zone serves to remove small amounts of residual liquid medium remaining in the coated layers and to remove liquid medium that has penetrated into web 10. As illustrated, the drying chambers in the first drying zone are of a flat-bed design while those in the second drying zone are of a festoon design in order to provide an extended residence time. After leaving the second drying zone, web 10 passes around guide roll 36 and is wound onto take-up roll 38.

FIG. 2 is an enlarged representation of drying chamber 20 which better illustrates the flow path of the drying air in relation to foraminous shield 28. As shown in FIG. 2, warm dry air is admitted to chamber 20 through inlet duct 21 and passes through distributing plate 23 beneath which are mounted a plurality of V-shaped baffles 25. The combined functioning of distributing plate 23 and baffles 25 serves to provide a uniform distribution of the air and to minimize the formation of air currents. Foraminous shield 28, which is comprised of upper and lower screen elements 31 and 33, is co-extensive in width with web 10 and mounted in a position in which it is parallel to the closely adjacent coated surface of web 10. The mounting of shield 28 is such as to permit precise up and down movement so that it can be adjusted to set an optimum spacing in relation to web 10. As web 10 travels through chamber 20 along a horizontal path defined by a plurality of guide rollers 35, a quiescent zone which is rich in solvent vapor is formed between the lower surface of screen element 33 and the surface of the coating on web 10. Spent gaseous drying medium flows transversely of the path of web 10 in the region between screen element 31 and distributing plate 23 and passes over the edges of web 10 to exit from chamber 20 via exit duct 37. Within the quiescent solvent-rich zone between screen element 33 and the coated surface of web 10, transverse flow of spent drying air is suppressed and the establishment of uniform heat transfer conditions is promoted.

As most clearly seen in FIG. 3, fresh drying air passes through distributing plate 23 and over the edges of baffles 25 to provide a steady, uniform, low velocity flow which promotes uniform drying. Spent drying air flows transversely of the path of web 10 and over the edges of web 10 to exit from duct 37.

FIG. 4 illustrates a drier of different design than that shown in FIGS. 1 to 3. As shown in FIG. 4, web 40 is unwound from supply roll 42 and passes around guide roller 44 into coater-drier 46 and then over coating roll 48 where it is coated with a layer of organic-solvent-containing coating composition by extrusion hopper 50. After being coated, web 40 travels vertically upward, over guide roller 52, through the wall of coater-drier 46, over guide rollers 54 and 56 and onto take-up roll 58. As web 10 passes between coating roll 48 and guide roller 52, it travels with its coated surface in close proximity to foraminous shield 60 which is composed of a single layer of stainless steel screening. Drying air is supplied via chambers 62 and 64, each of which is connected to a suitable blower (not shown), and exhausted via chambers 66 and 68 each of which is connected to a suitable vacuum source. Drying air admitted to chambers 62 and 64, passes through distributing plates 63 and 65, respectively, and then through a plurality of nozzles 67 and 69, respectively, so as to provide a uniform gentle flow of air. Warm drying air is also introduced into chamber 70 by a blower (not shown) where it impinges onto the uncoated surface of web 10 and thereby provides heat to web 10 which assists in bringing about evaporation of the solvent in the coated layer. As well as exhausting through chambers 66 and 68, spent drying air is also exhausted through chamber 72 via discharge duct 74 which is connected to a suitable vacuum source. As web 40 passes through the drying zone, a quiescent solvent-rich zone is formed between shield 60 and the coated surface of web 40 in which flow of spent drying air is suppressed and the establishment of uniform heat transfer conditions is promoted.

A drier of the type illustrated in FIGS. 1 to 3 is particularly useful in drying a coated web which requires a prolonged residence time, as is often the case where the web material is of such a nature that the coating composition is able to penetrate into it, for example a paper web. A drier of the type illustrated in FIG. 4 is particularly useful in drying a coating composition which is relatively viscous and is applied as a very thin layer, so that it has no tendency to run during the vertical travel through the drier, and which does not penetrate into the web so that drying can be carried out with a brief residence time, for example the coating of an aluminum support with an organic polymeric composition in the manufacture of lithographic printing plates. Many other types of driers can, of course, be utilized with equal effectiveness in putting the principles of this invention into practice.

Use of the present invention in combination with the invention disclosed and claimed in the aforementioned copending U.S. patent application Ser. No. 139,506, the disclosure of which is incorporated herein by reference, is often advantageous. In this regard, the foraminous shield can be constructed as a single element which substantially encloses the coating apparatus, to protect the coating operation from disturbance by ambient air currents, and which extends into the drier through the web entrance slot. In this way, the foraminous shield protects the coating operation, protects the coated web as it traverses the distance from the coating apparatus to the drier entrance, protects the coated web in the critical region surrounding the entrance slot where turbulent conditions frequently tend to arise, and protects the coated web during the drying operation. The forami-

nous shield need not, of course, be of the same construction throughout to be used in this way. For example, it could be of double-walled construction in the region surrounding the coating apparatus but of single-walled construction within the drier itself, or the perforations in the foraminous shield could be of a size and spacing in the region surrounding the coating operation that is best suited for the purpose of protecting the flow of coating composition but of a different size and spacing in the region that is located within the drier so as to provide optimum conditions for the drying operation.

Use of both the method of copending U.S. patent application Ser. No. 139,506 and the method of U.S. Pat. No. 4,051,278 in conjunction with the method of the present invention is often highly advantageous where it is important to achieve a very low level of mottle.

While the term "foraminous shield" is believed to be aptly descriptive of the device described herein, it could also be referred to as a "diffusion means" or as a "flow controlling means."

The invention is further illustrated by the following examples of its practice.

EXAMPLE 1

Coating and drying apparatus similar to that shown in FIG. 4 herein was used in the preparation of a lithographic printing plate. In preparing the printing plate, an anodized aluminum web having a thickness of 0.00381 millimeters was coated at a web speed of 45.7 cm/sec with a 10 percent by weight solution of a light-sensitive polymeric resin dissolved in methylene chloride. The coating composition was applied at a wet coverage of 26.91 cc/m^2. After passing the coating hopper, the web travelled a distance of about one meter within the coating compartment, and then passed through a slot into a drier composed of four chambers each about 0.3 meters in length. Drying of the coating was complete by the time the web left the fourth chamber, except for a small amount of residual solvent which was removed in a subsequent curing section.

Variables investigated in this example were the temperature of the aluminum support at the coating application point, the drier temperature, the pressure of air impingement, the air velocity through the slot between the coating compartment and the drier, and the use of a foraminous shield. Both single-wall and double-wall foraminous shields were utilized, with the shield, in each case, extending over the coated surface of the web from the coating hopper through the end of the fourth drying chamber, and being positioned at a distance of 2.6 cm from the surface of the coating and 7.6 cm from the adjacent wall of the plenum. The single-wall foraminous shield was formed from 20×20 mesh (per square centimeter) stainless steel screen composed of 0.023 cm diameter wire. The double-wall foraminous shield was formed from the same stainless steel screen with a 0.5 cm spacing between the walls. The test samples were visually inspected after drying and rated for mottle in accordance with a numerical rating scale in which 0 represents substantially no observable mottle and 10 represents severe mottle.

The conditions utilized and the results obtained are summarized in Table I below.

TABLE 1

Test No.	Type of Shield	Support Temperature (°C.)	Drier Temperature (°C.)	Pressure in Drying Chambers (Pascals) No. 1	No. 2	No.3	No. 4	Slot Velocity (cm/sec)	Mottle Rating
1	None	38	60	−50	50	−50	50	355	9
2	None	38	60	−50	50	−50	50	559	8.5
3	None	38	60	0	50	0	50	355	10
4	None	38	21	−50	50	−50	50	355	8
5	None	21	21	−50	50	−50	50	355	5
6	Single-Wall	38	60	−50	50	−50	50	355	4
7	Double-Wall	38	60	−50	50	−50	50	355	3
8	Double-Wall	38	21	−50	50	−50	50	355	3
9	Double-Wall	21	21	−50	50	−50	50	355	2
10	Double-Wall	38	60	−50	175	−50	175	355	3.5
11	None	21	21	−50	175	−50	175	355	7

As indicated by the results reported in Table I, increasing slot velocity (compare test 1 with test 2) and decreasing drier temperature (compare test 1 with test 4) results in moderate improvement in the degree of mottle formation. Also, control of the support temperature and drier temperature in accordance with the principles of U.S. Pat. No. 4,051,278 (compare test 4 with test 5) brings about a significant improvement. On the other hand, increasing air impingement pressure (compare test 5 with test 11) causes a substantial increase in the degree of mottle formation.

Incorporation into the drier of a single-wall foraminous shield (compare test 1 with test 6) greatly improves the results obtained with respect to mottle formation. Even better results are achieved with use of a double-wall foraminous shield (compare test 6 with test 7) and such a shield is effective even under conditions of high air impingement pressure (see test 10). Optimum results were obtained when the principles of U.S. Pat. No. 4,051,278 were utilized in combination with the use of the foraminous shield of this invention (see test 9).

EXAMPLE 2

Coating and drying apparatus having an enclosed coating zone, and a horizontally-disposed flat-bed drier similar to that shown in FIG. 1 herein, was used to coat a poly(ethylene terephthalate) web with a coating composition comprising a 10 percent by weight solution of a light-sensitive polymeric resin dissolved in methylene chloride. The web was coated at a speed of 15.2 cm/sec and the coating composition was applied at a wet coverage of 75.6 cc/m^2. The time in the coating zone was 1.9 seconds, while the total time from the coating application point to the dry point was 27 seconds. The temperature in the drier was 93° C.

Variables investigated in this example were air impingement pressure and the use of a foraminous shield. Both single-wall and double-wall foraminous shields were utilized, and these shields were constructed in the same manner and of the same material as used in Example 1. In each case, the shield was positioned at a distance of 2.5 cm from the surface of the coating, and 7.5

cm from the adjacent wall of the plenum. Variations tested included the use of a shield in the coating zone and the use of a shield in the first and/or second sections of the drier. The residence time for the web in each of the first and second sections of the drier was 5.2 seconds.

The conditions utilized and the results obtained are summarized in Table II below.

TABLE II

Test No.	Type of Shield: Coating Zone	Section 1 of Drier	Section 2 of Drier	Air Impingement Pressure (Pascals)	Heat Transfer Coefficient (Joules/m^2 sec °C.)[1]	Mottle Rating
1	None	None	None	250	115	10
2	None	None	None	125	104	9
3	None	None	None	63	93	7.5
4	Single-Wall	None	None	125	104	6
4	Single-Wall	Single-Wall	None	125	99	4
6	Single-Wall	Single-Wall	Single-Wall	125	95	3.5
7	None	Single-Wall	Single-Wall	125	95	7
8	Double-Wall	Double-Wall	Double-Wall	125	86	2
9	Double-Wall	Double-Wall	None	125	95	3
10	Double-Wall	Double-Wall	Double-Wall	250	86	3

[1]Estimated average heat transfer coefficient for drier sections 1 and 2.

As indicated by the results reported in Table II, a decrease in air impingement pressure results in an improvement in mottle (compare test 1 with test 3). Use of the foraminous shield substantially reduces mottle with best results being achieved where the shield is utilized close to the coating point (compare test 6 with test 7). The double-wall shield provides a significant improvement in performance as compared with the single-wall shield (compare test 6 with test 8).

EXAMPLE 3

In this example, the same coating composition, web and apparatus as are described in Example 2 were used to evaluate the effect of variation in the size of the perforations in the foraminous shield. Two types of shields were used, the first being a single-wall shield formed of the same 20×20 mesh stainless steel screen that was used in Examples 1 and 2 and the second being a single-wall shield formed of a 9.5×9.5 mesh stainless steel screen composed of 0.036 cm diameter wire. In each case, the screen was positioned at a distance of 2.6 cm from the surface of the coating, and 6.4 cm from the adjacent wall of the plenum. The drier was operated at a temperature of 82° C. and an air impingement pressure of 125 Pascals.

The conditions utilized and the results obtained are summarized in Table III below:

TABLE III

Test No.	Type of Shield: Coating Zone	Section 1 of Drier	Section 2 of Drier	Mottle Rating
1	None	None	None	10
2	20 × 20	None	None	6
3	20 × 20	20 × 20	None	4
4	20 × 20	20 × 20	20 × 20	4
5	9.5 × 9.5	None	None	8
6	9.5 × 9.5	9.5 × 9.5	None	6
7	9.5 × 9.5	9.5 × 9.5	9.5 × 9.5	5.5

As indicated by the data reported in Table III, both types of screen provide a significant improvement in mottle, but the 20×20 screen, which is of finer mesh, is more effective than the 9.5×9.5 screen.

While applicants are not sure of the exact mechanisms whereby their invention functions, it is apparent that the use of a foraminous shield, such as a screen or perforated plate, in close proximity to the surface of a coating, which is undergoing drying by a flowing gaseous medium, provides drying conditions which result in less formation of mottle, particularly with coating compositions that contain volatile organic solvents. This is an entirely unexpected result and provides a simple and easily implemented solution to the problem of mottle formation which has long plagued the coating industry, and especially that portion of the industry involved with the coating of photographic materials.

The invention has been described in detail with particular reference to preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

We claim:

1. In a method for drying a sheet material which has been coated on a surface thereof with at least one layer of a mottle-prone coating composition containing a liquid medium that is capable of being evaporated from said coating composition by contact with a gaseous drying medium, said method comprising the steps of advancing said coated sheet material along a predetermined path through a drying zone and uniformly directing a gaseous drying medium onto the coated surface of said sheet material so as to bring about evaporation of said liquid medium with resulting formation of spent gaseous drying medium which flows away from said path for discharge from said drying zone; the improvement which comprises advancing said sheet material with said coated surface in opposed closely spaced relationship with a foraminous shield which is permeable to said gaseous drying medium, so as to promote flow of said spent gaseous drying medium adjacent to the surface of said shield which is remote from said coated surface and to form a quiescent region between said shield and said coated surface which is rich in the vapor of said liquid medium and in which flow of said spent gaseous drying medium is suppressed and uniform heat transfer conditions are promoted, whereby formation of mottle in said coating is reduced.

2. A method as claimed in claim 1 wherein said sheet material is a synthetic organic polymeric film.

3. A method as claimed in claim 1 wherein said sheet material is a poly(ethylene terephthalate) film.

4. A method as claimed in claim 1 wherein said liquid medium comprises an organic solvent.

5. A method as claimed in claim 1 wherein said liquid medium comprises an organic solvent having a boiling

point at atmospheric pressure of from about 40° C. to about 85° C.

6. A method as claimed in claim 1 wherein said gaseous drying medium is warm dry air.

7. A method as claimed in claim 1 wherein said coating composition is a photographic coating composition.

8. A method as claimed in claim 1 wherein said foraminous shield is a single-walled structure.

9. A method as claimed in claim 1 wherein said foraminous shield is a multi-walled structure, each wall of which is comprised of a foraminous material.

10. A method as claimed in claim 1 wherein said foraminous shield is composed of screen material.

11. A method as claimed in claim 1 wherein said foraminous shield is composed of perforated plate material.

12. A method as claimed in claim 1 wherein said foraminous shield is composed of foraminous material having perforations with a size in the range of from about 0.25 to about 1.25 millimeters and a percentage open area in the range of from about 30 to about 50 percent.

13. A method as claimed in claim 1 wherein said foraminous shield extends from the start of said drying zone over a distance equal to about 5 to about 25 percent of the total length of said drying zone.

14. A method as claimed in claim 1 wherein said coated sheet material is a web comprised of aluminum coated with a layer of a coating composition adapted to form a lithographic printing plate, said coating composition comprising a light-sensitive polymeric resin dissolved in an organic solvent.

15. In a method for drying a web which has been coated on a surface thereof with at least one layer of a mottle-prone coating composition containing a liquid medium that is capable of being evaporated from said coating composition by contact with a gaseous drying medium, said method comprising the steps of advancing said coated web along a predetermined path through a drying zone and uniformly directing a gaseous drying medium onto the coated surface of said web so as to bring about evaporation of said liquid medium with resulting formation of spent gaseous drying medium which flows transversely to said path for discharge from said drying zone; the improvement which comprises advancing said sheet material with said coated surface in opposed closely spaced relationship with a foraminous shield which is substantially commensurate in width with said coated surface and permeable to said gaseous drying medium, so as to promote transverse flow of said spent gaseous drying medium adjacent to the surface of said shield which is remote from said coated surface and to form a quiescent region between said shield and said coated surface which is rich in the vapor of said liquid medium and in which transverse flow of said spent gaseous drying medium is suppressed and uniform heat transfer conditions are promoted, whereby formation of mottle in said coating is reduced.

16. A method for reducing mottle in the drying of a coated sheet material, said sheet material having been coated on a surface thereof with at least one layer of a mottle-prone coating composition containing a liquid medium that is capable of being evaporated from said coating composition by contact with a gaseous drying medium, and said drying being carried out by the steps of advancing said coated sheet material along a predetermined path through a drying zone and uniformly directing a gaseous drying medium onto the coated surface of said sheet material so as to bring about evaporation of said liquid medium with resulting formation of spent gaseous drying medium which flows away from said path for discharge from said drying zone; said method comprising interposing a foraminous shield, which is permeable to said gaseous drying medium, in opposed closely spaced relationship with said coated surface so as to promote flow of said spent gaseous drying medium adjacent to the surface of said shield which is remote from said coated surface and to form a quiescent region between said shield and said coated surface which is rich in the vapor of said liquid medium and in which flow of said spent gaseous drying medium is suppressed and uniform heat transfer conditions are promoted, whereby formation of mottle in said coating is reduced.

17. Apparatus for drying a sheet material which is coated on a surface thereof with at least one layer of a mottle-prone coating composition containing a liquid medium that is capable of being evaporated from said coating composition by contact with a gaseous drying medium, said apparatus comprising:

means for advancing said coated sheet material along a predetermined path through a drying zone,

means adjacent to said path for uniformly supplying a gaseous drying medium to said coated surface so as to bring about evaporation of said liquid medium with resulting formation of spent gaseous drying medium which flows away from said path for discharge from said drying zone, and

shield means for reducing the tendency for mottle formation in said coating, said shield means being comprised of a foraminous material which is permeable to said gaseous drying medium and being interposed between said path and said supply means in close proximity to said coated surface, so as to promote flow of said spent gaseous drying medium adjacent to the surface of said shield means which is remote from said coated surface and form between said coated surface and said shield means a quiescent region which is rich in the vapor of said liquid medium and in which flow of said spent gaseous drying medium is suppressed and uniform heat transfer conditions are promoted, whereby formation of mottle in said coating is reduced.

18. Apparatus for drying a sheet material which is coated on a surface thereof with at least one layer of a mottle-prone coating composition containing a liquid medium that is capable of being evaporated from said coating composition by contact with a gaseous drying medium, said apparatus comprising:

means for advancing said coated sheet material along a predetermined path through a drying zone,

means for supplying said gaseous drying medium to said drying zone,

a plenum which is located within said drying zone adjacent to said path and is connected to said supply means, said plenum serving to uniformly direct said gaseous drying medium onto the coated surface of said sheet material so as to bring about the evaporation of said liquid medium with resulting formation of spent gaseous drying medium which flows away from said path for discharge from said drying zone, and

a foraminous shield which is interposed between said plenum and said path, said shield being permeable to said gaseous drying medium and having one surface thereof in opposing spaced relationship

with said plenum and the opposite surface thereof in opposing spaced relationship with said path, said shield being in close proximity to said path, so as to form a quiescent region between said shield and said coated surface which is rich in the vapor of said liquid medium and in which flow of said spent gaseous drying medium is suppressed and uniform heat transfer conditions are promoted, and being spaced from said plenum to form a region therebetween in which flow of said spent gaseous drying medium can occur without disturbing said coated surface, whereby formation of mottle in said coating is reduced.

19. Apparatus as claimed in claim 18 wherein said foraminous shield is a single-walled structure.

20. Apparatus as claimed in claim 18 wherein said foraminous shield is a multi-walled structure, each wall of which is comprised of a foraminous material.

21. Apparatus as claimed in claim 18 wherein said foraminous shield is composed of screen material.

22. Apparatus as claimed in claim 18 wherein said foraminous shield is composed of perforated plate material.

23. Apparatus as claimed in claim 18 wherein said foraminous shield is composed of foraminous material having perforations with a size in the range of from about 0.25 to about 1.25 millimeters and a percentage open area in the range of from about 30 to about 50 percent.

24. Apparatus as claimed in claim 18 wherein the spacing between said foraminous shield and the opposing surface of said plenum is in the range of from about 5 to about 100 centimeters.

25. Apparatus as claimed in claim 18 wherein the spacing between said foraminous shield and said path is in the range of from about 1 to about 15 centimeters.

26. Apparatus as claimed in claim 18 wherein the ratio between (1) the spacing between said foraminous shield and the opposing surface of said plenum, and, (2) the spacing between said foraminous shield and said path, is in the range of from about 4 to 1 to about 20 to 1.

27. Apparatus as claimed in claim 18 wherein said foraminous shield extends from the start of said drying zone over a distance equal to about 5 to about 25 percent of the total length of said drying zone.

28. Apparatus for drying a web which is coated on a surface thereof with at least one layer of a mottle-prone coating composition containing a liquid medium that is capable of being evaporated from said coating composition by contact with a gaseous drying medium, said apparatus comprising:

means for advancing said coated web along a predetermined path through a drying zone,

means for supplying said gaseous drying medium to said drying zone,

a plenum which is located within said drying zone adjacent to said path and is connected to said supply means, said plenum serving to uniformly direct said gaseous drying medium onto the coated surface of said web so as to bring about the evaporation of said liquid medium with resulting formation of spent gaseous drying medium which flows transversely to said path for discharge from said drying zone, and

a foraminous shield which is substantially commensurate in width with said coated surface interposed between said plenum and said path, said shield being permeable to said gaseous drying medium and having one surface thereof in opposing spaced relationship with said plenum and the opposite surface thereof in opposing spaced relationship with said path, said shield being in close proximity to said path, so as to form a quiescent region between said shield and said coated surface which is rich in the vapor of said liquid medium, and in which transverse flow of said spent gaseous drying medium is suppressed and uniform heat transfer conditions are promoted, and being spaced from said plenum to form a region therebetween in which transverse flow of said spent gaseous drying medium can occur without disturbing said coated surface, whereby formation of mottle in said coating is reduced.

* * * * *

EXHIBIT M

US005881476A

United States Patent [19]

Strobush et al.

[11] **Patent Number: 5,881,476**

[45] **Date of Patent: Mar. 16, 1999**

[54] **APPARATUS AND METHOD FOR DRYING A COATING ON A SUBSTRATE EMPLOYING MULTIPLE DRYING SUBZONES**

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[73] Assignee: **Minnesota Mining and Manufacturing Company**, St. Paul, Minn.

[21] Appl. No.: **820,245**

[22] Filed: **Mar. 18, 1997**

Related U.S. Application Data

[63] Continuation of Ser. No. 625,469, Mar. 29, 1996, abandoned.

[51] **Int. Cl.**[6] **F26B 3/00**

[52] **U.S. Cl.** **34/451**; 34/464; 34/501; 34/540; 34/643; 34/210; 427/378

[58] **Field of Search** 34/273, 274, 364, 370, 421, 423, 464, 501, 507, 540, 620, 643, 651, 654, 210, 222, 451; 432/8, 59; 427/377, 378

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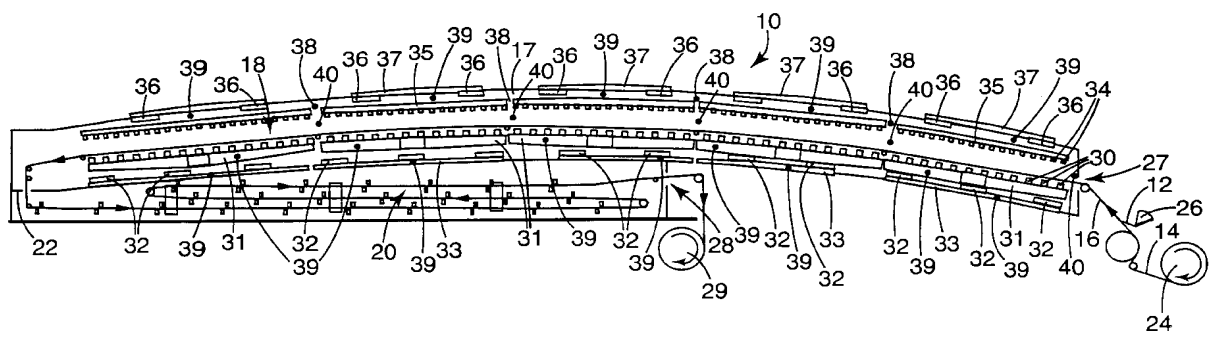
Primary Examiner—Henry Bennett
Assistant Examiner—Steve Gravini
Attorney, Agent, or Firm—William K. Weimer

[57] **ABSTRACT**

An apparatus and method for evaporating a coating solvent from a coating on a first substrate surface of a substrate and for minimizing the formation of mottle as the coating solvent is evaporating. A drying oven includes an enclosure having an inlet and an outlet and defining a first drying zone.



A plurality of drying subzones are within the first drying zone. At least two of the plurality of drying subzones employ different and controllable drying conditions. Physical barriers are not required to create the plurality of drying subzones.

59 Claims, 13 Drawing Sheets

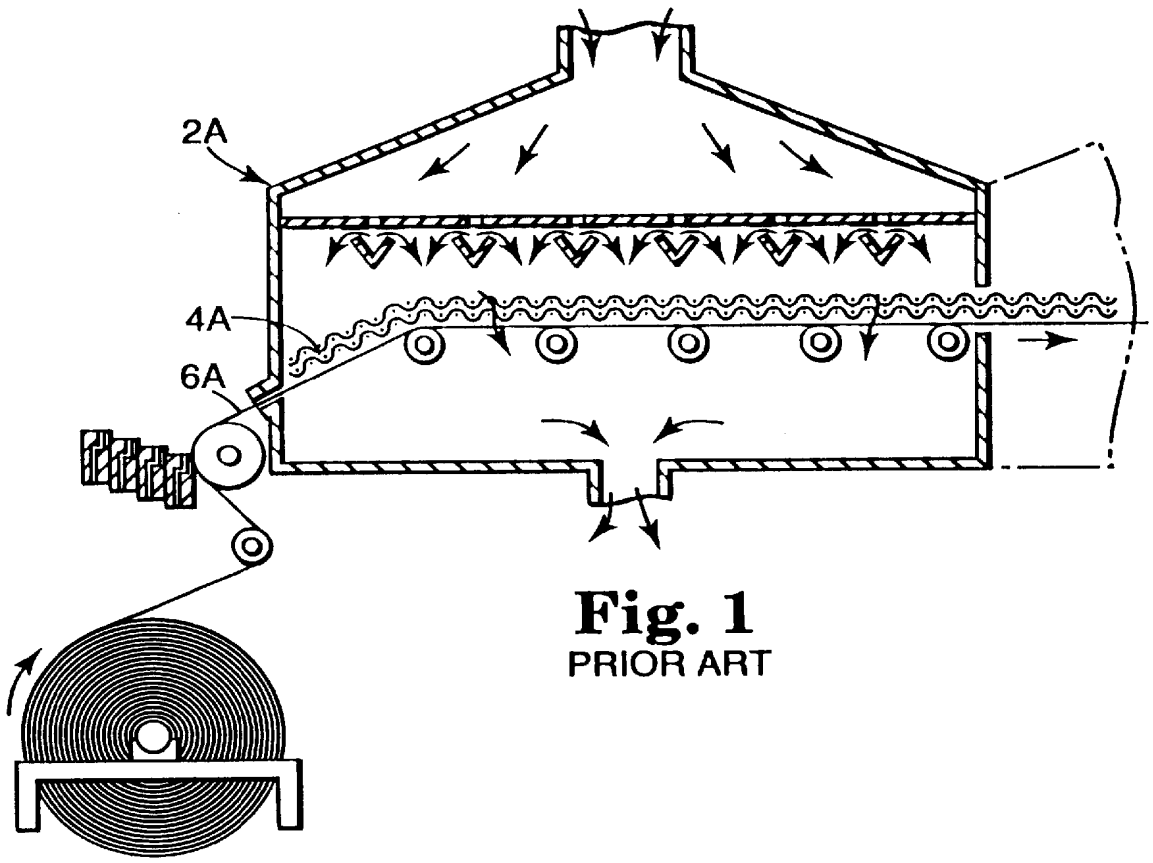


Fig. 1
PRIOR ART

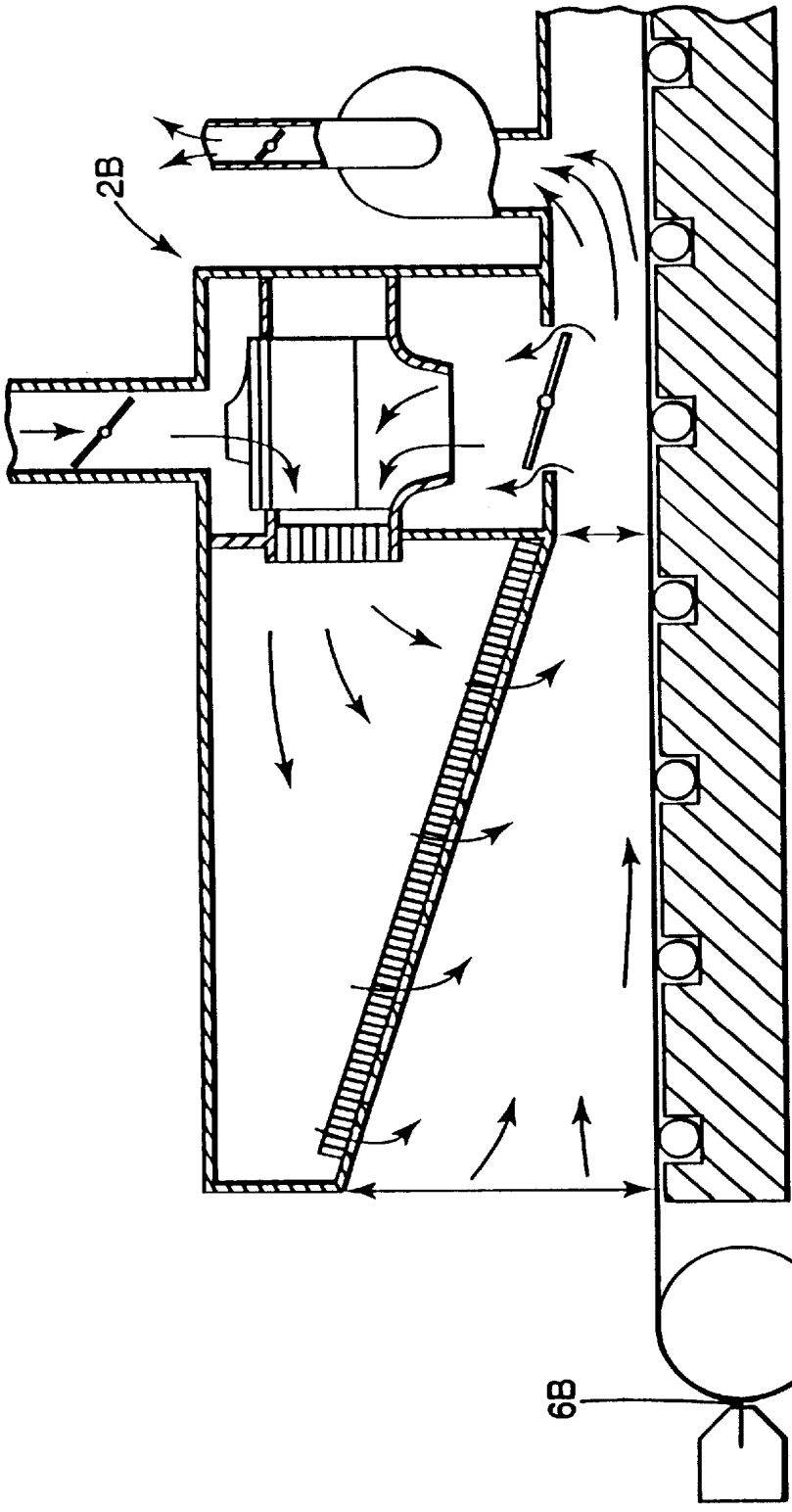


Fig. 2
PRIOR ART

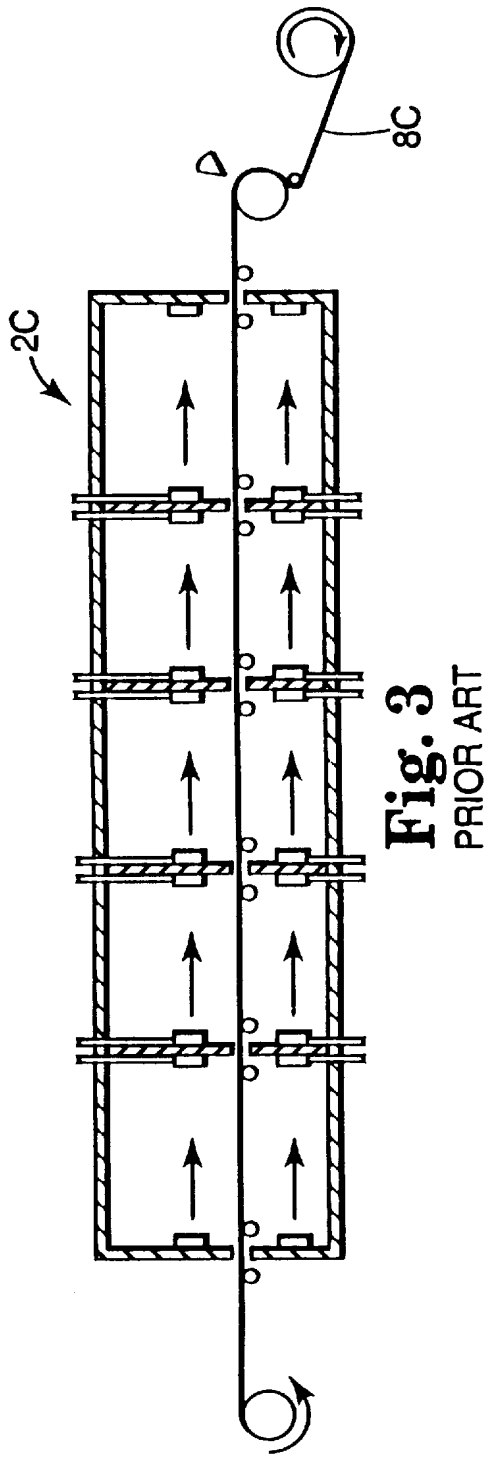


Fig. 3
PRIOR ART

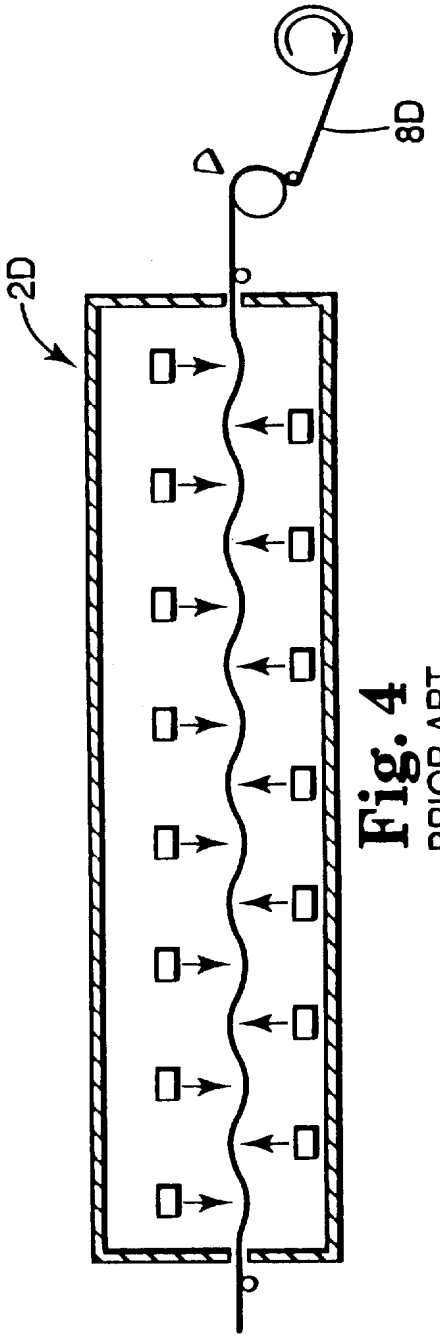


Fig. 4
PRIOR ART

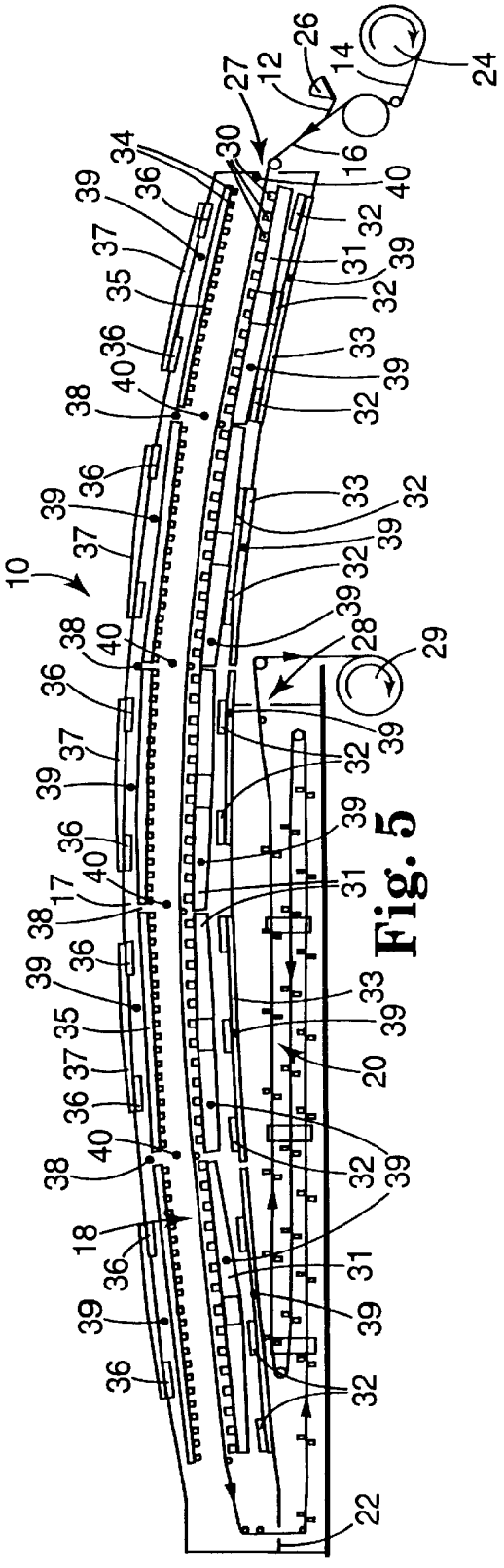


Fig. 5

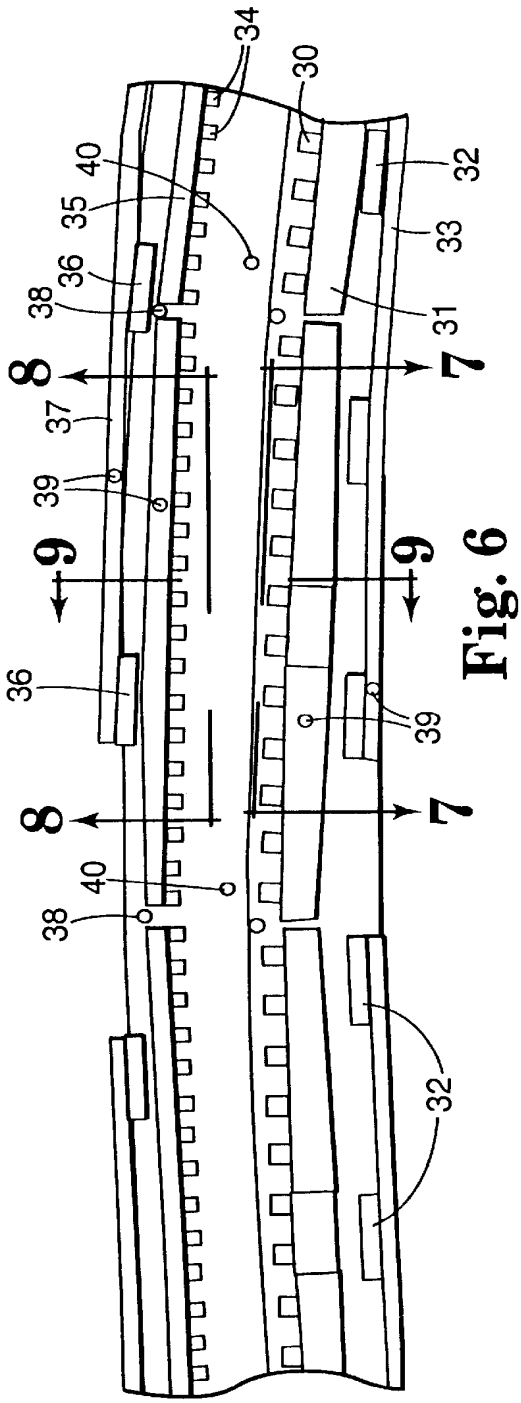


Fig. 6

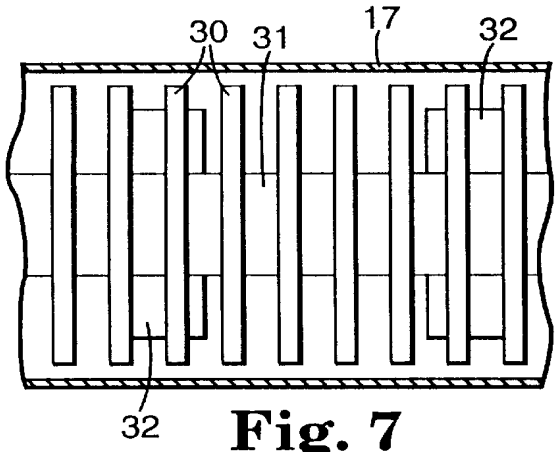


Fig. 7

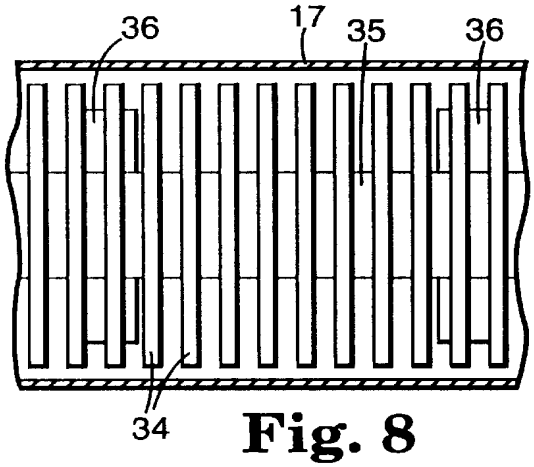


Fig. 8

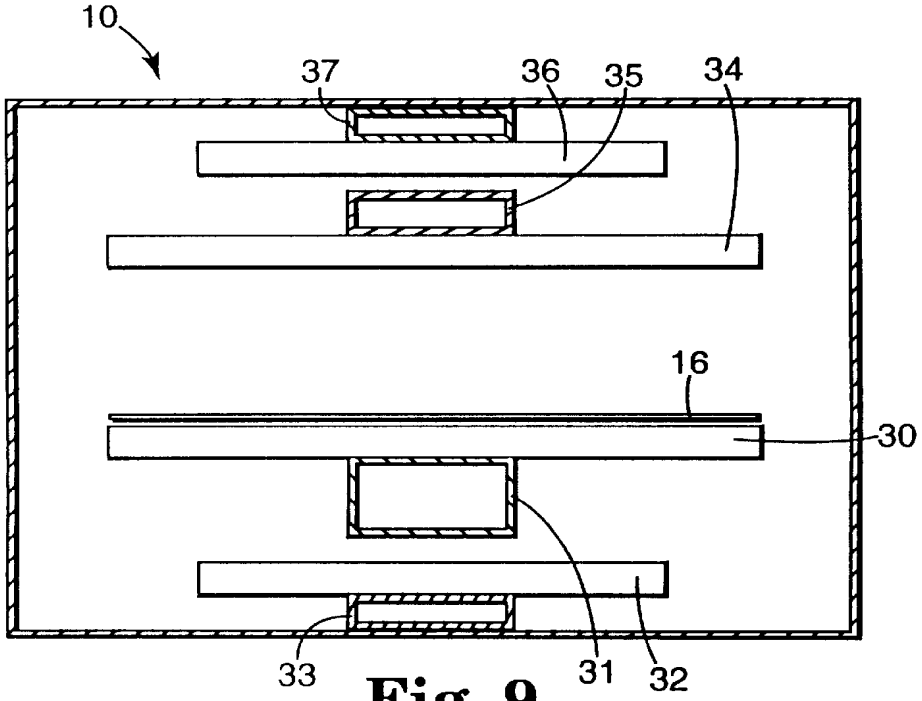


Fig. 9

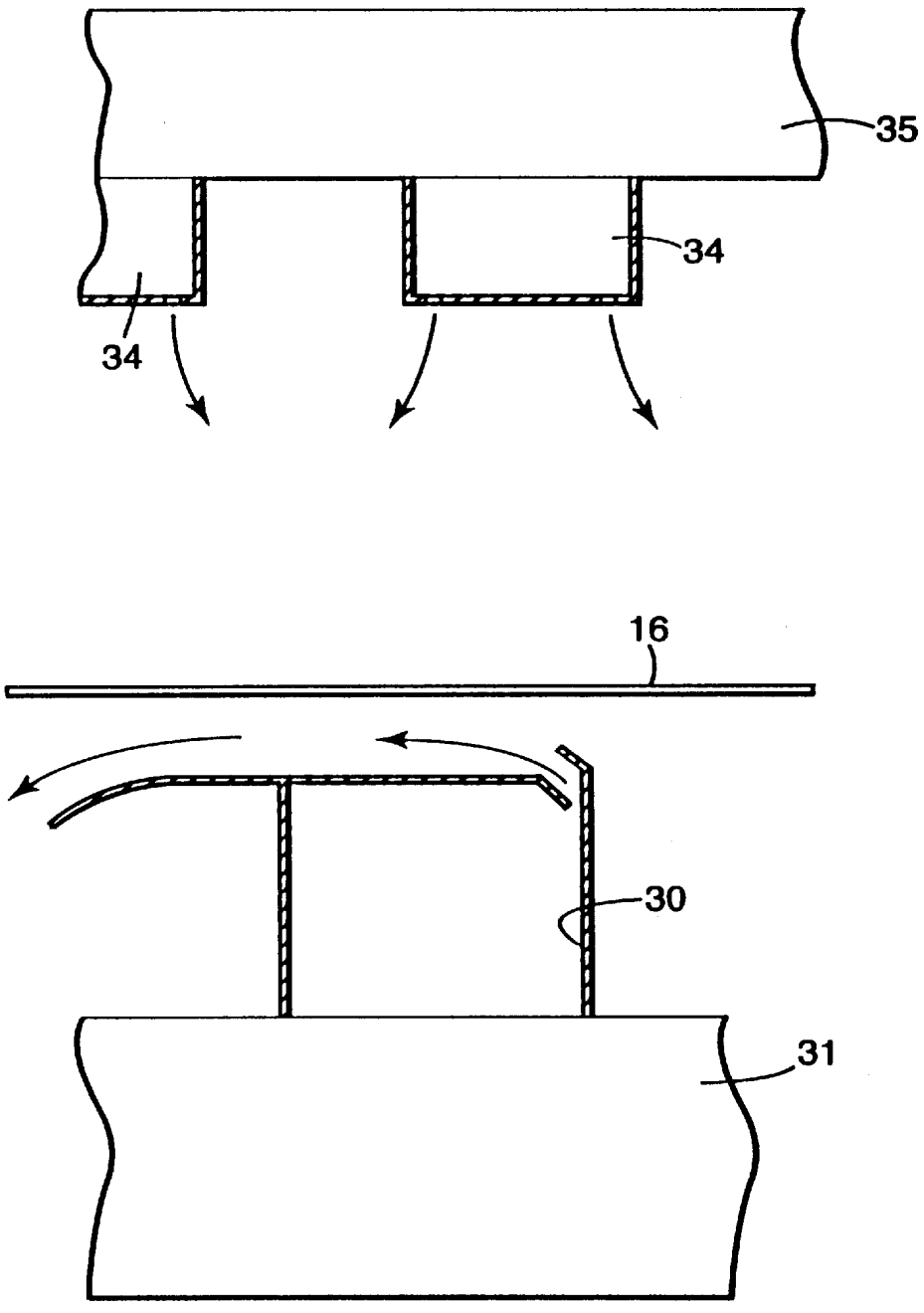


Fig. 10

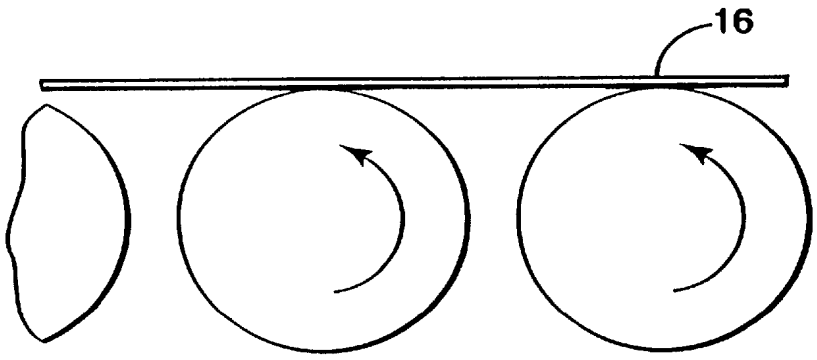


Fig. 11

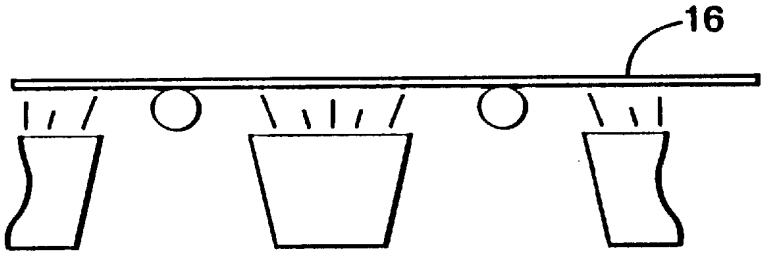


Fig. 12

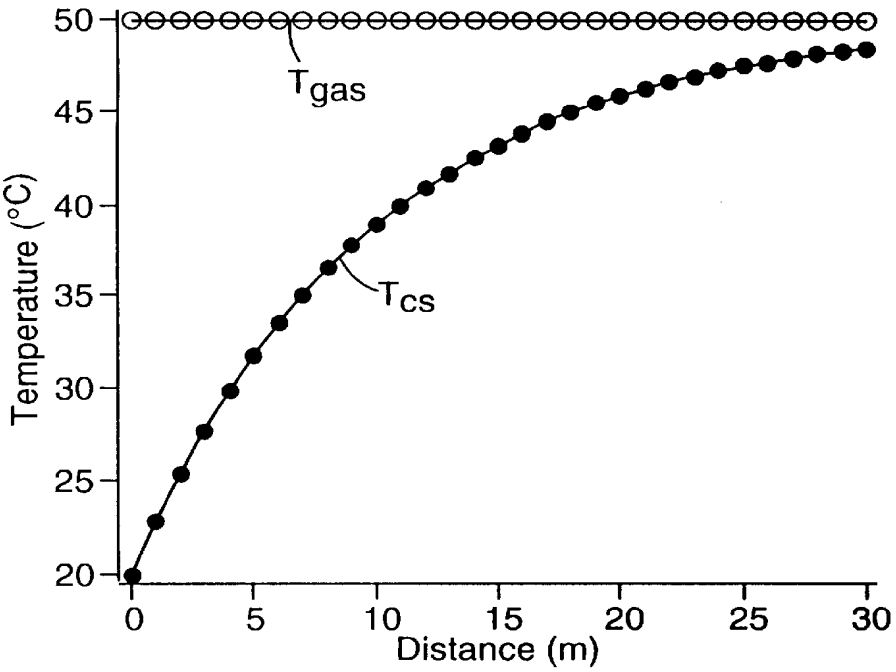


Fig. 13

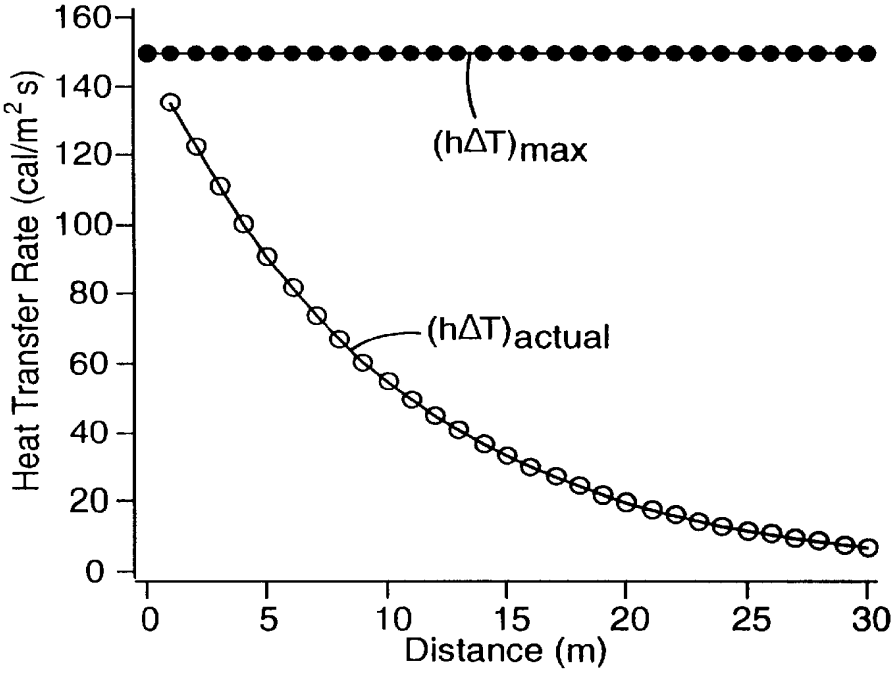


Fig. 14

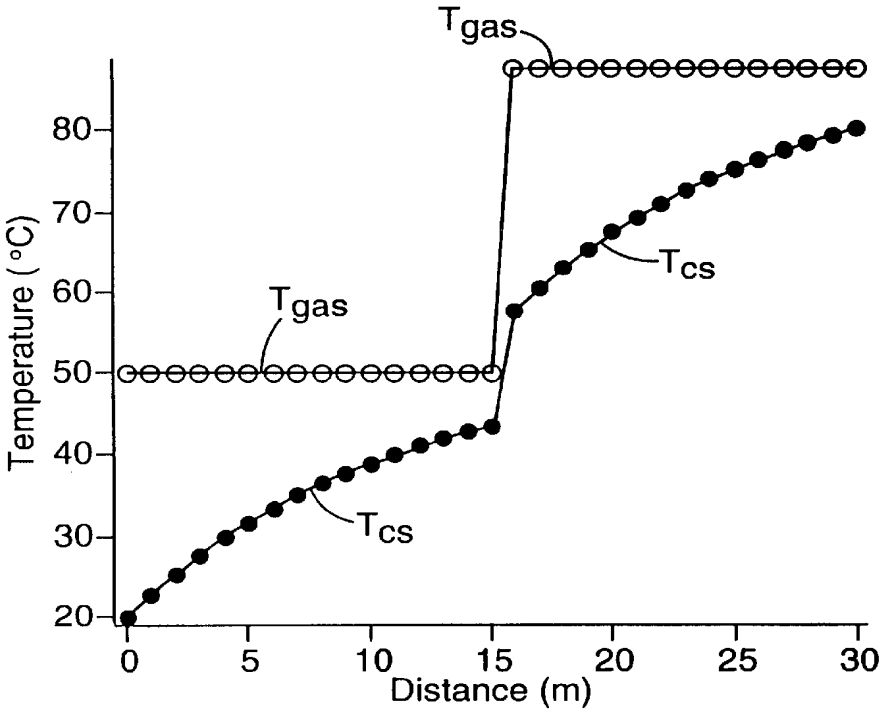


Fig. 15

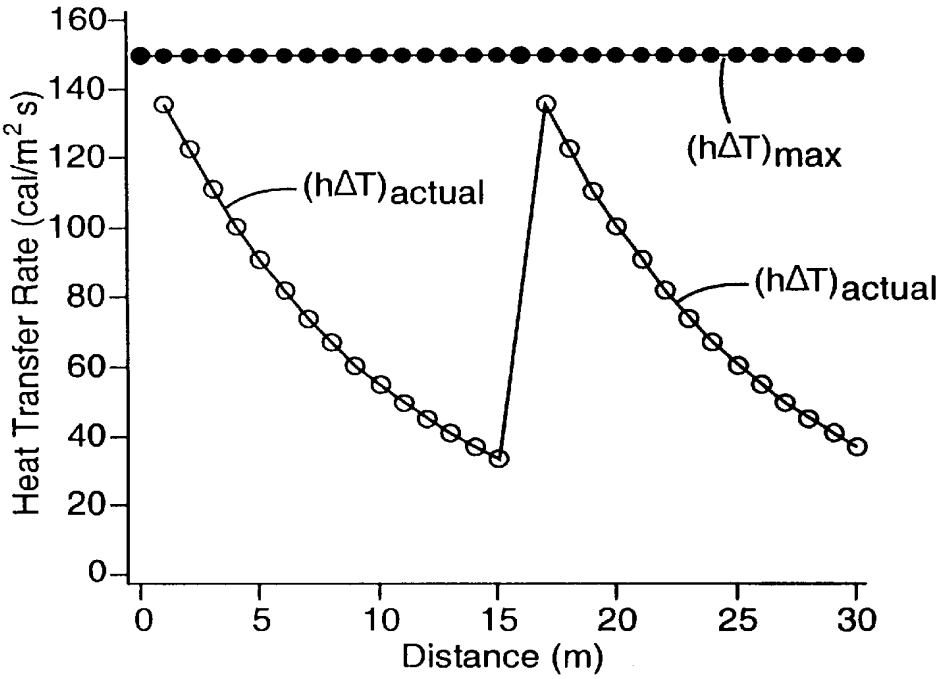


Fig. 16

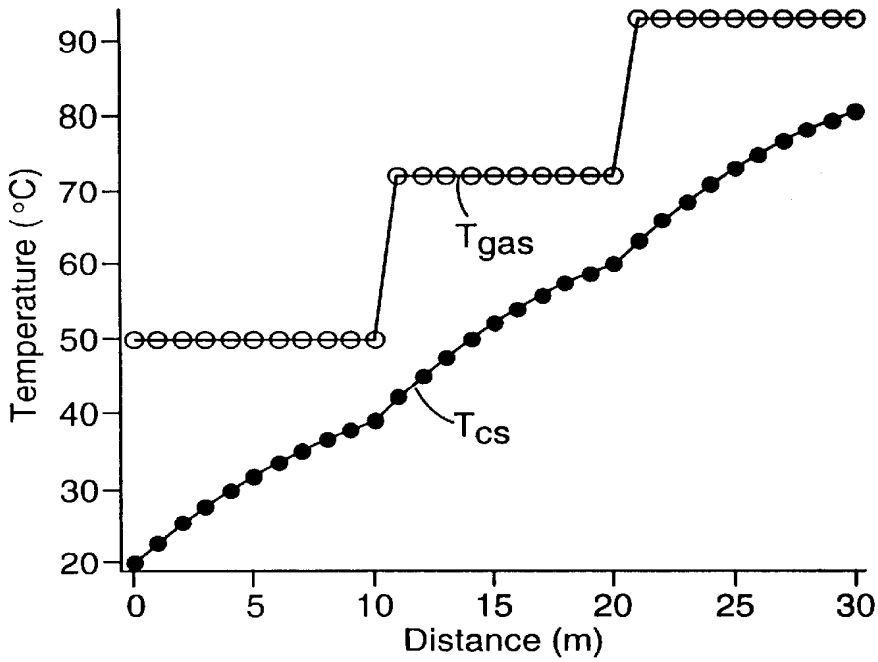


Fig. 17

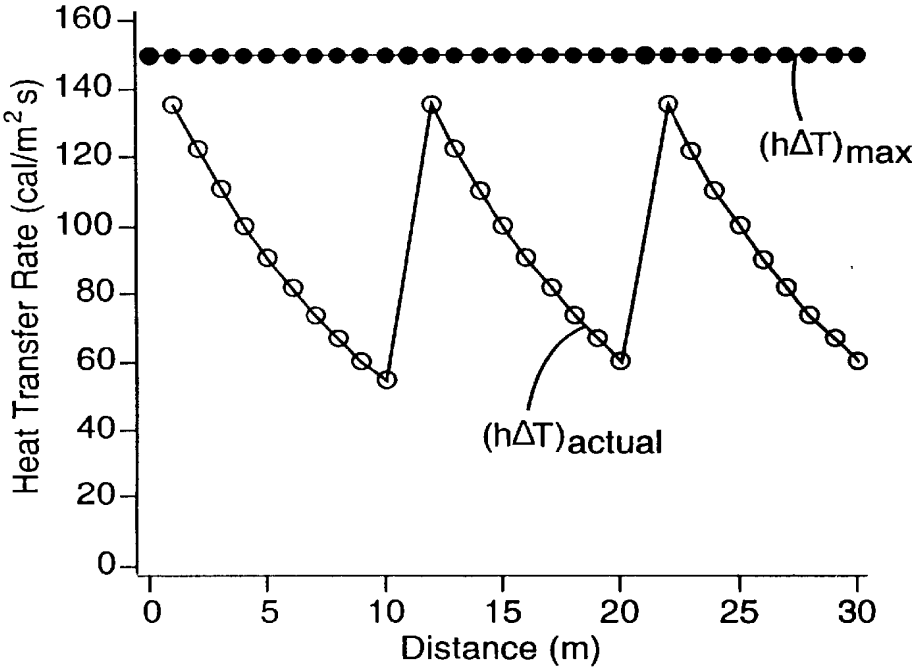


Fig. 18

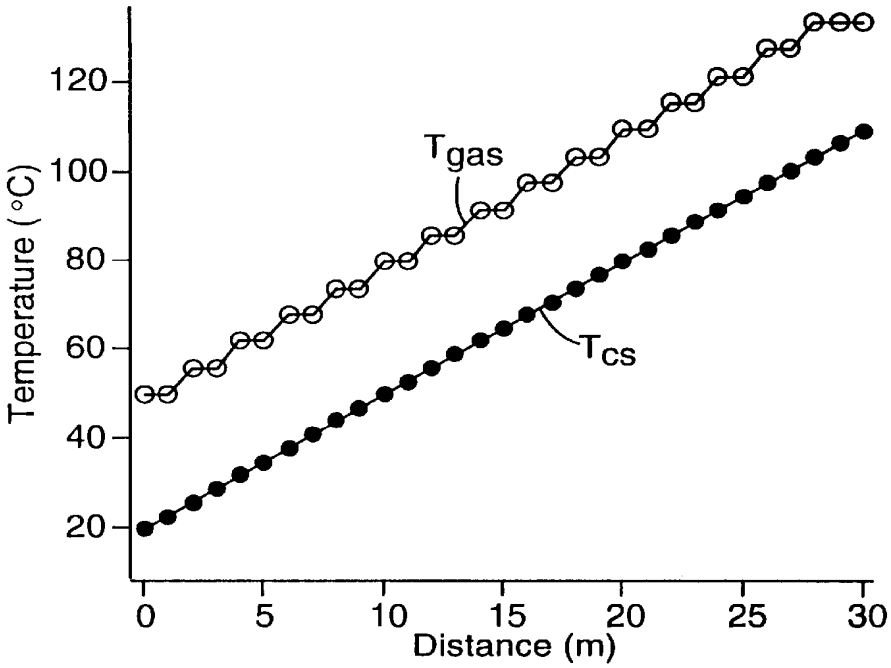


Fig. 19

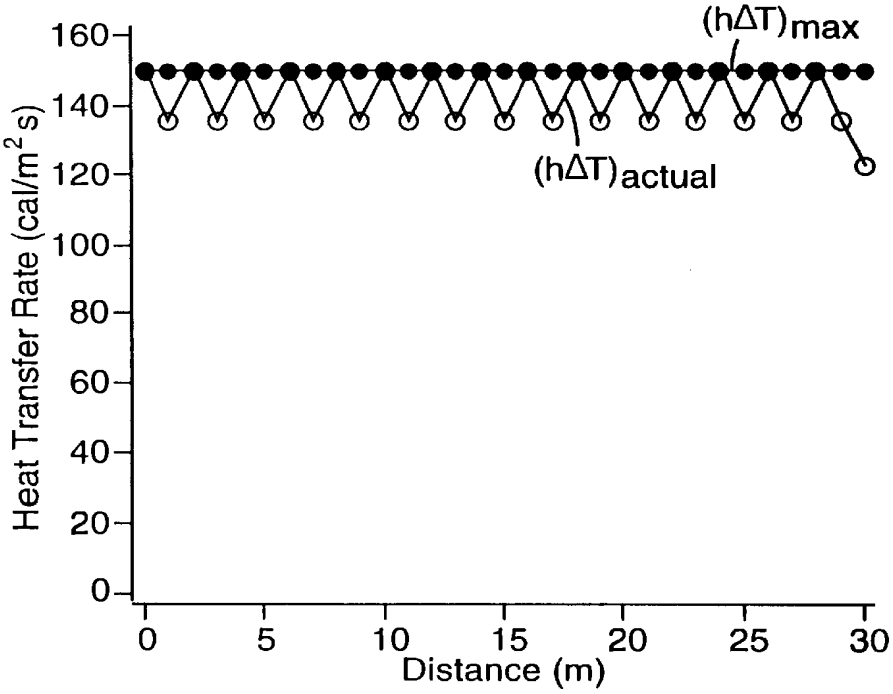


Fig. 20

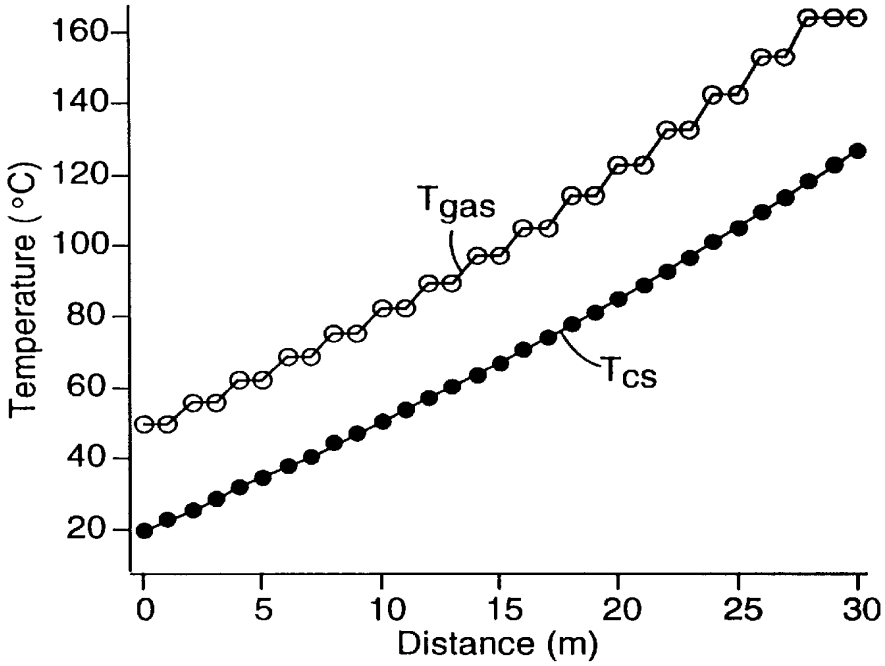


Fig. 21

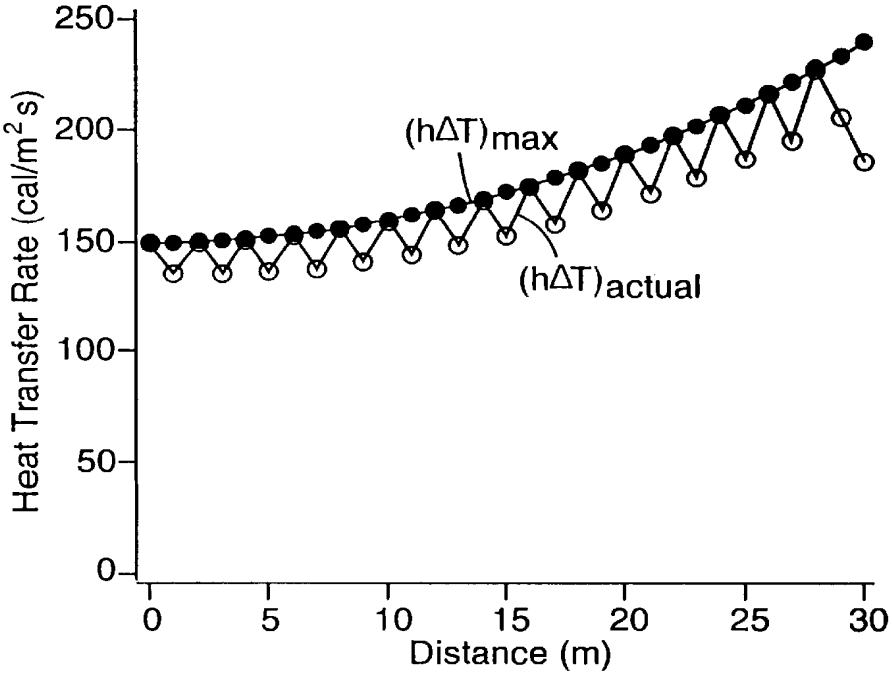


Fig. 22

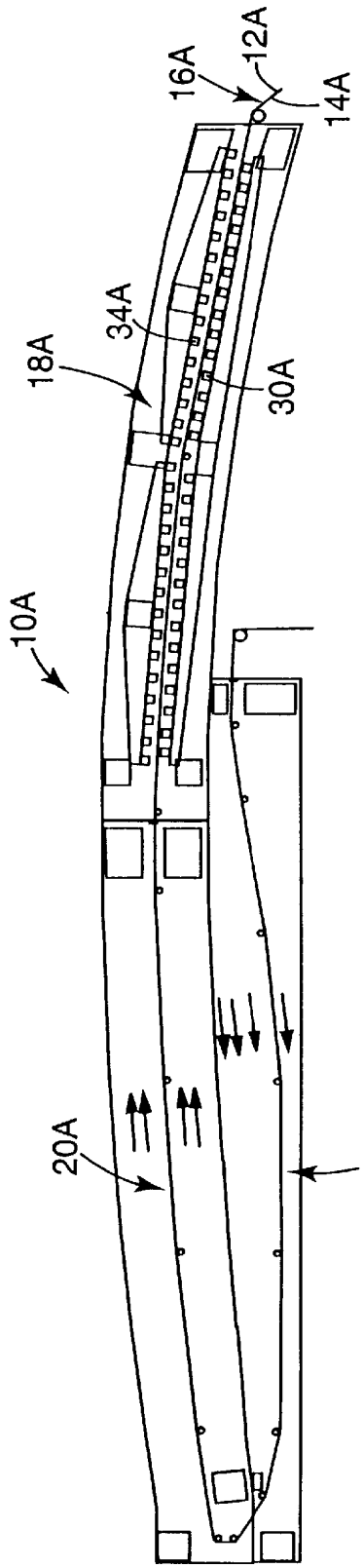


Fig. 23

APPARATUS AND METHOD FOR DRYING A COATING ON A SUBSTRATE EMPLOYING MULTIPLE DRYING SUBZONES

This is a continuation of application Ser. No. 08/625,469 filed Mar. 29, 1996 abandoned.

FIELD OF THE INVENTION

The present invention relates to methods for drying coatings on a substrate and more particularly to methods for drying coatings used in making imaging articles.

BACKGROUND OF THE INVENTION

The production of high quality articles, particularly photographic, photothermographic, and thermographic articles, consists of applying a thin film of coating solution onto a continuously moving substrate. Thin films can be applied using a variety of techniques including: dip coating, forward or reverse roll coating, wire-wound coating, blade coating, slot coating, slide coating, and curtain coating (see, for example, L. E. Scriven; W. J. Suszynski; *Chem. Eng. Prog.* 1990, September, p. 24). Coatings can be applied as single layers or as two or more superposed layers. While it is usually most convenient for the substrate to be in the form of a continuous substrate, it can also be in the form of a succession of discrete sheets.

The initial coating is either a mixture of solvent and solids or a solution and must be dried to obtain the final dried article. While the cost of a coating process is determined by the coating technique, the cost of a drying process is often proportional to the desired line speed (see E. D. Cohen; E. J. Lightfoot; E. B. Gutoff; *Chem. Eng. Prog.* 1990, September, p. 30). The line speed is limited by the capabilities of the oven. To reduce costs, it is desirable that the removal of solvent from the coating be as efficient as possible. This is generally accomplished by transferring heat to the coated article as efficiently as possible. This is often accomplished by increasing the velocity of the drying gas at the coating surface, thereby increasing heat transfer and solvent evaporation and thus drying the coating more quickly. The resulting turbulent air, however, increases the tendency for defect formation.

The process of applying a coating to and drying that coating on a substrate can inherently create defects, including Benard cells, orange peel, and mottle. Benard cells are defects arising from circulatory motion within the coating after it has been applied (see C. M. Hanson; P. E. Pierce; *Cellular Convection in Polymer Coatings-An Assessment*, 12 Ind. Eng. Chem. Prod. Res. Develop. 1973, p. 67).

Orange peel is related to Benard cells. Orange peel is most common in fluid coatings which have a high viscosity to solids ratio. This is due to the tendency of such systems to "freeze in" the topography associated with Benard cells upon loss of relatively small amounts of solvent. The topography can be observed as a small scale pattern of fine spots like the surface of an orange peel. The scale of the pattern is on the order of millimeters and smaller.

Mottle is an irregular pattern or non-uniform density defect that appears blotchy when viewed. This blotchiness can be gross or subtle. The pattern may even take on an orientation in one direction. The scale can be quite small or quite large and may be on the order of centimeters. Blotches may appear to be different colors or shades of color. In black-and-white imaging materials, blotches are generally shades of gray and may not be apparent in unprocessed articles but become apparent upon development. Mottle is usually caused by air movement over the coating before it enters the dryer, as it enters the dryer, or in the dryer (see for example, "*Modern Coating and Drying Technology*," Eds. E. D Cohen, E. B. Gutoff, VCH Publishers, NY, 1992; p. 288).

Mottle is a problem that is encountered under a wide variety of conditions. For example, mottle is frequently encountered when coatings comprising solutions of a polymeric resin in an organic solvent are coated onto webs or sheets of synthetic organic polymer substrates. Mottle is an especially severe problem when the coating solution contains a volatile organic solvent but can also occur to a significant extent even with aqueous coating compositions or with coating compositions using an organic solvent of low volatility. Mottle is an undesirable defect because it detracts from the appearance of the finished product. In some instances, such as in imaging articles, it is further undesirable because it adversely affects the functioning of the coated article.

Substrates that have been coated are often dried using a drying oven which contains a drying gas. The drying gas, usually air, is heated to a suitable elevated temperature and brought into contact with the coating in order to bring about evaporation of the solvent. The drying gas can be introduced into the drying oven in a variety of ways. Typically, the drying gas is directed in a manner which distributes it uniformly over the surface of the coating under carefully controlled conditions that are designed to result in a minimum amount of disturbance of the coated layer. The spent drying gas, that is, drying gas which has become laden with solvent vapor evaporated from the coating, is continuously discharged from the dryer.

Many industrial dryers use a number of individually isolated zones to allow for flexibility in drying characteristics along the drying path. For example, U.S. Pat. No. 5,060,396 describes a zoned cylindrical dryer for removing solvents from a traveling substrate. The multiple drying zones are physically separated, and each drying zone may operate at a different temperature and pressure. Multiple drying zones are desirable because they permit the use of successively lower solvent vapor composition. German Pat. No. DD 236,186 describes the control of humidity and temperature of each drying zone to effect maximum drying at minimum cost. Soviet Pat. No. SU 620766 describes a multistage timber dryer with staged temperature increases that reduce the stress within the timber.

Usually, when multiple zones are present in an oven, they are isolated from one another. The coated substrate is transferred between the zones through a slot. In order to minimize the air and heat flow between zones and to be able to effectively control the drying conditions in each zone, this slot typically has as small a cross-section as possible that will still allow the substrate to pass between zones. However, the adjacent zones are in communication with one another through the slot and thus there is typically a pressure difference between zones. Air flows from one zone to another; and since the dimensions of the slot are small, the air gas velocity is high. Therefore the slots between ovens tend to be sources for mottle defects.

U.S. Pat. No. 4,365,423 discloses an apparatus and method for drying to reduce mottle. FIG. **1** shows an embodiment of this invention. The drying apparatus **2**A uses a foraminous shield **4**A to protect the liquid coating **6**A from air disturbances. The foraminous shield **4**A is described to be a screen or perforated plate that sets up a "quiescent" zone above the substrate promoting uniform heat and mass trans-

fer conditions. The shield **4**A is also noted to restrict the extent to which spent drying gas, which is impinged toward the liquid coating **6**A, comes in contact with the surface of the coating. This method is reported to be especially advantageous in drying photographic materials, particularly those comprising one or more layers formed from coating compositions that contain volatile organic solvents. This apparatus and method has the limitation that it slows the rate of drying.

U.S. Pat. No. 4,999,927 discloses another apparatus and method for drying a liquid layer that has been applied to a carrier material moving through a drying zone and which contains both vaporizable solvent components and non-vaporizable components. FIG. **2** illustrates this apparatus **2**B and method. Drying gas flows in the direction of the carrier material **8**B and is accelerated within the drying zone in the direction of flow. In this manner, laminar flow of the boundary layer of the drying gas adjacent to the liquid layer on the carrier material is maintained. By avoiding turbulent air flow, mottle is reduced.

Examples of two other known drying apparatuses and methods are shown in FIGS. **3** and **4**. FIG. **3** schematically shows a known drying apparatus **2**C in which air flows (see arrows) from one end of an enclosure to the other end. The airflow is shown in FIG. **3** as being parallel and counter to the direction of travel of the coated substrate (i.e., countercurrent). Parallel cocurrent airflow is also known.

FIG. **4** schematically shows a known drying apparatus **2**D which involves the creation of impingement airflow (see arrows), that is more perpendicular to the plane of the substrate **8**D. The impinging air also acts as a means for floating or supporting the substrate through the oven.

U.S. Pat. No. 4,051,278 describes a method for reducing mottle caused by solvent evaporation in the coating zone. Coating a substrate with reduced mottle, such as coating a composition comprising a film-forming material in an evaporable liquid vehicle onto a flexible web or synthetic organic polymer, is achieved by maintaining at least two of the following at a temperature substantially equivalent to the equilibrium surface temperature of the coated layer at the coating zone: (1) the temperature of the atmosphere at the location of coating; (2) the temperature of the coating composition at the location of coating; and (3) the temperature of the substrate at the coating zone. The equilibrium surface temperature is defined as the temperature assumed by the surface of a layer of the coating composition under steady state conditions of heat transfer following evaporative cooling of the layer at the coating zone. After coating, drying of the coated layer is carried out by conventional techniques. This invention includes methods of drying while preventing mottle formation by controlling temperature (i.e., by cooling) at the coating zone and does not address temperature control or mottle formation within the drying oven. Furthermore, this method would be useful only for coatings that cool significantly due to evaporative cooling which subsequently causes mottle.

U.S. Pat. No. 4,872,270 describes a method of drying latex paint containing water and one or more high boiling organic solvents coated onto a carrier film. The process yields a dried paint layer free of blisters and bubble defects. The coated film is passed continuously through a series of at least three drying stages in contact with warm, moderately humid air and more than half of the heat required for evaporation is supplied to the underside of the film. Drying conditions in at least each of the first three stages are controlled to maintain a film temperature profile which causes the water to evaporate at a moderate rate but more rapidly than the organic solvents, thus achieving coalescence of the paint and avoiding the trapping of liquids in a surface-hardened paint layer. Bubble formation is reportedly eliminated by controlling the vapor pressure of the volatile solvent within the film. The formation of mottle occurs due to a different mechanism than blisters and requires different methods for control and elimination.

U.S. Pat. No. 4,894,927 describes a process for drying a moving web coated with a coating composition containing a flammable organic solvent. The web is passed through a closed-type oven filled with an inert gas and planer heaters on top and bottom of the web. The coating surface is reported to be barely affected by movement of the inert drying gases due to the small amounts of gas required. No discussion of the criticality of the gas flow system or of the need to prevent mottle is given.

U.S. Pat. No. 5,077,912 describes a process for drying a continuously traveling web coated with a coating composition containing an organic solvent. The coating is first dried using hot air until the coating is set-to-touch. It is sufficient that the drying conditions, such as temperature and hot air velocity, are adjusted so as to obtain the set-to-touch condition. Set-to-touch corresponds to a viscosity of 10^8 to 10^{10} poise. Residual solvent is then removed using a heated roll. This method is said to reduce drying defects, decrease drying time, and reduce oven size. No discussion on the construction of the oven, methods of drying, or the criticality of the gas flow system and path is given.

U.S. Pat. No. 5,147,690 describes a process and apparatus for drying a liquid film on a substrate which includes a lower gas or air supply system and an upper gas or air supply system. Heated gas on the underside of the substrate forms a carrying cushion for the substrate and at the same time supplies drying energy to the substrate. The exhaust air is carried away through return channels. Slots for the gas supply and return are arranged alternately in the lower gas system. The upper gas or air supply system has a greater width than the lower gas or air supply system. In the upper gas or air supply system, the supply air or gas is diverted by baffles onto the substrate and returned over the substrate web as return air or gas. The upper gas or air supply system is subdivided into sections for the supply air and exhaust air, each section includes two filter plates of porous material.

U.S. Pat. No. 5,433,973 discloses a method of coating a magnetic recording media onto a substrate, wherein the coating is substantially free of Benard cells. The method comprises the steps of: (a) providing a dispersion comprising a polymeric binder, a pigment, and a solvent; (b) coating the dispersion onto the surface of a substrate; (c) drying the dispersion; (d) calculating values comprising μ, β, and d representing the viscosity, temperature gradient, and wet caliper of the dispersion respectively; and (e) during the course of carrying out steps (a), (b), and (c), maintaining the ratio

$$\beta\, d^2/\mu$$

below a threshold value sufficient to substantially prevent the formation of Benard Cells in the magnetic recording media coating. No discussion of the interior of the drying oven and arrangement of air inlets and exhausts is given.

A number of methods involve the control of the drying gas within the oven. For example, U.S. Pat. No. 5,001,845 describes a control system for an industrial dryer used to remove a flammable solvent or vapors from a traveling web of material. Sensors within each zone measure the oxygen content of the pressurized atmosphere. If the oxygen content

exceeds a given limit, an inert gas is added. At the same time, the pressure is maintained within the oven body by releasing excess gas to the atmosphere.

U.S. Pat. No. 5,136,790 describes a method and apparatus for drying a continuously moving web carrying a liquid, wherein the web is passed through a dryer in which the web is exposed to a recirculating flow of heated drying gas. Exhaust gas is diverted and discharged from the recirculating gas flow at a gas velocity which is variable between maximum and minimum levels, and makeup gas is added to the recirculating gas flow at a gas velocity which is also variable between maximum and minimum levels. A process variable is sensed and compared to a selected set point. A first of the aforesaid flow rates is adjusted to maintain the process variable at the selected set point, and a second of the aforesaid flow rates is adjusted in response to adjustments to the first drying gas velocity in order to insure that the first drying gas velocity remains between its maximum and minimum levels. No discussion of the interior of the drying oven and arrangement of air inlets and exhausts is given.

Soviet Pat. No. SU 1,276,889 describes a method for controlling drying gas by controlling the air gas velocity within the oven. In this method, fan speed in one zone is adjusted, controlling the air flow rate, in order to maintain the web temperature at the outlet to a specified temperature. This approach is limited in that increasing the air gas velocity in order to meet a drying specification can lead to mottle.

The physical state of the drying web can also be used to control the drying ovens. For example, in Soviet Pat. No. SU 1,276,889, noted above, the temperature of the web at the outlet of the oven was used to set the air flow rate.

U.S. Pat. No. 5,010,659 describes an infrared drying system for monitoring the temperature, moisture content, or other physical property at particular zone positions along the width of a traveling web, and utilizing a computer control system to energize and control for finite time periods a plurality of infrared lamps for equalizing physical property and drying the web. The infrared drying system is particularly useful in the graphic arts industry, the coating industry and the paper industry, as well as any other applications requiring physical property profiling and drying of the width of a traveling web of material. No discussion of the interior of the drying oven and arrangement of air inlets and exhausts is given.

U.S. Pat. No. 4,634,840 describes a method for controlling the drying temperature in an oven used for heat-treating thermoplastic sheets and films. A broad and continuous sheet or film is uniformly heated in a highly precise manner and with a specific heat profile by using a plurality of radiation heating furnaces, wherein in the interior of each radiation heating furnace, a plurality of rows of heaters are arranged rectangularly to the direction of delivery of the sheet or film to be heated. A thermometer for measuring the temperature of the sheet or film is arranged in the vicinity of an outlet for the sheet or film outside each radiation heating furnace. Outputs of heaters arranged within the radiation heating furnaces located just before the respective thermometers are controlled based on the temperatures detected by the respective thermometers by using a computer.

Two other patents address drying problems, but fail to address the problem of mottle. U.S. Pat. No. 3,849,904 describes the use of a mechanical restriction of air flow at the edge of a web. Adjustable edge deckles are noted as forming a seal with the underside of a fabric allowing for different heating conditions to occur at the edge. This allows the edge of the fabric to be cooled while the remainder of the fabric is heated. This approach, however, is not advantageous when a polymer substrate is used. Possible scratching of the polymer substrate can generate small particulates which can be deposited on the coating. U.S. Pat. No. 3,494,048 describes the use of mechanical means to divert air flow at the edge of the web. Baffles are noted as deflecting air and preventing air from penetrating behind paper in an ink dryer and from lifting the paper from a drum. Keeping the paper on the drum prevents the drying ink from being smeared.

A need exists for a drying apparatus and method which reduces, if not eliminates, one or more coating defects such as mottle and orange peel, yet permits high throughput. In addition to the drying of coatings used to make photothermographic, thermographic, and photographic articles, the need for improved drying apparatus and methods extends to the drying of coatings of adhesive solutions, magnetic recording solutions, priming solutions, and the like.

SUMMARY OF THE INVENTION

The present invention can be used to dry coated substrates, and particularly to dry coated substrates used in the manufacture of photothermographic, thermographic, and photographic articles. More importantly, the present invention can do this without introducing significant mottle and while running at higher web speeds than known drying methods.

One embodiment includes a method for evaporating a coating solvent from a coating on a first substrate surface of a substrate and minimizing the formation of mottle as the coating solvent is evaporating. The method includes the step of providing a drying oven having an enclosure having an inlet and an outlet and defining at least a first drying zone. The oven also includes the ability to create a plurality of drying subzones within the at least one first drying zone. At least two of the plurality of drying subzones employ different drying conditions. Physical barriers are not required to create the plurality of drying subzones. Another step includes controlling the drying conditions within the at least two of the plurality of drying subzones.

Another embodiment of the present invention is similar to the first embodiment but where a first plurality of subzones adjacent to the second substrate surface predominantly causes the evaporating of the coating solvent.

Another embodiment of the present invention is similar to the first embodiment but where an opening between the plurality of subzones is sufficiently large such that a pressure differential within the plurality of subzones created by the opening is insufficiently large to minimize the formation of mottle.

Another embodiment of the present invention is similar to the first embodiment but where the oven includes at least a first drying gas supply port and a second drying gas supply port and at least a first drying gas removal port and a second drying gas removal port. The first drying gas removal port is positioned relative to the first drying gas supply port to create a first drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the first drying gas supply port. The second drying gas removal port is positioned relative to the second drying gas supply port to create a second drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the second drying gas supply port.

Another embodiment of the present invention includes an apparatus for evaporating a coating solvent from a coating on a first substrate surface of a substrate and minimizing the

formation of mottle as the coating solvent is evaporating. The apparatus includes a drying oven having an enclosure having an inlet and an outlet and defining at least a first drying zone. The oven has the ability to create a plurality of drying subzones within the at least one first drying zone. At least two of the plurality of drying subzones employ different drying conditions. Physical barriers are not required to create the plurality of drying subzones. The apparatus has the ability to control the drying conditions within the at least two of the plurality of drying subzones.

Another embodiment of the present invention is similar to the previous embodiment, but where a first plurality of subzones adjacent to the substrate second surface predominantly causes the evaporating of the coating solvent.

Another embodiment is similar to the first apparatus embodiment noted above, but where an opening between the plurality of subzones is sufficiently large such that a pressure differential within the plurality of subzones created by the opening is insufficiently large to minimize the formation of mottle.

Another embodiment is similar to the first apparatus embodiment noted above, but includes a first drying gas supply port and a second drying gas supply port and at least a first drying gas removal port and a second drying gas removal port. The first drying gas removal port is positioned relative to the first drying gas supply port to create a first drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the first drying gas supply port. The second drying gas removal port is positioned relative to the second drying gas supply port to create a second drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the second drying gas supply port.

As used herein:

"photothermographic article" means a construction comprising at least one photothermographic emulsion layer and any substrates, top-coat layers, image receiving layers, blocking layers, antihalation layers, subbing or priming layers, etc.

"thermographic article" means a construction comprising at least one thermographic emulsion layer and any substrates, top-coat layers, image receiving layers, blocking layers, antihalation layers, subbing or priming layers, etc.

"emulsion layer" means a layer of a photothermographic element that contains the photosensitive silver halide and non-photosensitive reducible silver source material; or a layer of the thermographic element that contains the non-photosensitive reducible silver source material.

Other aspects, advantages, and benefits of the present invention are disclosed and apparent from the detailed description, examples, and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing advantages, construction, and operation of the present invention will become more readily apparent from the following description and accompanying drawings.

FIG. **1** is a side view of a known drying apparatus;

FIG. **2** is a side view of another known drying apparatus;

FIG. **3** is a side schematic view of another known drying apparatus;

FIG. **4** is a side schematic view of another known drying apparatus;

FIG. **5** is a side view of a drying apparatus in accordance with the present invention;

FIG. **6** is a partial side view of the drying apparatus shown in FIG. **5**;

FIG. **7** is a partial sectional view of the drying apparatus shown in FIG. **6**;

FIG. **8** is a partial sectional view of the drying apparatus shown in FIG. **6**;

FIG. **9** is a sectional front view of the drying apparatus shown in FIG. **6**;

FIG. **10** is a side schematic view of an air foil and an air bar which are shown in FIGS. **5–9**;

FIG. **11** is a side view of an alternative embodiment of the drying apparatus shown in FIGS. **5–10**;

FIG. **12** is a side view of alternative embodiment of the drying apparatus shown in FIGS. **5–11**;

FIG. **13** is a graph illustrating the constant temperature of a drying gas within a drying oven and the resulting coating temperatures as a function of distance traveled within the oven;

FIG. **14** is a graph illustrating the maximum allowable heat transfer rate and actual heat transfer rate to the coating as a result of the constant drying gas temperature illustrated in FIG. **13**;

FIG. **15** is a graph illustrating the resulting coating temperatures as a function of distance traveled within an oven when the coating is subjected to two different drying gas temperatures;

FIG. **16** is a graph illustrating the maximum allowable heat transfer rate and the actual heat transfer rate to the coating as a result of being subjected to the two drying gas temperatures illustrated in FIG. **15**;

FIG. **17** is a graph illustrating the resulting coating temperatures as a function of distance traveled within an oven when the coating is subjected to three different drying gas temperatures;

FIG. **18** is a graph illustrating the maximum allowable heat transfer rate and the actual heat transfer rate to the coating as a result of being subjected to the three drying gas temperatures illustrated in FIG. **17**;

FIG. **19** is a graph illustrating the resulting coating temperatures as a function of distance within an oven when the coating is subjected to fifteen different drying gas temperatures;

FIG. **20** is a graph illustrating the maximum allowable heat transfer rate and the actual heat transfer rate to the coating as a result of being subjected to the fifteen drying gas temperatures illustrated in FIG. **19**;

FIG. **21** is a graph illustrating the resulting coating temperatures as a function of distance within an oven when the coating is subjected to fifteen different drying gas temperatures where the maximum allowable heat transfer rate increases along the length of the oven;

FIG. **22** is a graph illustrating the maximum allowable heat transfer rate and the actual heat transfer rates to the coating as a result of being subjected to the fifteen drying gas temperatures illustrated in FIG. **19**; and

FIG. **23** is a side view of another embodiment of the drying apparatus shown generally in FIG. **5**.

DETAILED DESCRIPTION OF THE INVENTION

A drying apparatus **10** is illustrated generally in FIG. **5** and more specifically in FIGS. **6–10**. This drying apparatus **10** is useful for drying a coating **12** which has been applied to (i.e., coated onto) a substrate **14** forming a coated sub-

strate **16**. When the coating **12** comprises a film-forming material or other solid material dissolved, dispersed, or emulsified in an evaporable liquid vehicle, drying means evaporating the evaporable liquid vehicle (e.g., solvent) so that a dried, film or solids layer (e.g., an adhesive layer or a photothermographic layer) remains on the substrate **14**. Hereinafter, the more generic "evaporable liquid vehicle" will herein be referred to as a "solvent."

While suitable for a wide variety of coatings, the drying apparatus **10** is particularly suited for drying photothermographic and thermographic coatings to prepare photothermographic and thermographic articles. The drying apparatus **10** has the ability to dry such coatings in a relatively short period of time while minimizing the creation of drying-induced defects, such as mottle. The following disclosure describes embodiments of the drying apparatus **10**, embodiments of methods for using the drying apparatus **10**, and details pertaining to materials particularly suited for drying by the drying apparatus **10**.

The Drying Apparatus **10**

FIGS. **5–10** show an embodiment of the drying apparatus **10** which generally can include a drying enclosure **17** with a first zone **18** and a second zone **20**. The first and second zones **18**, **20** can be divided by a zone wall **22**. As will become more apparent later within this disclosure, the first zone **18** is of primary importance. The first zone **18** and the second zone **20** can each provide different drying environment. In addition, the first zone **18** can provide a plurality of drying environments therein, which will be discussed further.

The substrate **14** can be unwound by a substrate unwinder **24**, and the coating **12** is shown as being coated onto the substrate **14** by coating apparatus **26**. The coated substrate **16** can enter the drying apparatus **10** through a coated substrate entrance **27** and be dried when traveling through the first and second zones **18**, **20**. The coated substrate can exit the drying apparatus **10** through a coated substrate exit **28** then be wound at the coated substrate winder **29**. Although the coated substrate **16** is shown as following an arched path through the first zone **18**, the path could be flat or have another shape. And, although the coated substrate **16** is shown being redirected within zone **2** such that the coated web takes three passes through zone **2**, the drying apparatus **10** could be designed such that fewer or more passes occur.

The first zone **18** is more specifically shown in FIGS. **6–10** as including a number of air foils **30** which are located below the coated substrate **16** along the length of the first zone **18**. The air foils **30** supply drying gas (e.g., heated air, inert gas) toward the bottom surface of the coated substrate **16** such that the coated substrate can ride on a cushion of drying gas. Drying gas is supplied to a group of air foils **30** by an air foil plenum **31**.

The temperature and gas velocity of the drying gas supplied from a group of air foils **30** can be controlled by controlling the temperature and pressure of the drying gas in the corresponding air foil plenum **31**. Consequently, independent control of the temperature and pressure of the drying gas within each air foil plenum **31** allows for independent control of the temperature and gas velocity of the drying gas supplied by each group of air foils **30**.

Although each air foil plenum **31** is shown as supplying a group of either twelve or fifteen air foils **30**, other ducting arrangements could be used. An extreme example would be for one air foil plenum **31** to supply drying gas to only one air foil **30**. With this arrangement, independent control of the temperature and pressure for each air foil plenum **31** would result in independent control of the temperature and gas velocity of the drying gas exiting from each air foil **30**.

Each of the air foils can have a foil slot (the side view of which is shown in FIG. **10**) through which a stream of drying gas enters into the drying apparatus **10**. The foil slot can have a slot width which is not significantly wider than the substrate width such that mottle on the first and second coating edges is minimized. Setting the width in this way affects the flow of the drying gas around the edges of the substrate. When the foil slot width is approximately equal to or narrower than the width of the substrate, mottle on the edges of the liquid is reduced.

FIG. **10** illustrates the flow of air out of a foil slot of an air foil **30** and FIG. **7** illustrates the length of air foils **30**. Because the slot can be made to extend to the ends of the air foil **30**, the slot length can virtually be as long as the length of the air foil **30**. Because the drying apparatus **10** can be used to dry coated substrates **16** having a widths which are significantly less than the foil slot length (as well coated substrates **16** having widths approximately equal to or even wider than the foil slot length), one or both of the ends of the foil slot can be deckled such that the foil slot length is approximately equal to the width of the narrower coated substrates. The length of the slots can be deckled or adjusted by covering more or less of the ends of the slots with a material such as an adhesive tape. Alternatively, a metal plate at each edge of the foil slots could be inwardly and outwardly movable to close off more or less of the foil slot. Also, ends of the slots could be plugged with a material, such as a conformable material (e.g., rubber).

Lower exhaust ports **32** are positioned below the air foils **30** to remove the drying gas, or at least a portion of the drying gas, supplied by the air foils **30**. The drying gas exhausted by a group of lower exhaust ports **32** is exhausted into a lower exhaust plenum **33**. Five lower exhaust plenums **33** are shown, each of which is connected to two lower exhaust ports **32**. Lower exhaust ports **32** are distributed throughout the lower interior portion of the drying apparatus **10** to remove drying gas throughout the drying apparatus **10** rather than at concentrated points. Other similar ducting arrangements are envisioned.

The velocity of the drying gas through a lower exhaust port **32** can largely be controlled by controlling the static pressure difference between the lower interior portion of the drying apparatus **10** (the interior portion below the coated substrate level) and some suitable reference point (e.g., the coating room in which the coating apparatus **26** is positioned; or, each lower exhaust plenum **33**). As a result, independent control of the static pressure difference between the lower interior portion of the drying apparatus **10** and each lower exhaust plenum **33** allows for independent control of the gas velocity exhausted by the group of lower exhaust ports **32** of each lower exhaust plenums **33**.

The combination of the ability to independently control the drying gas supplied by each air foil plenum **31** (temperature and gas velocity) and the ability to independently control the drying gas exhausted by each exhaust plenum **33** allows for the creation of lower subzones within the first zone **18** of the drying apparatus **10**. As shown, the first zone **18** has five lower subzones due to the independent control of five air foil plenums **31** and five lower exhaust plenums **33**. As a result, the five lower subzones can contain drying gas with a unique temperature and a unique gas velocity (or other heat transfer coefficient factor). In other words, the coated substrate **16** can be subjected to five different drying environments (subzones).

The flow direction of the drying gas from the air foils **30** can be controlled based on the configuration of the air foils. As shown in FIG. **10**, the air foils **30** can be configured to

initially supply drying gas cocurrently with the travel direction of the coated substrate and against the bottom surface of the coated substrate **16** to create a cushion of air on which the coated substrate floats. The airfoils **30** can be designed such that the drying gas flows essentially parallel to the coated substrate **16** and such that the coated substrate **16** floats approximately 0.3 to 0.7 centimeters above the upper portion of the airfoils **30**. While shown as causing cocurrent gas flow to the substrate travel direction, the air foils **30** could configured to cause the drying gas to impinge on the substrate second surface, to flow generally countercurrently to the substrate travel direction, to flow generally orthogonally to the substrate travel direction, or to flow generally diagonally to the substrate travel direction.

Air bars **34** are located above the coated substrate **16** along the length of the first zone **18**. The air bars **34** can be used to supply top-side gas (e.g., fresh air, inert gas) which can be useful for added drying, to carry away evaporated solvent, and/or to dilute the solvent if it is necessary to control the solvent level within the drying enclosure **17**. The top-side gas is supplied to a group of air bars **34** by an air bar plenum **35**. Although each air bar plenum **35** is shown as supplying a particular number of air bars **34**, other ducting arrangements are envisioned. If desired, the drying apparatus **10** can be used such that no gas is supplied by the air bars **34** when top-side gas is not needed or desired (e.g., when the drying apparatus **10** is filled with inert gas).

The velocity of the top-side gas supplied from a group of air bars **34** can be controlled by controlling the static pressure difference between the upper interior portion of the drying apparatus **10** (the portion above the coated substrate level) and the corresponding air bar plenum **35**. Independent control of the static pressure difference between the upper interior portion of the drying apparatus **10** and an air bar plenum **35** allows for independent control of the temperature and gas velocity of the top-side gas supplied by the corresponding group of air bars **34**.

Upper exhaust ports **36** are positioned above the air bars **34** to remove at least a portion of the gas supplied by the air bars **34** and can remove at least a portion of the solvent which is evaporating from the coated substrate **16**. The top-side gas exhausted by a group of upper exhaust ports **36** is exhausted into an upper exhaust plenum **37**. Five upper exhaust plenums **37** are shown, each of which is connected to two upper exhaust ports **36**. Upper exhaust ports **36** are distributed throughout the upper interior portion of the drying apparatus **10** to remove top-side gas throughout the drying apparatus **10** rather than at concentrated points. Other similar ducting arrangements are envisioned.

The gas velocity of the top-side gas through a group of upper exhaust ports **36** can largely be controlled by controlling the static pressure difference between the upper interior portion of the drying apparatus **10** and some suitable reference point (e.g., the coating room in which the coating apparatus **26** is position, or each upper exhaust plenum **37**). Consequently, independent control of the static pressure difference between the upper interior portion of the drying apparatus **10** and each upper exhaust plenum **37** allows for independent control of the gas velocity exhausted by the group of upper exhaust ports **36** of each upper exhaust plenum **37**.

FIG. **10** illustrates a side view of an air bar **34**. Top-side gas is shown exiting two openings. The length of the openings for the air bar **34** can be approximately equal to or less than the length of the air bar **34**. If each opening were instead a series of discrete holes rather than a single opening, the air bar **34** would be considered a perforated plate, or even a foraminous plate. A perforated or formanous plate could be used in place of the air bar **34**, as could other sources of top-side gas (e.g., air turn, air foil).

The locations of pyrometers **38**, static pressure gages **39**, and anemometers **40** are shown in FIG. **5**. These known instruments can be used to measure the temperature, static pressure, and gas velocity of the drying gas at various locations within the drying apparatus **10**. The measurements taken by these instruments can be directed to a central processing unit or other controlling mechanism (not shown) which can be used to control the conditions within the oven **10** by altering the drying gas temperature and pressure within the plenums.

To provide the necessary heat to the coated substrate to evaporate the coating solvent (i.e., the solvent portion of the coating), the drying gas can be air or an inert gas. Or, the use of a drying gas can be replaced or augmented with the use of heated rolls **50** on which the coated substrate can ride, as shown in FIG. **11**. Similarly, infrared heat can be used in place of the drying gas such as with the spaced infrared heaters shown in FIG. **12** or with a heated plate positioned above or below the coated substrate **16**. The temperature of each heated roller **50** or infrared heater **52** (or a group of rollers **50** or infrared heaters **52**) can be independently controlled.

Methods For Drying Using the Drying Apparatus **10**

It has been found that coatings can be dried without introducing significant mottle defects by controlling the heat transfer rate to the coating **12** and by minimizing disturbances of the gas adjacent to the coated side of the coated substrate **16** (i.e., top-side gas; see Examples Section). When the coating solvent is evaporated using a drying gas, as for example in a drying apparatus **10**, the heat transfer rate ($h\Delta T$) to the coated substrate is the product of the heat transfer coefficient of the drying gas (h) and the difference in temperature (ΔT), between the temperature of the drying gas in contact with it (T_{gas}) and the temperature of the coated substrate (T_{cs}). (The temperature of the coating **12** is assumed to equivalent to the temperature of the coated substrate. The heat transfer rate to the coating **12** is the key to preventing or minimizing mottle formation.) In order to prevent mottle formation in the coating **12** during drying, this heat transfer rate ($h\Delta T$) to the coating **12** must be kept below a threshold mottle-causing value. When a particular substrate **14** is used, the heat transfer rate to the coated substrate **16** must be kept below a corresponding threshold mottle-causing value.

As a particular coating **12** is dried (or otherwise solidified), it will eventually reach a point in which it becomes virtually mottle-proof At this point, the heat transfer rate can be significantly increased by increasing the temperature difference ΔT and/or by increasing the heat transfer coefficient h (e.g., by increasing the velocity of the drying gas on either the coated side or the non-coated side of the coated substrate **16**).

For a typical drying zone, the heat transfer coefficient h and the drying gas temperature T_{gas} are relatively constant and the temperature of the coated substrate **16** (and the coating **12**) increases as the coated substrate **16** is heated. Therefore, the product ($h\Delta T$) has its maximum value at the initial point of the zone. Often, it is sufficient to keep the initial heat transfer rate to the coating ($h\Delta T_i$) below a maximum allowable (threshold) value in order to avoid mottle in a particular drying zone.

The most efficient process for drying a coating (i.e., evaporating a coating solvent) will be one that adds heat most quickly without causing mottle. As the coated substrate

temperature T_{cs} increases, the heat transfer rate (hΔT) decreases along the drying zone making the drying zone less efficient (due to the smaller ΔT). The total amount of heat transferred to the coated substrate (q) can be calculated by integrating the product (hΔT) across the length of the oven and the width of the coating. When the coating width is relatively constant, the total amount of heat transferred to the coated substrate **16** is proportional to the area under the heat transfer rate curves described and shown below. Maximizing the area under the curve maximizes the heat transferred to the coated substrate and maximizes the efficiency of the drying process.

The maximum allowable or threshold heat transfer rate of a particular coating varies proportionately to the viscosity of the coating **12**. A coating having less thickness or a higher viscosity would have a higher maximum allowable or threshold heat transfer rate. This also means that, as the coating **12** is further dried, the viscosity will increase and the coating thickness will decrease thereby increasing the threshold heat transfer rate. Consequently, the coating can be heated at an increasingly higher heat transfer rate as the threshold temperature curve allows. Furthermore, the coating **12**, as previously noted, will eventually be dried to a point of being mottle-proof (i.e., not susceptible to mottle by the gas temperature nor by the gas velocity and any other factor affecting the heat transfer coefficient h).

In the following discussion, the heat transfer coefficient h, of the drying gas is kept constant and the drying gas temperature T_{gas} is allowed to vary. When there is a maximum heat transfer rate $(h\Delta T)_{max}$ that can occur without causing mottle, there will then be a given maximum allowable difference between the temperature of the drying gas and the temperature of the coated substrate **16**.

Instead of varying the gas temperature, the temperature can be held constant while varying the heat transfer coefficient h. If the velocity of the drying gas is used to vary the heat transfer coefficient, the velocity must be kept below a maximum allowable or threshold velocity to prevent mottle.

The advantage of the additional zones is described in the Examples Section and illustrated in FIGS. **13–22**. Table 1 below shows typical drying gas and coated substrate temperatures for the drying conditions described below and for a particular coated substrate **16**. Cooling of the web due to solvent evaporation is assumed negligible for the discussion below.

TABLE 1

Typical Drying Conditions Which Correspond With FIGS. 13–22.

Heat Transfer Coefficient - h	5 cal/sec-m^2-° C.
Initial Coated Substrate Temperature T_{csi}	20° C.
Maximum Heat Transfer Rate Without Mottle Formation - hΔT	150 cal/sec-m^2
Drying Length	30 m
Width of Coating on Substrate	1 m

FIG. **13** shows typical temperature curves for the coated substrate **16**. The coated substrate **16**, initially at 20° C., is subjected to a constant drying gas temperature of 50° C. The temperature of the coated substrate **16** slowly increases over the length of the drying zone (30 m) until it reaches the temperature of the drying gas. FIG. **14** shows the product hΔT at any given location as drying proceeds. At all times, the heat transfer rate is at or below the maximum allowable heat transfer rate of 150 cal/sec-m^2 and mottle is not caused. The amount of heat transferred to the coated substrate **16** per unit time drops off as the temperature of the coated substrate T_{cs} increases. At the end of the drying zone this amount is significantly less than the maximum allowable heat transfer rate. Thus, the process is much less efficient than it could be.

FIGS. **15** and **16**, demonstrate the advantage when the drying process is divided into two equal zones. The advantage of the second zone is that the drying gas temperature, T_{gas} can be increased allowing the product hΔT to increase and drying in the second zone can take place more rapidly. Again, at all times the product hΔT is kept below 150 cal/sec-m^2, the maximum allowable heat transfer rate without causing mottle. It should be noted that the total heat transferred to the coated substrate, represented by the area under the heat transfer rate curve in FIG. **16** is now considerably larger than for the case where only one zone is used.

Similarly, FIGS. **17** and **18** demonstrate that the total amount of heat transferred for drying is even greater and the process more efficient when three heating environments or zones are used. When 15 heating environments or zones are used as shown in FIGS. **19** and **20**, the process is even more efficient. In an extreme limit, where the drying environments or zones are infinitesimally small in size and infinite in number, the drying gas temperature can be continuously increased to maximize the allowable heat transfer rate to the coated substrate while still avoiding mottle.

FIGS. **13–20** represent a simplified case. In reality, as the coating solvent begins to evaporate (e.g., coating begins to dry), its viscosity increases and its thickness decreases. As a result, the maximum possible heat transfer rate (hΔT) to the partially dried coating can be increased without formation of mottle. FIGS. **21–22** show that by increasing the heat transfer rate to correspond to the increasing maximum allowable heat transfer rate, the rate of drying can be increased even more rapidly than the simplified case shown in FIGS. **19–20** in which maximum allowable heat transfer rate is assumed constant.

Table 2 shows the total amount of heat (q) transferred to the coated substrate for different numbers of drying environments or zones.

TABLE 2

Drying Variables for FIGS. 13–19, and 22.

Subzones	Total Amount of Heat Transferred (cal/sec)	Corresponding Figs.
1	1427	13, 14
2	2389	15, 16
3	2936	17, 18
15	4269	19, 20
∞	4500	No Fig.
15*	5070	21, 22

*With increasing maximum allowable heat transfer rate.

Further advantages and efficiency can be gained by using subzones of unequal size. For example, a larger number of smaller subzones will be advantageous in regions where the maximum allowed heat transfer rate is changing most quickly. It is also possible for evaporative cooling to lower the temperature of the coated substrate T_{cs} within a drying subzone and the product (hΔT) would then be at a maximum at some intermediate point within the subzone.

As previously noted, one aspect of a method for drying includes controlling the temperature and the heat transfer coefficient h within locations or subzones of the drying oven **10**, in particular, the first zone **18**. This can be accomplished primarily by controlling the temperature and gas velocity of the drying gas delivered by the air foil plenums **31** and

removed by the lower exhaust plenum **33**. The rate at which a particular air foil plenum **31** supplies drying gas and the rate at which the corresponding lower exhaust plenum **33** removes the drying gas allows a user to balance the two and virtually create a subzone having a particular gas temperature and velocity. Similar control of corresponding pairs of plenums **31**, **33** allow for control of the temperature and gas velocity of the drying gas within several subzones. As a result, the heat transfer rate to the coating **12** can be controlled and maximized within several subzones. Within a first subzone, for example, the velocity of the gas on the coated side and relative to the coated side should be not greater than a top-side gas velocity threshold, such as 150 ft/min (46 m/min) to protect a mottle-susceptible photothermographic coating **12** (e.g., the photothermographic coating described in Example 1 below).

It is important to further note that the first zone **18** is shown as an open body. In other words, the first zone **18** is shown as not including slotted vertical walls (or other physical structures with openings) to act as a barriers between the previously described subzones. Control of the heat transfer rate within individual subzones can be accomplished without the need for physical barriers. Although physical barriers could be used, they are not needed nor preferred due to possibly adverse air flow effects which can result (i.e., high velocity flow of drying gas through the slot in a vertical wall). In addition, physical barriers with openings between the subzones (to allow transport of the moving coated substrate) could be used. But, preferably, the openings would be sufficiently large to minimize the pressure differential between subzones such that the formation of mottle is minimized or prevented.

It is also important to note that the temperature and gas velocity of the drying gas within a particular subzone and within the first zone **18** as a whole can be controlled with the use of the previously noted pyrometers **38**, static pressure gauges **39**, anemometers **40**, and the previously noted controlling mechanism (not shown). The pyrometers **38** can sense the temperature of the coated substrate T_{cs}. The static pressure gauges **39** can sense the static pressure difference between a location within the interior of the drying apparatus **10** and some reference point (such as outside the drying apparatus **10** or within a nearby plenum). The anemometers **40** can sense the velocity of the drying gas.

The measurements from the pyrometers **38**, static pressure gauges **39**, and the anemometers **40** can allow the controlling mechanism and/or a user to adjust the heat transfer rate (temperature of the drying gas, heat transfer coefficient) to minimize mottle formation (at or below the maximum allowable or threshold heat transfer rate). For example, the pyrometers **38** can be positioned to sense the actual temperature of the coated substrate T_{cs} as the coated substrate is exiting one subzone and entering a downstream subzone. Based on that actual temperature versus a targeted temperature, the previously noted controlling mechanism can determine and set the heat transfer rate in the downstream subzone to be at or below the maximum allowable or threshold heat transfer rate. This controlling ability could be referred to as a feedforward strategy for a temperature set point.

Similarly, the controlling mechanism could compare the actual and the targeted temperatures and adjust the heat transfer rate in an upstream subzone to be at or below the maximum allowable or threshold heat transfer rate. This controlling ability could be referred to as a feedback loop or strategy. The targeted temperature, previously noted, can be experimentally determined so that the heat transfer rate to the coated substrate **16** can be monitored and adjusted accordingly.

Having both static pressure gauges **39** and anemometers **40**, a user has the choice as to how to control the gas velocity and direction. These two instruments could be used individually or in a coordinated fashion to control gas velocity and direction by controlling the volume of gas being exhausted from the drying apparatus **10**.

Control of the static pressure differences within the first zone **18** can be used to manage the gas flow through the first zone **18**. While the gas within each subzone was previously described as being managed such that gas flow from subzone to another is minimized, controlling static pressure differences across the entire first zone **18** can provide the ability to create a controlled degree of gas flow from one subzone to another. For example, the pressure P_1 within an upstream upper exhaust plenum **37** could be slightly higher than the pressure P_2 in a downstream upper exhaust plenum **37** such that the top-side gas flows at a low velocity in the downstream direction (i.e., cocurrent flow). This could be intentionally done to create a gas velocity of the top-side gas that approximately matches the velocity of the coated substrate **16**. Matching the velocities in this way can minimize disturbances on the coated side of the coated substrate **16**. Alternatively, a countercurrent flow could be induced instead of the cocurrent flow; or, a combination of cocurrent and countercurrent flows could be induced.

One can control static pressure differences to manage gas flow between the upper and lower interior portions of the drying apparatus **10**. For example, setting the pressure P_{top} above the coated substrate **16** at a higher value than the pressure P_{bottom} below the coated substrate **16** biases the exhaust of the gas to the lower interior portion. This approach may be desired to prevent the hotter drying gas below the coated substrate from flowing upwardly and contacting the coating. Alternatively, the pressures could be biased oppositely so that a portion of the drying gas below the coated substrate flows upwardly and is exhausted from the upper exhaust ports **36**, or the pressures could be adjusted such that flow between the upper and lower interior portions of the drying apparatus **10** is minimized.

It is also important to note that when the temperature of the coating **12** is increased to be virtually the same as the temperature of the drying gas, the flow of the drying gas can be reduced. Similarly, when the temperature of the coating **12** is increased to a desired temperature (even if different from the drying gas temperature), again, the flow of the drying gas can be reduced. This results in more a more efficient evaporating process. In other words, less energy is required and less cost is involved.

It is also important to note that the heat transfer coefficient h has been primarily discussed as being controlled by the velocity of the drying gas. Other factors that affect the heat transfer coefficient h include the distance between the air foil **30** and the coated substrate **16**, the density of the drying gas, and the angle at which the drying gas strikes or impinges upon the coated substrate **16**. For embodiments of the present invention which includes heating means other than air foils and air bars (e.g., perforated plates, infrared lamps, heated rollers, heated plates, and/or air turns), additional factors affecting the heat transfer coefficient are present.

Materials Particularly Suited For Drying By Drying Apparatus **10**

Any mottle-susceptible material, such as graphic arts materials and magnetic media, can be dried using the above-described drying apparatus **10** and methods. Materials particularly suited for drying by the drying apparatus **10** are photothermographic imaging constructions (e.g., silver halide-containing photographic articles which are developed

with heat rather than with a processing liquid). Photothermographic constructions or articles are also known as "dry silver" compositions or emulsions and generally comprise a substrate or support (such as paper, plastics, metals, glass, and the like) having coated thereon: (a) a photosensitive compound that generates silver atoms when irradiated; (b) a relatively non-photosensitive, reducible silver source; (c) a reducing agent (i.e., a developer) for silver ion, for example for the silver ion in the non-photosensitive, reducible silver source; and (d) a binder.

Thermographic imaging constructions (i.e., heat-developable articles) which can be dried with the drying apparatus **10** are processed with heat, and without liquid development, are widely known in the imaging arts and rely on the use of heat to help produce an image. These articles generally comprise a substrate (such as paper, plastics, metals, glass, and the like) having coated thereon: (a) a thermally-sensitive, reducible silver source; (b) a reducing agent for the thermally-sensitive, reducible silver source (i.e., a developer); and (c) a binder.

Photothermographic, thermographic and photographic emulsions used in the present invention can be coated on a wide variety of substrates. The substrate (also known as a web or support) **14**, can be selected from a wide range of materials depending on the imaging requirement. Substrates may be transparent, translucent or opaque. Typical substrates include polyester film (e.g., polyethylene terephthalate or polyethylene naphthalate), cellulose acetate film, cellulose ester film, polyvinyl acetal film, polyolefinic film (e.g., polethylene or polypropylene or blends thereof), polycarbonate film and related or resinous materials, as well as aluminum, glass, paper, and the like.

EXAMPLES

The following examples provide exemplary procedures for preparing and drying articles of the invention. Photothermographic imaging elements are shown. All materials used in the following examples are readily available from standard commercial sources, such as Aldrich Chemical Co., Milwaukee, Wis., unless otherwise specified. All percentages are by weight unless otherwise indicated. The following additional terms and materials were used.

Acryloid™ A-21 is an acrylic copolymer available from Rohm and Haas, Philadelphia, Pa.

Butvar™ B-79 is a polyvinyl butyral resin available from Monsanto Company, St. Louis, Mo.

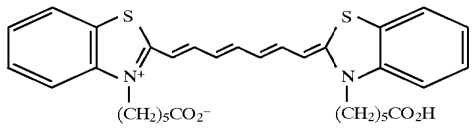
CAB 171-15S is a cellulose acetate butyrate resin available from Eastman Kodak Co.

CBBA is 2-(4-chlorobenzoyl) benzoic acid.

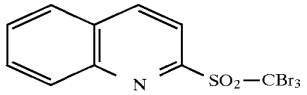
1,1-bis(2-hydroxy-3,5-dimethylphenyl)-3,5,5-trimethylhexane [CAS RN=7292-14-0] is available from St-Jean Photo Chemicals, Inc., Quebec. It is a reducing agent (i.e., a hindered phenol developer) for the non-photosensitive reducible source of silver. It is also known as Nonox™ and Permanax™ WSO.

THDI is a cyclic trimer of hexamethylenediisocyanate. It is available from Bayer Corporation Co., Pittsburgh, Pa. It is also known as Desmodur™ N-3300.

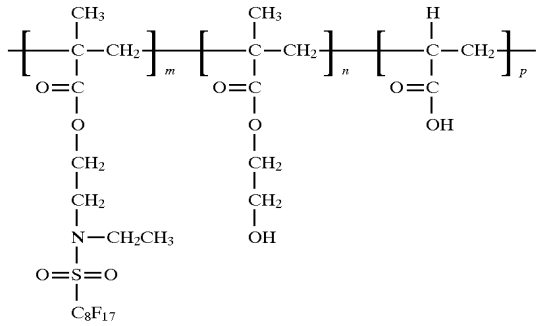
Sensitizing Dye-1 is described in U.S. Pat. No. 5,393,654 which is hereby incorporated by reference. It has the structure shown below.



2-(Tribromomethylsulfonyl)quinoline is disclosed in U.S. Pat. No. 5,460,938 which is hereby incorporated by reference. It has the structure shown below.



The preparation of Fluorinated Terpolymer A (FT-A) is described in U.S. Pat. No. 5,380,644, which is hereby incorporated by reference. It has the following random polymer structure, where m=70, n=20 and p=10 (by weight % of monomer).



Example 1

A dispersion of silver behenate pre-formed core/shell soap was prepared as described in U.S. Pat. No. 5,382,504 which is hereby incorporated by reference. Silver behenate, Butvar™ B-79 polyvinyl butyral and 2-butanone were combined in the ratios shown below in Table 3.

TABLE 3

Silver behenate dispersion	
Component	Weight Percent
Silver behenate	20.8%
Butvar ™ B-79	2.2%
2-Butanone	77.0%

Then, a photothermographic emulsion was prepared by adding 9.42 lb. (4.27 Kg) of 2-butanone and a premix of 31.30 g of pyridinium hydrobromide perbromide dissolved in 177.38 g of methanol to 95.18 lb. (43.17 Kg) of the preformed silver soap dispersion. After 60 minutes of mixing, 318.49 g of a 15.0 wt % premix of calcium bromide in methanol was added and mixed for 30 minutes. Then, a premix of 29.66 g of 2-mercapto-5-methylbenzimidazole, 329.31 g of 2-(4-chlorobenzoyl)benzoic acid, 6.12 g of Sensitizing Dye-1, and 4.76 lb. (2.16 Kg) of methanol was added. After mixing for 60 minutes, 22.63 lb. (10.26 Kg) of Butvar™ B-79 polyvinyl butyral resin was added and allowed to mix for 30 minutes. After the resin had dissolved, a premix of 255.08 g of 2-(tribromomethylsulfonyl)

quinoline in 6.47 lb. (2.93 Kg) of 2-butanone was added and allowed to mix for 15 minutes. Then 5.41 lb. (2.45 Kg) of 1,1-bis(2-hydroxy-3,5-dimethylphenyl)-3,5,5-trimethylhexane was added and mixed for another 15 minutes. Then a premix of 144.85 g of THDI and 72.46 g of 2-butanone was added and mixed for 15 minutes. Next, 311.61 g of a 26.0% solution of tetrachlorophthalic acid in 2-butanone was added and mixed for 15 minutes. Finally, a solution of 243.03 g of phthalazine and 861.64 g of 2-butanone was added and mixed for 15 minutes.

A top-coat solution was prepared by adding 564.59 g of phthalic acid to 30.00 lb. (13.61 Kg) of methanol and mixing until the solids dissolved. After adding 174.88 lb. (79.3 Kg) of 2-butanone, 149.69 g of tetrachlorophthalic acid was added and mixed for 15 minutes. Then, 34.38 lb. (15.59 Kg) of CAB 171-15S resin was added and mixed for 1 hour. After the resin had dissolved, 2.50 lb. (1.13 Kg) of a 15.0 wt-% solution of FT-A in 2-butanone was added and mixed for 10 minutes. Then a premix of 26.33 lb. (11.94 Kg) of 2-butanone and 630.72 g of Acryloid A-21 resin and a premix of 26.33 lb. (11.94 Kg) of 2-butanone, 796.60 g of CAB 171-15S resin, and 398.44 g of calcium carbonate were added and mixed for 10 minutes.

A drying apparatus **10**A like that shown in FIG. **23** herein was used to prepare a photothermographic article. (The first zone **18**A within the drying apparatus **10**A shown in FIG. **23** does not have the ability to create subzones.) A polyester substrate having a thickness of 6.8 mil (173 μm) was simultaneously coated with the photothermographic emulsion and top-coat solutions at 75 ft/min (0.38 meters per second). The photothermographic emulsion layer was applied at a wet thickness of 3.2 mil (81.3 μm). The top-coat solution was applied at a wet thickness of 0.75 mil (19.1 μm). After passing the coating die, the coated substrate **16**A traveled a distance of about 13 feet (4 meters) and passed through an entrance slot into a dryer composed of 3 zones. The first zone **18**A was comprised of air foils **30**A below the coated substrate **16**A which provided drying gas and also provide flotation for the coated substrate **16**A. There were also perforated plate-type air bars **34**A positioned 20 centimeters above the coated substrate **16**A which provided top-side gas to maintain safe operating conditions below the lower flammability limit of the solvent. The majority of the drying heat is provided by the backside airfoils **30**A (i.e., heat provided from below the substrate **14**A to the coating **12**A). The air temperature was set to the same value in each zone, however, the air pressure, hence the air velocity, was independently controlled for the air foils **30**A and air bars **34**A. The coating **12**A was dried to be mottle proof within the first oven zone. The second and third oven zones **20**A, **21**A used counter-current parallel air flow and served to remove the residual solvent. (In the figures, air flow direction is shown with the included arrows.)

The variables investigated were the temperature of the drying gas T_{gas} and heat transfer coefficient h. The heat transfer coefficient h was varied by adjusting the air foil pressure drop and was measured independently.

The presence and severity of mottle was determined by preparing "greyouts." Greyouts are samples that have been uniformly exposed to light and developed at 255° F. (124° C.) using a heated roll processor (not shown) so that they have a uniform Optical Density, for example between 1.0 and 2.0.

The amount of mottle was subjectively determined by comparing samples placed on a light box. The developed films were visually inspected for mottle and rated relative to one another. Mottle was rated as high, medium, or low.

The conditions used in the first zone **18**A and results obtained are summarized below in Table 4. As ΔP_{bot} or T_{gas} was increased, the level of mottle was increased.

TABLE 4

	First Zone Conditions				
Example	ΔP_{bot} (kPa)	ΔP_{top} (kPa)	T_{gas} (° C.)	ΔP_{static} (Pa)	Mottle Rating
1-1	0.125	0.025	37.8	−0.5	Low
1-2	0.500	0.025	37.8	−0.5	Medium
1-3	0.125	0.025	60.0	−0.5	High

ΔP_{bot} is the pressure drop across the airfoils 31A.
ΔP_{top} is the pressure drop across the air bars 34A.
T_{gas} is the temperature of the heated drying gas.
ΔP_{static} is the pressure drop between the first zone 18A and the coater room (not shown).
The negative sign indicates that the drying apparatus 10A is at lower pressure than the coater room. This value was maintained by modulating the exhaust fan (not shown).

Drying more harshly increased the severity of the mottle. If one were to consider increasing the drying conditions only in terms of the available operating parameters, one would not make the appropriate conclusions concerning the affects on mottle. Changing the pressure drop from 0.125 to 0.5 kPa is a factor of 4 increase. An appropriate temperature measure is the difference between the drying gas and the substrate as it enters the zone. This temperature measure increases a factor of 2.3 as the gas temperature increased from 37.8 to 60° C. One would expect that changing the air foil pressure drop would have the larger effect on mottle, however, the opposite is true.

In order to determine the effect on mottle, one needs to consider a more appropriate measure such as the product of the heat transfer coefficient and the difference between the temperature of the drying gas T_{gas} and the temperature of the coated substrate T_{cs} as it enters the zone. This product is the rate of heat transferred to the film and is a direct measure of the rate of heating of the film. As shown below in Table 5, increasing the initial rate of heat transfer to the film, ($h\Delta T_i$), increased the severity of mottle.

TABLE 5

Example	ΔP_{bot} (kPa)	T_{gas} (° C.)	$T_{CS(i)}$ (° C.)	h (cal/m^2 s K)	$h\Delta T_i$ (cal/m^2 s)	Mottle Rating
1-1	0.125	37.8	21.1	13.7	229	Low
1-2	0.500	37.8	21.1	19.4	324	Medium
1-3	0.125	60.0	21.1	13.7	532	High

The term ΔT_i indicates the difference between T_{gas} and $T_{cs(i)}$.
The term $T_{CS(i)}$ is the initial temperature of the coated substrate just before it enters the drying apparatus 10A.

Example 2

Using the coating materials and oven described in Example 1, the photothermographic emulsion and top-coat solution were simultaneously coated at 3.6 mil (91.4 μm) and 0.67 mil (17.0 μm) respectively on 6.8 mil (173 μm) polyester substrate. Greyouts were prepared and rated as described in Example 1. The drying conditions used and results obtained, which are shown below in Table 6, demonstrate that as the initial heat transfer rate to the film ($h\Delta T_i$) was increased, the severity of mottle increased. More specifically, at a constant heat transfer coefficient, as the initial temperature difference between the coating **12**A and the drying gas was increased, the severity of mottle increased.

TABLE 6

Example	T_{gas} (° C.)	$T_{cs(i)}$ (° C.)	h (cal/m^2 s K)	$h\Delta T_i$ (cal/m^2 s)	Mottle Rating
2-1	37.8	21.1	13.7	229	Low
2-2	51.7	21.1	13.7	419	Medium
2-3	82.2	21.1	13.7	837	High

Example 3

Solutions were prepared as described in Example 1 and were simultaneously coated on a polyester substrate at 100 ft/min (0.508 meters per second). After passing the coating die, the substrate traveled a distance of approximately 10 feet (3 meters) and then passed through a slot into a dryer with 3 zones similar to FIG. **3**. The gas velocity of the counter-current parallel flow air was held constant and the temperature was varied as shown below in Table 7. As the initial rate of heat transfer ($h\Delta T_i$) to the coated substrate **16** was increased, the severity of mottle increased. Without considering the value of the heat transfer coefficient h, no direct comparisons between the ovens in Examples 2 and 3 is possible.

TABLE 7

Example	T_{gas} (° C.)	$T_{cs(i)}$ (° C.)	h (cal/m^2 s K)	$h\Delta T_i$ cal/m^2 s)	Mottle Rating
3-1	93.3	21.1	2.85	206	Low
3-2	71.1	21.1	2.58	129	Very Low

Example 4

Solutions were prepared as described in Example 1 and were simultaneously coated on a polyester substrate at 25 ft/min (0.127 meters per second). After passing the coating die, the substrate traveled a distance of 10 ft (3 meters) and then passed through a slot into a dryer with 3 zones similar the first zone **18**A of FIG. **23**. This is an oven with air foils on the bottom, air bars on the top, and an overall flow of air through the oven. The atmosphere is inert gas and the partial pressure of solvent could be controlled using a condenser loop. The experimental conditions are shown below in Tables 8 (Zone 1) and 9 (Zone 2). As the product ($h\Delta T_i$) was increased in the Zone 1, the severity of mottle was increased. Also, for a given product ($h\Delta T_i$) in Zone 1, the product ($h\Delta T_i$) in Zone 2 affected mottle. When the coating was not yet mottle-proof and was entering Zone 2, decreasing the product ($h\Delta T_i$) in Zone 2 caused a reduction in the severity of mottle.

TABLE 8

Zone 1

Example	T_{gas} (° C.)	$T_{cs(i)}$ (° C.)	h (cal/m^2 s K)	$h\Delta T_i$ (cal/m^2 s)
4-1	82.2	21.1	29.0	1770
4-2	37.8	21.1	18.9	316
4-3	37.8	21.1	18.9	316

TABLE 9

Zone 2

Example	T_{gas} (° C.)	$T_{cs(i)}$ (° C.)	h (cal/m^2 s K)	$h\Delta T_i$ (cal/m^2 s)	Mottle Rating
4-1	82.2	71.1	29.7	329	High
4-2	60	26.7	24.0	799	Medium
4-3	60	37.8	24.2	537	Low

Reasonable modifications and variations are possible from the foregoing disclosure without departing from either the spirit or scope of the present invention as defined by the claims.

We claim:

1. A method for evaporating a coating solvent from a coating on a first substrate surface of a substrate and reducing the formation of mottle as the coating solvent is evaporating, the method comprising:

providing a drying oven, the drying oven comprising:

an enclosure having an inlet and an outlet and defining at least a first drying zone;

a plurality of drying subzones within the at least first drying zone, at least two of the plurality of drying subzones employing different drying gas flow conditions without the influence of physical barriers; and

controlling the drying gas flow conditions within at least two of the plurality of drying subzones.

2. The method of claim **1**, the substrate having a second substrate surface opposite to the first substrate surface, the method further comprising creating a first plurality of subzones adjacent to the second substrate surface, the first plurality of subzones predominantly causing the evaporating of the coating solvent.

3. The method of claim **2**, further comprising creating a second plurality of subzones adjacent to the first substrate surface.

4. The method of claim **1**, further comprising defining at least one opening between the plurality of subzones, the at least one opening being sufficiently large such that a pressure differential within the plurality of subzones created by the at least one opening is insufficiently large to reduce the formation of mottle.

5. The method of claim **1**, further comprising providing at least a first drying gas supply port and a second drying gas supply port and at least a first drying gas removal port and a second drying gas removal port, the first drying gas removal port being positioned relative to the first drying gas supply port to create a first drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the first drying gas supply port, the second drying gas removal port being positioned relative to the second drying gas supply port to create a second drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the second drying gas supply port.

6. The method of claim **5**, the first drying gas supply port comprising one of an air foil, air bar, air turn, and perforated plate.

7. The method of claim **5**, the first drying subzone having a first static pressure and the second drying subzone having a second static pressure, the method further comprising:

adjusting the first static pressure such that the drying gas supplied by the first drying gas supply port is substantially removed by the first drying gas removal port; and

adjusting the second static pressure such that the drying gas supplied by the second drying gas supply port is substantially removed by the second drying gas removal port.

8. An apparatus for evaporating a coating solvent from a coating on a first substrate surface of a substrate and reducing the formation of mottle as the coating solvent is evaporating, the apparatus comprising:

a drying oven, the drying oven comprising:

an enclosure having an inlet and an outlet and defining at least a first drying zone;

a plurality of drying subzones within the at least one first drying zone, at least two of the plurality of drying subzones employing different drying gas flow conditions without the influence of physical barriers; and

means for controlling the drying gas flow conditions within the at least two of the plurality of drying subzones.

9. The apparatus of claim 8, the substrate having a second substrate surface opposite to the first substrate surface, the apparatus further comprising a first plurality of subzones adjacent to the second substrate surface, the first plurality of subzones predominantly causing the evaporating of the coating solvent.

10. The apparatus of claim 9, further comprising a second plurality of subzones adjacent to the first substrate surface.

11. The apparatus of claim 8, the apparatus defining at least one opening between the plurality of subzones, the at least one opening being sufficiently large such that a pressure differential within the plurality of subzones created by the at least one opening is insufficiently large to reduce the formation of mottle.

12. The apparatus of claim 8, further comprising at least a first drying gas supply port and a second drying gas supply port and at least a first drying gas removal port and a second drying gas removal port, the first drying gas removal port being positioned relative to the first drying gas supply port to create a first drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the first drying gas supply port, the second drying gas removal port being positioned relative to the second drying gas supply port to create a second drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the second drying gas supply port.

13. The apparatus of claim 12, the first drying gas supply port comprising one of an air foil, air bar, air turn, and perforated plate.

14. The apparatus of claim 12, the first drying subzone having a first static pressure and the second drying subzone subzone having a second static pressure, the apparatus further comprising:

means for adjusting the first static pressure such that the drying gas supplied by the first drying gas supply port is substantially removed by the first drying gas removal port; and

means for adjusting the second static pressure such that the drying gas supplied by the second drying gas supply port is substantially removed by the second drying gas removal port.

15. A method for evaporating a coating solvent from a coating on a first substrate surface of a substrate and reducing the formation of mottle as the coating solvent is evaporating, the method comprising:

providing a drying oven having at least a first drying zone;

creating a plurality of drying subzones within the at least first drying zone without requiring physical barriers to create the plurality of drying subzones, the plurality of drying subzones being capable of employing different drying gas flow conditions for evaporating the coating solvent;

employing different drying gas flow conditions within at least two of the plurality of drying subzones; and

transporting the substrate through the plurality of drying subzones to evaporate the coating solvent.

16. The method of claim 15, further comprising coordinating the act of creating the plurality of drying subzones and the act of employing different drying gas flow conditions within at least two of the plurality of drying subzones in order to reduce the creation of mottle while evaporating the coating solvent and maximize throughput of the substrate through the drying oven.

17. The method of claim 15, the substrate having a second substrate surface opposite the first substrate surface, the creating act including creating a first plurality of subzones adjacent the second substrate surface, the first plurality of subzones being the predominant cause of the evaporation of the coating solvent.

18. The method of claim 17, the creating act including creating a second plurality of subzones adjacent the first substrate surface.

19. The method of claim 15, the creating act including forming at least one opening between the plurality of subzones, the at least one opening being sufficiently large such that a pressure differential within the plurality of subzones created by the at least one opening is insufficiently large to reduce the formation of mottle.

20. The method of claim 15, the creating act including providing at least a first drying gas supply port, the first drying gas supply port comprising one of at least one air foil, at least one air bar, at least one air turn, and at least one perforated plate.

21. The method of claim 15, the plurality of drying subzones including a first drying subzone and a second drying subzone, the first drying subzone having a first static pressure and the second drying subzone having a second static pressure, the method further comprising:

adjusting the first static pressure such that the drying gas supplied by the first drying gas supply port is substantially removed by the first drying gas removal port; and

adjusting the second static pressure such that the drying gas supplied by the second drying gas supply port is substantially removed by the second drying gas removal port.

22. The method of claim 15, the creating act including providing at least first and second drying gas supply ports and at least first and second drying gas removal ports, the first drying gas removal port being positioned relative to the first drying gas supply port to create a first drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the first drying gas supply port, the second drying gas removal port being positioned relative to the second drying gas supply port to create a second drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the second drying gas supply port.

23. An apparatus for evaporating a coating solvent from a coating on a first substrate surface of a substrate and reducing the formation of mottle as the coating solvent is evaporating, the apparatus comprising:

an enclosure having an inlet and an outlet and defining at least a first drying zone; and

a plurality of drying subzones within the at least one first drying zone, at least two of the plurality of drying subzones employing different drying gas flow conditions; and

at least first and second drying gas supply ports and at least first and second drying gas removal ports, the first

drying gas removal port being positioned relative to the first drying gas supply port to create a first drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the first drying gas supply port, and the second drying gas removal port being positioned relative to the second drying gas supply port to create a second drying subzone of the plurality of drying subzones by substantially removing drying gas supplied by the second drying gas supply port.

24. The apparatus of claim **23**, wherein physical barriers are not required between the plurality of drying subzones to create the plurality of drying subzones.

25. The apparatus of claim **23**, further comprising means for independently controlling the drying conditions within the at least two of the plurality of drying subzones.

26. The apparatus of claim **23**, the substrate having a second substrate surface opposite the first substrate surface, the apparatus comprising a first plurality of subzones adjacent the second substrate surface, the first plurality of subzones being the predominant cause of the evaporation of the coating solvent.

27. The apparatus of claim **26**, the apparatus further comprising a second plurality of subzones adjacent the first substrate surface.

28. The apparatus of claim **23**, the apparatus defining at least one opening between the plurality of subzones, the at least one opening being sufficiently large such that a pressure differential within the plurality of subzones created by the at least one opening is insufficiently large to reduce the formation of mottle.

29. The apparatus of claim **23**, the first drying gas supply port comprising one of at least one air foil, at least one air bar, at least one air turn, and at least one perforated plate.

30. The apparatus of claim **23**, the first drying subzone having a first static pressure and the second drying subzone having a second static pressure, the apparatus further comprising:

means for adjusting the first static pressure such that the drying gas supplied by the first drying gas supply port is substantially removed by the first drying gas removal port; and

means for adjusting the second static pressure such that the drying gas supplied by the second drying gas supply port is substantially removed by the second drying gas removal port.

31. The method of claim **1**, wherein the drying gas flow conditions include drying gas flow velocity.

32. The method of claim **1**, wherein the drying gas flow conditions include drying gas pressure.

33. The method of claim **1**, further comprising providing different drying gas temperatures within at least two of the drying subzones.

34. The apparatus of claim **8**, wherein the drying gas flow conditions include drying gas flow velocity.

35. The apparatus of claim **8**, wherein the drying gas flow conditions include drying gas pressure.

36. The apparatus of claim **8**, further comprising a temperature controller that provides different drying gas temperatures within at least two of the drying subzones.

37. The method of claim **15**, wherein the drying gas flow conditions include drying gas flow velocity.

38. The method of claim **15**, wherein the drying gas flow conditions include drying gas pressure.

39. The method of claim **15**, further comprising providing different drying gas temperatures within at least two of the drying subzones.

40. The apparatus of claim **23**, wherein the drying gas flow conditions include drying gas flow velocity.

41. The apparatus of claim **23**, wherein the drying gas flow conditions include drying gas pressure.

42. The apparatus of claim **23**, further comprising a temperature controller that provides different drying gas temperatures within at least two of the drying subzones.

43. An apparatus for evaporating a coating solvent from a coating on a substrate, the apparatus comprising:

an enclosure defining a drying zone;

a first drying gas supply port disposed within the drying zone;

a first drying gas removal port disposed within the drying zone, the first drying gas supply port and the first drying gas removal port being arranged to define a first drying subzone;

a second drying gas supply port disposed within the drying zone;

a second drying gas removal port disposed within the drying zone, the second drying gas supply port and the second drying gas removal port being arranged to define a second drying subzone, wherein no substantial barrier exists between the first and second drying subzones; and

a flow controller that controls flow of the drying gas between the first drying gas supply port and the first drying gas removal port and between the second drying gas supply port and the second drying gas removal port to produce different drying gas flow conditions within the first and second drying subzones.

44. The apparatus of claim **43**, wherein the controller controls drying gas removal pressure, the controller controlling drying gas removal pressure associated with the first drying gas removal port independently of drying gas removal pressure associated with the second drying gas removal port.

45. The apparatus of claim **43**, wherein the controller controls drying gas supply pressure, the controller controlling drying gas supply pressure associated with the first drying gas supply port independently of drying gas supply pressure associated with the second drying gas supply port.

46. The apparatus of claim **43**, wherein the controller controls drying gas flow conditions within the first and second drying subzones such that drying gas supplied by the first drying gas supply port is substantially removed by the first drying gas removal port, and drying gas supplied by the second drying gas supply port is substantially removed by the second drying gas removal port.

47. The apparatus of claim **43**, wherein the first drying subzone has a first static pressure and the second drying subzone has a second static pressure, the first and second static pressures being selected such that the drying gas supplied by the first drying gas supply port is substantially removed by the first drying gas removal port, and the drying gas supplied by the second drying gas supply port is substantially removed by the second drying gas removal port.

48. The apparatus of claim **43**, wherein the drying gas flow conditions include drying gas flow velocity.

49. The apparatus of claim **43**, wherein the drying gas flow conditions include drying gas pressure.

50. The apparatus of claim **43**, further comprising a temperature controller that provides different drying gas temperatures within the first and second drying subzones.

51. A method for evaporating a coating solvent from a coating on a substrate, the method comprising:

passing the substrate through an enclosure defining a drying zone;

arranging a first drying gas supply port and a first drying gas removal port within the drying zone to define a first drying subzone;

arranging a second drying gas supply port and a second drying gas removal port within the drying zone to define a second drying subzone, wherein no substantial barrier exists between the first and second drying subzones; and

controlling flow of the drying gas between the first drying gas supply port and the first drying gas removal port and between the second drying gas supply port and the second drying gas removal port to produce different drying gas flow conditions within the first and second drying subzones.

52. The method of claim **51**, further comprising controlling drying gas removal pressure associated with the first drying gas removal port independently of drying gas removal pressure associated with the second drying gas removal port.

53. The method of claim **51**, further comprising controlling drying gas supply pressure associated with the first drying gas supply port independently of drying gas supply pressure associated with the second drying gas supply port.

54. The method of claim **51**, further comprising controlling drying gas flow conditions within the first and second drying subzones such that drying gas supplied by the first drying gas supply port is substantially removed by the first drying gas removal port, and drying gas supplied by the second drying gas supply port is substantially removed by the second drying gas removal port.

55. The method of claim **51**, wherein the first drying subzone has a first static pressure and the second drying subzone has a second static pressure, the method further comprising adjusting the first and second static pressures such that the drying gas supplied by the first drying gas supply port is substantially removed by the first drying gas removal port, and the drying gas supplied by the second drying gas supply port is substantially removed by the second drying gas removal port.

56. The apparatus of claim **51**, wherein the drying gas flow conditions include drying gas flow velocity.

57. The apparatus of claim **51**, wherein the drying gas flow conditions include drying gas pressure.

58. The apparatus of claim **51**, further comprising a temperature controller that provides different drying gas temperatures within the first and second drying subzones.

59. A method for evaporating a coating solvent from a coating on a substrate with reduced formation of mottle, the method comprising:

providing an enclosure defining a drying zone with a plurality of drying subzones;

transporting the substrate through the enclosure; and

selectively controlling a static pressure difference between a lower interior portion of the enclosure within each of the subzones and a reference point to reduce the formation of mottle.

* * * * *

EXHIBIT N

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of the Inter Partes Reexamination Comments Under 37 CFR § 1.947 by the Third Party Requester; the associated Exhibits A, B, C, D, E, F, G, H, I, J, K, L, and M; and this certificate of first class service have been served, by first class mail, on April 12, 2013, in their entirety on the Patent Owner in accordance with 37 C.F.R. §§ 1.903 and 1.248. The name and address of the party served is:

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EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)
US Patent No. 7,897,080	)
Issued: March 1, 2011	) Confirmation No.: 6418
Named Inventor: Robert K. Yang *et al.*	) Group Art Unit: 3991
Control No.: 95/002,170	) Examiner: Diamond, Alan D.
Filed: September 10, 2012	) M&E Docket: 117744-00023
Title: POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	) H&B Docket: 1199-26 RCE/CON/REX

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION BY MAUREEN REITMAN, SC.D.
UNDER 37 CFR § 1.132

Sir/Madam:

I, Maureen Reitman, do hereby make the following declaration:

I. Technical Background

1. I am a Principal and the Director of the Polymer Science and Materials Chemistry Practice at Exponent. I hold two academic degrees: (1) a Bachelor of Science in Materials Science and Engineering from the Massachusetts Institute of Technology (MIT), and (2) a Doctor of Science in Materials Science and Engineering, with a thesis in the field of polymers, from MIT. I have been practicing in the field of polymer science and engineering for more than 20 years as a researcher at MIT, in a variety of technical roles at the 3M Company, and as a consultant with Exponent. I provide consulting engineering services in all aspects of polymer science and engineering including, but not limited to material selection, product design and development, mechanical and chemical testing, failure analysis, polymer chemistry, polymer

physics, and polymer processing. My specialties include formulation, processing and performance evaluation of polymeric materials, including films, coatings, adhesives and transdermal drug delivery systems. I have been directly involved in product development, product line extensions, transfer of new products to manufacturing, qualification of alternative materials and manufacturing equipment, evaluating field performance, and assessing intellectual property. I am a past chairman and continue to serve as a member of the board of directors of the Medical Plastics Division of the Society of Plastics Engineers. My *curriculum vitae* is provided in Appendix A.

2. While Exponent is being paid for my time, I am not an employee of, nor do I have any financial interest in, BioDelivery Sciences International, Inc.

3. I have been asked to carefully review International Publication No. WO 00/42992 ("*Chen*"), and manufacture a film as described in *Chen*. I carefully reviewed *Chen*. Under my direction, my team manufactured a film in accordance with Example 7 of *Chen*. I have also been asked to take samples and perform various analytical tests to confirm the uniform distribution of the pharmaceutical active in substantially equal sized individual dosage units of the film, which we did.

4. Manufacturing Example 7 of *Chen*

Chen states: "According to Examples 1-8, the hydrocolloid [Methocel E5(HPMC)] was dissolved in water under agitated mixing to form a uniform and viscous solution." Chen 17:7-8.

- Methocel E5(HPMC) was dissolved in water under agitated mixing to form a uniform and viscous solution, by my team.

Chen states: "Additional ingredients were then added sequentially to the viscous solution such as peppermint, aspartame, propyl[ene] glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid." Chen 17:8-11.

- Additional ingredients were then added sequentially to the viscous solution including peppermint oil, aspartame, propylene glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid, by my team.

- Kolliphor EL was also added to the viscous solution.

Chen states: "Therapeutic agents were added to the homogeneous mixture (coating solution) prior to forming the film." *Chen* 20:19-20.

- Oxybutynin chloride (the therapeutic agent of Example 7) was added to the homogeneous mixture (coating solution) prior to forming the film, by my team.

Chen's Table 5 specifies the composition for Example 7.

- We used the ingredients in the amounts identified in *Chen*'s Table 5. *See* Table 1.

Table 1			
Formulation, Ex. 7, Table 5, *Chen*	% Weight	Formulation, Prepared by Maureen Reitman Team	% Weight
Oxybutynin	3.71	Oxybutynin chloride	3.71
Methocel E5 (HPMC)	21.06	Methocel E5 Premium LV	21.06
Water	70.72	Water, distilled	70.72
Cremophor EL40	1	Kolliphor EL[1]	1
Propylene glycol	1	Propylene glycol	1
Peppermint	1	Peppermint oil	1
Aspartame	0.8	Aspartame	0.8
Benzoic acid	0.013	Benzoic acid	0.013
Citric acid	0.7	Citric acid, monohydrate	0.7

Chen states: "The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed." Chen 17:11-12.

- The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed, by my team.

Chen states: "The formulation was then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes." Chen 17:13-15.

- The formulation was then coated on a non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for up to 9 minutes, on commercial manufacturing equipment by my team.

Chen states: "Methods for manufacturing the dosage unit include the solvent casting methods as shown in Figure 2." Chen 15:13-14. "The manufacturing process for forming the dosage unit is illustrated in Figure 2. The dry film formed by this process is a glossy, stand alone, self supporting, non-tacky and flexible film (12)." Chen 15:29-31.

- A solvent casting manufacturing process for forming the dosage unit as illustrated in Figure 2 was used[2], by my team.

[1] The Cremophor line of products now owned by BASF and renamed Kolliphor. Based on the naming convention of the Cremophor/ Kolliphor products, EL40 is Polyoxyl 40 Castor Oil and EL is Polyoxyl 35 Castor Oil (*i.e.*, they are based on a 1:40 and 1:35 ratio, respectively, of castor oil:ethylene oxide). They are different materials. However, one of skill in the art would recognize Kolliphor EL as an appropriate substitute, as Cremophor EL40 is no longer available.

- The film was manufactured using a controlled drying process.

- As illustrated in Figure 2, the drying oven featured aeration controller with 3 zones set such that in each successive zone air impingement on the surface of the film increased.

- The dry film formed by the process is a glossy, stand alone, self-supporting, non-tacky and flexible film.

Chen states: "A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying." Chen 17:15-16.

- A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying, by my team.

5. Verification of Content Uniformity – Visual Inspection

   - By examination with the naked eye, uniformity was verified by my team.

6. Verification of Content Uniformity – Unit Dose Weight

   - By weighing individual dosage units of substantially identical size, uniformity was verified by my team. *See* Table 2.

Table 2	
Sample	Weight of 5 cm[2] dosage unit (grams)
1	0.034
2	0.034
3	0.034
4	0.034
5	0.034
6	0.034
7	0.034

7. Verification of Content Uniformity – Dissolution Test (HPLC)

   - By dissolution of individual dosage units of substantially identical size and analysis by High Performance Liquid Chromatography (HPLC) active content uniformity was verified by my team. *See* Table 3.

[2] Our backing was not looped and we did not die cut in line, but the solvent casting and drying under aeration is matched.

Table 3	
Sample	Oxybutynin weight (mg)
A	4.4
B	4.4
C	4.3
D	4.4
E	4.1

- As can be seen in Table 3, the active varies by less than 10%.

8. Additional Observations

   - The components of the formulation, including the active component, were uniformly distributed in the viscous solution, which was used to cast the film, as was verified by my team.

   - The viscous solution, which was used to cast the film, exhibited the flow properties of honey (around 10,000 cps), as observed by my team.

   - Water content of the film was less than 10%, as verified by my team.

   - Within about 4 minutes after initiation of drying, the film was self-supporting, non-tacky, flexible and viscoelastic, as verified by my team.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patents issued thereon.

Dated: February 28, 2013

Maureen Reitman, Sc.D.

Appendix A

Exponent
Failure Analysis Associates

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Maureen T. F. Reitman, Sc.D.
Principal and Practice Director

Professional Profile

Dr. Maureen Reitman is a Principal and the Director of Exponent's Polymer Science and Material Chemistry practice. Her expertise includes polymer and composite technology, mechanics of materials, adhesion science, fiber mechanics, history and technology of plastics, and material failure analysis. She is skilled in the development and use of testing tools and methods and has applied them to plastic, rubber, textile, metal, glass, ceramic, and composite materials and systems. She is experienced in major aspects of product development, including materials selection, formulation, scale-up, end-use testing, failure analysis, certification procedures and issues related to intellectual property.

Dr. Reitman has conducted research in the areas of packaging and barrier materials; paints and coatings; plastic pipes; transdermal drug delivery; adhesives, sealants, and encapsulants; molding compounds; high temperature resins; nanoparticles; fibers and textiles; protective coatings and finishes; polymer chemical resistance; plastic insulation; connectors and splices; plastic packaging; medical devices; environmental effects on durability; and product aging. She has used her expertise to solve a broad range of problems related to coatings, fibers, films, and extruded and molded products, and their use in the telecom, electronics, electrical, transportation, construction, fire protection, medical, and consumer products markets.

Dr. Reitman is a member of the Board of Directors of the Medical Plastics Division of the Society of Plastics Engineers and an active member of two Underwriters Laboratories Standard Technical Panels, addressing Polymeric Materials (UL 94, UL 746, UL 1694) and Appliance Wiring (UL758).

Prior to joining Exponent, Dr. Reitman worked for the 3M Company in both research and management roles. Her activities included technology identification, materials selection and qualification, product development, customer support, program management, acquisition integration, intellectual property analysis, and patent litigation support.

Academic Credentials and Professional Honors

Sc.D., Materials Science and Engineering/ Program in Polymer Science and Technology, Massachusetts Institute of Technology, 1993
B.S., Materials Science and Engineering, Massachusetts Institute of Technology, 1990

National Academy of Engineering Frontiers of Engineering, 2009; Tau Beta Pi; Sigma Xi
John Wulff Award; Carl Loeb Fellowship; NCAA Postgraduate Scholarship;
Malcolm G. Kispert Award; GTE Academic All-American

Patents

Patent 6,311,524: Accelerated Method for Increasing the Photosensitivity of a Glassy Material, issued November 6, 2001.

European Patent EP0830428: Tackified Polydiorganosiloxane Polyurea Segmented Copolymers and a Process for Making Same, published March 25, 1998.

Patent 5,371,051: Fiber Optic Fusion Splice Protector Sleeve, issued March 24, 1998.

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Selected Invited Presentations

Reitman MTF. Failure analysis tools. Workshop on Future Needs for Service Life Prediction of Polymeric Materials. NIST and Underwriters Laboratories, Gaithersburg, MD, October 2012.

Hoffman J, MacLean S, Ralston B, Reitman M, Ledwith P. Fractography of unfilled thermoplastic materials experiencing common mechanical failure modes. Materials Science & Technology 2012 Conference, Pittsburgh PA, October 2012.

Hoffman J, Reitman M, Ledwith P. Microscopic characterization of CPVC failure. Materials Science & Technology 2012 Conference, Pittsburgh PA, October 2012.

Reitman MTF. Polymer material properties for next generation medical devices. Invited Speaker: MedTech Polymers, UBM Canon, Chicago, IL, September 2012.

Reitman MTF. Polymers for medical applications. Fundamentals and Fellows Forum, ANTEC 2012, Orlando FL, April 2012.

Reitman MTF. Plastic and composite product failures. Invited lecture in Failure Analysis of Emerging Technologies. Stanford University Department of Materials Science and Engineering, Menlo Park, CA October 2009.

Reitman MTF. Factors for success: Plastics in injection molded medical devices. Part of *Injection Molding Works for Medical Design*, Design News Webcast, October 2008.

Reitman MTF. Plastic and composite product failures. Keynote Speaker: Third International Conference on Engineering Failure Analysis (ICEFA III), Elsevier, Sitges Spain, July 2008.

Reitman MTF. Multiphase materials for medical device applications, an overview. Medical Device and Manufacturing (MDM), Canon Communications, various locations, January- June 2008.

Reitman MTF. Nanotechnology and plastics for medical devices. Capitalizing on Nanoplastics, Intertek PIRA San Antonio TX, February 2008.

Reitman MTF. Nano additives in composites and coatings for medical device applications. Medical Device and Manufacturing Minneapolis, Canon Communications, Minneapolis MN, October 2007.

Reitman MTF, Swanger LA. Practical tips on how to manage your technical expert in patent disputes. Ropes & Gray IP Master Class, Live Teleconference, June 2007.

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Current Professional Appointments

- Underwriter's Laboratory Standards Technical Panel STP 746 (Polymeric Materials, includes UL94, UL 746 and UL1694)
- Underwriter's Laboratory Standards Technical Panel STP 758 (Appliance Wires/ UL758)
- Medical Plastics Division Board of Directors, Society of Plastics Engineers

Committee and Review Activities

- UL Forum on Initiatives to Improve the Long Term Aging Program, LTTA Tools Working Groups, Underwriters Laboratories
- Research and Engineering Technology Award Committee, Society of Plastics Engineers
- Reviewer, Medical Plastics Technical Program Committee, Society of Plastics Engineers
- Reviewer, Failure Analysis and Prevention Technical Program Committee, Society of Plastics Engineers
- Reviewer, various book proposals and submissions related to polymer science, ASM International, Elsevier, John Wiley

Professional Affiliations

- American Association for the Advancement of Science (member)
- American Association of Textile Chemists and Colorists—AATCC (senior member)
- American Chemical Society (member)
- ASTM International (member)
- Society for the Advancement of Material and Process Engineering (member)
- Society of Plastics Engineers (senior member)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	
Issued: March 1, 2011	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
	)	
Control No.: 95/002,170	)	Examiner: Alan D. Diamond
	)	
Request Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	)	H&B Docket: 1199-26 RCE/CON/REX
	)	
Date: April 12, 2013	)	

Mail Stop *Inter Partes* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

***INTER PARTES* REEXAMINATION COMMENTS UNDER 37 CFR § 1.947**

Pursuant to 37 CFR § 1.947, the Third Party Requester hereby submits the following comments to the Office Action re-mailed on November 29, 2012 (the "Office Action") and the Applicant's Amendment and Reply thereto dated March 13, 2013 (the "Reply"). These Comments are filed on April 12, 2013, which date is 30 days from the service of the Reply.

TABLE OF CONTENTS

I. INTRODUCTION

Applicant has elected to add recitations of desired results to its method claims, not the steps required to achieve them. These new recitations are not entitled to patentable weight and do not overcome the rejections of record. Moreover, the desired results added to the claims are still anticipated and rendered obvious by *Chen*, *Staab, Le Person,* and *Horstmann*. In addition, the new recitations lack clarity, support, and enablement as explained in the new proposed rejections. Finally, Applicant has failed to establish that even one of the outstanding rejections of record was incorrect and should be withdrawn. Instead, Applicant either argues limitations that are not in the claims or relies solely on the newly added recitations.

Applicant also attempts to rely on two Declarations that purport to distinguish the "inventive method." In the Bogue Declaration, Applicant presents data that does not correspond to any claimed method and does not correspond to any claimed result. In the Lin Declaration, Applicant criticizes *Chen* for not being an FDA new drug application and then concludes with a logical fallacy. It is unclear how the Declarations could be useful to address the existing rejections.

For the Examiner's convenience, Requester attaches a chart comparing each independent claim, as amended, to claim 82 (Exhibit A).

A. Applicant has not added any new process limitations to patentably distinguish its Exhibitclaimed process from the prior art

In its own specification, Applicant has admitted that its only newly added method steps—directed to sampling and testing for uniformity—are conventional. Specifically, the new steps are:

- "performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled …." *See* step (f) in claim 1, and step (e) in claims 82, 161 and 315-318; and
- "repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than…" *See* step (f) in claim 82 and 315.

As support for these new steps, Applicant cites the passage spanning col. 28, line 66, through col. 29, line 6 and the passage at col. 29, lines 20-35 of the '080 Patent. *See* Reply p. 45. But in the very next sentence of the specification, Applicant admits that the newly recited steps were known and obvious to those of skill in the art:

> Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical testing, and any other suitable means known to those skilled in the art.
>
> '080 Patent 29:35-39.

Thus, by Applicant's own admission, the conventional sampling and testing steps recited, as the only new method limitations in the claims, are obvious and anticipated. In short, the only added process steps are admitted in the prior art.

Also, while the objective of each of the claimed methods is the manufacture of a film suitable for commercialization, the film must already be manufactured before it can be tested. And later testing cannot make an unsuitable film suitable for commercialization. For example, any variation in the distribution of active in manufactured film is not improved by testing. In short, the new testing steps are at best known, post-solution activity that cannot render the claimed methods for manufacturing film patentable.

B. Applicant's bread analogy falls flat.

Applicant misleadingly characterizes the '080 Patent claims as "requir[ing] a uniformity of content in amount of active (i) in individual dosage units sampled from a resulting film of 10% or less (. . .), and (ii) in individual dosage units sampled from two or more resulting films of 10% or less as a percentage difference from a desired amount (. . .)." Reply pp. 48-49 (emphasis added) (erroneously suggesting that each claim includes two "uniformity" requirements when most of the claims do not). Applicant proposes to use a bread-making analogy to explain its alleged "uniformity" requirements. Requester agrees that the bread-making analogy may be useful so we elaborate on it as a means for conceptually explaining why the pending claims are not patentable.

The following bread-making claim very closely relates to claim 82, which is one of the two pending independent claims that actually recites two "uniformity" requirements:[1]

> **82_bread.** A process for manufacturing resulting loaves of bread suitable for commercialization and regulatory approval, said regulatory approval including testing which meets the standards of the US Food and Drug Administration (FDA) relating to variation of a flavoring in individual bites, said loaves of bread having a substantially uniform distribution of ingredients comprising a substantially uniform distribution of a desired amount of said flavoring in bites of said resulting loaves of bread, comprising the steps of:
>
> (a) forming a dough comprising a milled grain selected from the group consisting of a water-soluble grain, and water-swellable grain and combinations thereof, a liquid and the flavoring, the dough having a substantially uniform distribution of the flavoring;
>
> (b) casting the dough into a loaf pan, said dough having a viscosity from about 400 to about 100,000 cps;
>
> (c) controlling drying though a process comprising conveying the loaf pan through an oven and evaporating at least a portion of said water from said dough to form visco-elastic dough, having said flavoring substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said dough upon initiation of drying to maintain substantially uniform distribution of said flavoring by locking-in or substantially preventing migration of said flavoring within the visco-elastic dough, wherein during said drying the dough temperature is 100 ºC or less, and wherein the uniformity of content of flavoring in substantially equal sized bites of said visco-elastic dough is such that the amount of the flavoring varies by no more than 10%;
>
> (d) forming said resulting loaf of bread from said visco-elastic dough, wherein the resulting loaf of bread has a water content of 10% or less and said substantially uniform distribution of flavoring by said locking-in or substantially preventing migration of said flavoring is maintained;
>
> (e) performing analytical taste tests for uniformity of said flavoring in substantially equal sized bites from different slices of the resulting loaf,

[1] Applicant begins the discussion of the '080 Patent by attempting to subvert the plain meaning of "uniform." Applicant states that "'uniform' from a practical standpoint must of necessity allow for some variance." *See* Reply p. 48. Merriam-Webster disagrees: its first definition of "uniform" is "not varying." *See* http://www.merriam-webster.com/dictionary/uniform (attached as Exhibit D). In other words, Applicant starts by proposing to define "uniform" as "not uniform." Applicant apparently uses "uniform" and variations of that term to mean "having an acceptable variance," but the acceptable variance is not always identified.

> the tests indicating that uniformity of content in the amount of said flavoring varies by no more than 10% and the resulting loaf is suitable for commercial sale and regulatory approval, wherein the approval is provided by the US FDA; and
>
> (f) repeating steps (a) through (e) to form resulting additional loaves of bread, such that uniformity of content in the amount of said flavoring in said resulting loaf of bread and said additional resulting loaves of bread varies by no more than 10% from the desired amount of the flavoring as indicated by said analytical taste tests.

The foregoing claim, claim 82_bread, includes analogous ingredients and the same or analogous process limitations as pending claim 82. But no one would consider claim 82_bread a good recipe for making bread. Indeed, the process limitations of claim 82_bread are so general and devoid of detail that it is not clear that they would necessarily produce bread. Because claim 82_bread leaves the question of how to make the target product largely unanswered, substantial experimentation would be required before a baker would expect to be able to use the process limitations of claim 82_bread to make bread. More experimentation would be required before a baker would expect to be able to use the process limitations of claim 82_bread to make bread with the recited desired properties.

Surprisingly, although an improved understanding of the requirements of the pending claims was the apparent purpose of the analogy, Applicant fails to relate the proposed bread "uniformity" requirements to the actual limitations of any pending claim. Instead, Applicant relates the bread "uniformity" requirements to "lots." But no pending claim recites one or more lots. And Applicant fails to equate one or more lots with any recited claim term. Applicant also fails to relate the lots back to its bread analogy. Applicant's failure to make the proposed connection may be due to the limitations of its data, which relates to lots as opposed to recited claim terms.

Applicant's failure to make the proposed connection may also be due to the limitations of the '080 Patent specification. As quoted in the Reply, the '080 Patent specification only includes *two* passages that potentially support numerical values for allowable active variation. Reply pp. 45, 46. First, the specification states that "as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active." '080 Patent 2:27-46.

Second, the specification states that a pharmaceutical dosage form or film product having no more than 10% variance of pharmaceutical active by weight per unit area may be deemed substantially uniform. *See* '080 Patent 15:28-43. The plain language of these passages simply does not support the two distinct "uniformity" requirements that Applicant has added to its claims. In short, Applicant's bread analogy falls flat.

C. The Reitman Declaration: Third Party Requestor has demonstrated that films made by the method of *Chen* are at least as uniform as the films made by the method of the '080 Patent.

Despite the fact that the burden has shifted to Applicant to show that *Chen* does not inherently produce the desired properties, Requester nonetheless reinforces the existing evidence and demonstrates that *Chen* does produce films having at least the same properties as films produced by the presently claimed methods. In order to expedite prosecution of this reexamination, the Declaration of Maureen Reitman is provided. *See* Reitman Decl. (Exhibit B). Her team manufactured a film in accordance with Example 7 of *Chen*. *See* Reitman Decl. ¶¶ 3-4. The sampling and "chemical testing" of dosage units sampled from films manufactured in accordance with *Chen* verified that the active varies by less than 10% (*i.e.*, as presently claimed by Applicant). *See* Reitman Decl. ¶ 7 and Table 3. Visual inspection and unit dose weight analysis also verified that the individual dosage units of *Chen* have uniform active content. *See* Reitman Decl. ¶ 5-6 and Table 2. Thus, even though the burden falls on Applicant to prove that the films of *Chen* do not inherently possess the claimed desired uniformity, Dr. Reitman has proved that the films of *Chen* do inherently possess the claimed desired uniformity.

II. APPLICANT'S DECLARATIONS ARE INEFFECTIVE TO REBUT THE EXAMINER'S *PRIMA FACIE* CASE OF ANTICIPATION

A. Lin Declaration: Applicant has not met its burden of proving that *Chen* does not inherently possess the desired property

With regard to the Lin Declaration, Applicant misses the point. To anticipate the instant claims, *Chen* need only teach everything claimed, expressly or inherently. The standard is not whether *Chen* provides the thousands of pages of documentation required for the FDA to approve a drug product for administration to humans. To the extent that Applicant insists that

Chen does not possess an enabling disclosure because it does not provide the type and volume of information required by the FDA for approval, Applicant's own '080 Patent lacks such an enabling disclosure.

1. *Dr. Lin's Declaration proves that the '080 Patent claims lack an enabling disclosure.*

The Lin Declaration states:

> After review of the patent in light of FDA practice and procedure, it is my opinion that there is insufficient disclosure to allow FDA to determine that a drug product as described can be manufactured for commercial distribution, manufactured in a consistent manner and meet specification that will ensure the identity, strength, quality, purity, and potency of the drug product. In particular, *Chen* lacks any disclosure which would necessarily lead to the manufacture of films with uniformity of content (strength) of drug active required for FDA approval.
>
> Lin Decl. ¶ 17.

While it may be true that a submission of *Chen* to the US Food and Drug Administration as a New Drug Application would not result in FDA approval of a drug product, it is unclear how Dr. Lin's Declaration is relevant other than to prove that the '080 Patent claims lack enablement. As amended, every single claim of the '080 Patent recites a "process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to the variation of an active in individual dosage units." *See* Reply pp. 2, 11, 20, 36, 37, 39, 40 (the amended preambles of independent claims 1, 82, 161, and 315-318). If *Chen* lacks sufficient disclosure to meet this recitation, as Applicant argues, then its own patent is similarly deficient. *See* MPEP 716.07 citing *In re Epstein*, 32 F.3d 1559, 31 USPQ2d 1817 (Fed. Cir. 1994) (lack of diagrams, flow charts, and other details in the prior art references does not render them nonenabling in view of the fact that applicant's own specification failed to provide those details and that one skilled in the art would have known how to implement the features of the references). Indeed, *Chen* demonstrates uniformity to the same degree as the '080 Patent, and in fact, goes beyond the '080 Patent in providing the results of so-called "analytical chemical tests" that the '080 Patent lacks. In fact, the Lin Declaration goes on to provide a litany of disclosure requirements that the '080 Patent lacks (*see* Lin Decl. ¶¶ 18-20), as described in great detail

below with respect to the first proposed rejection of all claims under 35 USC § 112 for lack of enablement, written description, and clarity.

2. *Dr. Lin's statements related to Chen's release data must be dismissed as illogical, unsupported, and conclusory.*

Lin concludes his Declaration with a logical fallacy. Based on a possible relationship between data and a film problem, and despite evidence that indicates an alternative possibility is more likely, Lin illogically finds that the data necessarily shows a film problem. Lin states that *Chen*'s interim release data indicates a problem with the test method "and/or" a variation in dosage unit active content. *See* Lin Decl. ¶ 20 (emphasis added). Reduced to its logical components, Lin's premise is that X (*Chen*'s interim release data) indicates A (test problem) and/or B (film problem). As an initial matter, the fact that *Chen*'s maximum release error bars decrease over time indicates that the error noted by Lin is an artifact of the test method—not a characteristic of the film. Nonetheless, without further support or explanation, Lin concludes that *Chen*'s data demonstrates unacceptable variation in dosage unit active content (film problem). Reduced to its logical components, Lin's conclusion (X demonstrates B) does not follow from Lin's own premise (X indicates A and/or B). In other words, Lin's conclusion is logically invalid based on Lin's own stated premise. Because it lacks viable support or explanation, Lin's conclusory allegation based on *Chen*'s interim release data cannot overcome any rejections based on *Chen*. *See* MPEP 716.01(C).III (requiring consideration of the absence of factual support for an expert opinion in assessing its probative value).

B. Bogue Declaration: Applicant Presents Irrelevant Information

The purpose of the Bogue Declaration is unclear to Requester. Bogue's Declaration does not show any unexpected results and so cannot be used to overcome any obviousness rejection. Bogue does not even attempt to address anticipation. Accordingly, the Bogue Declaration is insufficient to overcome any prior art rejection.

1. *The method recited in the Bogue Declaration is not the method of any of the amended or proposed claims.*

Dr. Bogue's description of the method used to make "lots" of resulting films is so general and devoid of detail that it is impossible to know to which, if any, claim(s) the data is applicable. In other words, it is impossible to know whether Bogue's method met all of the limitations of any claimed method. Applicant itself suggests that any evidence that fails to demonstrate that the "process [was] followed exactly, with all of the components exactly as listed, and all other conditions . . . exactly met" must be discounted. Reply pp. 66. Furthermore, Bogue's evidence of non-uniformity in mystery lots prepared by a vague method provides no useful insight into the uniformity of the films of the prior art.

2. *It is not clear what a "lot" may be and how it may relate to the claimed "resulting film" or "resulting films".*

According to Bogue, "[t]he results shown in the appendices establish … the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film." Bogue Decl. at ¶ 11. Thus, it appears that a lot may be a subset of a "resulting film." But there is no certainty as to how a "resulting film" or "resulting films" may relate to one or more "lots." Neither Applicant nor Bogue equates a "lot" to any recited claim element. In short, there is no support for Dr. Bogue's conclusion that "[t]he results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity based on analytical chemical testing." Bogue Decl. at ¶ 11.

3. *Applicant has failed to show that even the "lots" meets its own claimed criteria.*

Even if the Bogue process were commensurate with a single recited claim, which has not been demonstrated, the data presented in the Bogue Declaration does not fall within the recited desired maximum variance in active content. As can be clearly seen from the data presented in Appendix B, the amount of pharmaceutical active varies between individual dosage units from less than 94% on the far left of the figure, to nearly 106% on the upper right. That is, the amount of pharmaceutical active varies by more than 10%. The issued and amended claims recite that "the amount of the pharmaceutical active . . . varies by no more than 10%" between individual dosage unit samples. *See e.g.*, claim 1.

Applicant attempts to resuscitate its data by amending its independent claims to refer to a first "uniformity" within a "resulting film" and then a second, newly-defined "uniformity" between "resulting films." First, there is absolutely no support for two "uniformity" standards in the '080 Patent. And certainly there is no support for a first standard of "uniformity" that only applies within a film and a second standard of "uniformity" that applies between "resulting films." Second, Appendix A does not indicate whether the amount of active in each film varies by no more than 10% per unit area. Appendix A does not even mention film.

Moreover, Appendix A conveniently conceals variation—by dividing the difference between the maximum and the minimum active dosages by the average active dosage in the lot samples. Thus, Appendix A does not indicate the actual variation between the amount of active in individual dosage units. For example, consider a sample set including 10 dosage units with active in the following amounts: 6, 4, 4, 4, 2, 4, 4, 4, 4, and 4 mcg. The actual variation between the dosage unit having 6 mcg and the dosage unit having 2 mcg is well over 20%. But according to Bogue's calculation, the variation would be 0%.

Finally, because Applicant chose only to provide the results of its calculations and not the underlying data, the Office has no way of determining if the data, analyzed in Appendix A, supports the claims. But the Office can readily see that the data in Appendix B does not support the claims.

III. PROPOSED REJECTIONS OF ALL PENDING CLAIMS UNDER 35 USC § 314

Applicant's amendments attempt to "redefine" issued claim limitations by adding an implicit definition that goes well beyond the scope of the issued claims.

A. Proposed rejection of all pending claims under 35 USC § 314 as enlarging the scope of the patent claims – broadening "flowable" to include non-flowable viscosities.

Applicant amends every independent claim to broaden the term "flowable" to encompass viscosities that are not flowable. Step (c) of issued claim 1 and step (b) of issued claims 82 and 161 have been amended as follows:

> casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

Each and every new independent claim also includes this recitation. Exhibit E provides the viscosity of common materials. As Exhibit E indicates, a viscosity of 100,000 cps corresponds to mincemeat. Materials having the viscosity of mincemeat are not flowable. The new recitation expands the polymer matrix cast in this step beyond that claimed in issued claims 1, 82, and 161—*i.e.*, to include a polymer matrix that is not flowable—and thereby impermissibly broadens the scope of the claims beyond those issued in the '080 Patent.

B. Proposed rejection of all pending claims under 35 USC § 314 as enlarging the scope of the patent claims – broadening the drying step.

The issued claims referred to forming a visco-elastic film in less than 10 minutes. The only discussion in the specification, including the examples, for drying for 10 minutes is referring to total drying time:

> For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80 ºC for 10 minutes produces a temperature differential of about 5 ºC. This means that after 10 minutes of drying, the temperature of the inside of the film is 5 ºC less than the outside exposure temperature.
>
> '080 Patent 13:23-28.

The '080 Patent teaches in this passage that keeping the total drying time short, allows the films to be dried at higher temperatures without heat degradation.

Applicants amends every independent claim to broaden the drying step to require only that viscosity be increased in the first 4 minutes. Step (d) of issued claim 1 and step (c) of issued claims 82 and 161 have been amended as follows:

> …evaporating at least a portion of said solvent… to form a visco-elastic film…within about the first [10] 4 minutes [or fewer] by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution…of said film….

Each and every new independent claim also includes this recitation.

This amendment attempts to "redefine" the evaporating step by shifting from what would be construed as a total drying requirement to what is now merely an initial drying requirement. This amendment thus broadens the step. As newly recited, this step now is accomplished "by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying." This new claim does not require 10 minutes drying time, but only requires an increase in viscosity in the first 4 minutes.

IV. PROPOSED REJECTIONS OF ALL CLAIMS UNDER 35 USC § 112

A. Proposed rejection of all pending claims under 35 USC § 112, first and second paragraph – new recitation "suitable for commercialization and regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units"

The preambles of claims 1, 82, and 161 have been amended to add the above recitation. Claims 315-318 also include the same recitation.

1. *Lack of enablement*

The Applicant has taken the position that *Che*n lacks an enabling disclosure because it lacks "sufficient information contained within to allow regulatory FDA approval" of its films. Lin Decl. ¶ 17. If FDA-approvability is the standard for enablement, then Applicant's own specification is similarly lacking. The '080 Specification discloses none of the following, which the Lin Declaration proclaims is required for an enabling disclosure:

> disclosure to allow FDA to determine that a drug product as described can be manufactured for commercial distribution, manufactured in a consistent manner and meet specification that will ensure the identity, strength, quality, purity, and potency of the drug product. *See* Lin Decl. ¶ 17.
>
> ✓ Without a doubt, the '080 Patent does not qualify as an FDA CMC submission, which is the bar set by Dr. Lin and Applicant.
>
> disclosure which would necessarily lead to the manufacture of films with uniformity of content (strength) of drug active required for FDA approval. *See* Lin Decl. ¶ 17.

- ✓ Although the '080 Patent does have some uniformity data from physical tests, *i.e.,* data from visual inspection tests ('080 Patent 31:38-45) and weight variation tests ('080 Patent 31:46-32:34), Applicant has taken the position that these test are not relevant (Reply at p. 58-59). Thus, according to Applicant, there is no uniformity data that can be relied upon in the '080 Patent.

sufficient information that the films containing drug can be produced consistently with respect to uniformity of content of the drug. *See* Lin Decl. ¶ 18.

- ✓ The '080 Patent does not include any data or other information regarding the reproducibility of films made according to the methods described.

demonstrat[ing] uniformity of content in the amounts of drug in individual dosage units. *See* Lin Decl. ¶ 18.

- ✓ Again, according to Applicant, there is no uniformity data that can be relied upon in the '080 Patent.

no specific test methods, and hence no test results, that could allow for the determination of the actual amount of drug (active) in individual dosage units. *See* Lin Decl. ¶ 18.

- ✓ The '080 Patent specification fails to describe or exemplify any specific test methods, and hence no test results.

disclose sufficient information regarding the manufacturing process and process controls…[to] ensure that films containing drug could be manufactured to meet specifications that ensure consistent strength. *See* Lin Decl. ¶ 19.

- ✓ The '080 Patent fails to disclose or claim any information about manufacturing processes or controls to ensure consistent strength that *Chen* also does not provide. So, to the extent that *Chen* is lacking, so is the '080 Patent.

…there is no information regarding the test methods that are necessary to determine the amount of drug in individual dosage units. *See* Lin Decl. ¶ 20.

- ✓ Beyond its so-called physical tests (which Applicant claims are irrelevant), the '080 Patent is devoid of any information regarding "test methods that are necessary to determine the amount of drug in individual dosage units." There is only a general reference to dissolution tests, but with no actual test methods are referred to or described.

In short, to the extent that *Chen* lacks an enabling disclosure with respect to this new recitation, the '080 Patent also lacks an enabling disclosure. In the words of Dr. Lin, the '080 Patent "is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products." Lin Decl. ¶ 21.

Even the Bogue Declaration fails to provide evidence that its "lots" meet the recited standards. As Dr. Clevenger explains:

> The analysis in the Bogue Declaration is not consistent with the currently adopted definition of content uniformity as described in USP <905> Uniformity of Dosage Units. The calculation in paragraphs 9 and 10 of the Bogue Declaration are not included within the definition of content uniformity as described in USP <905> Uniformity of Dosage Units.
>
> Clevenger Decl. ¶ 6.

2. *Lack of clarity*

The "suitable for . . . regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration . . ." recitation is ambiguous and unclear because there is no set chemical tests or standards required. As Dr. Clevenger explains:

> In my experience, the route to regulatory approval is an ongoing negotiation with the FDA through the New Drug Application (NDA) process. In this negotiation process, analytical testing and standards are determined for each product depending on its particular properties and characteristics. Different active agents and dosage forms have different properties, and would thus generally have different standards and testing requirements. Also, standardized test methods can change over time (*e.g.*, USP <905> was revised in 2007 and 2011), so regulations from 2000 will not provide adequate information for present approval processes.
>
> Clevenger Decl. ¶ 4.

Indeed, the FDA standard cited by Lin demonstrates that different active strengths alone, in products that are otherwise the same, can require different tests. *See* Exhibit J, USP Chapter <905> Uniformity of Dosage Forms (2011), cited in Lin Decl. at ¶ 16. To add to the

confusion, in some cases, a "chemical test" is not even required. If the amount of active is high enough, a Weight Variation Test is acceptable. *See* Exhibit K at pp. 6-7, Q&A5.

Applicant also implies that certain claim limitations are the FDA standard. *See* Claim 1 (varies by no more than 10%), claim 82 (varies by no more than 10% above the desired amount), and Lin Decl. ¶ 22 (no "greater than the 110% level (from and expected amount of 100%) that is considered acceptable to FDA for regulatory approval"). In fact, USP General Chapter <905>, which is cited by Applicant in the Lin Declaration, sets forth a number of standards, each of which is entirely different from anything claimed, argued or described in the '080 Patent. *See* Exhibit K at pp. 2-6.

Because a person of ordinary skill in the art would not be able to determine what is encompassed by a method for manufacturing a film "suitable for regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units," the claims are lacking in clarity.

3. *Lack of written description*

Finally, because the new "suitable…" recitation in the pending claims extends beyond what was disclosed or referenced in the specification, the claims lack written description. That is, even if the FDA did have one standard that would apply to all of the films manufactured by the methods claimed in the '080 Patent—which it does not—the standards have changed over time. For example, in order to harmonize with international standards, the USP General Chapter <905> cited by Applicant in the Lin Declaration, was updated at least twice (*i.e.*,on April 20, 2007, and again on December 1, 2011). *See* Exhibit J and Exhibit K, and Clevenger Decl. ¶ 4. Accordingly, this new recitation appears to reference something that did not exist when the application was filed, and therefore the claims lack written description.

B. Proposed rejection of all pending claims under 35 USC § 112, first and second paragraph – new recitation "analytical chemical tests"

1. *Lack of clarity*

Independent claims 1, 82, 161 and 315-318 newly recite the term "analytical chemical tests." The term "analytical chemical tests" is vague and unclear. What is an "analytical

chemical test" and how does it differ from a non-chemical test or a non-analytical test? Applicant does not disclose any analytical chemical tests or testing of active in the specification, but rather the desirability of testing for chemical and physical uniformity. Testing for chemical uniformity would include weight variation testing according to the FDA, but Applicant insists this is not an analytical chemical test. Compare Exhibit J at p. 1 to Reply at p. 58-59.

Is a chemical transformation required? If so, HPLC testing would not be an analytical chemical test. And HPLC testing is commonly used to assess active content. The confusion is compounded by Applicant's statements that weighing cannot be relied upon to assess uniformity of content data. However, the FDA clearly provides that weight variation testing is a content uniformity test. Exhibit J at p. 1. In short, based upon the plain language in the '080 Patent and compounded by Applicant's arguments, it is not clear what is, and what is not, an analytical chemical test.

2. *Lack of written description*

Nowhere in the '080 Patent does the Applicant describe the type, much less the amount, of analytical chemical testing required for regulatory approval. And even if it did, as discussed above, requirements for regulatory approval vary greatly, and change over time. Nowhere in the specification is the term "analytical chemical tests" written or described.

C. Proposed rejection of all pending claims under 35 USC § 112, first and second paragraphs - new recitation "varies by no more than 10%, 5%, 2%, 1%, 0.5%"

Step (f) of claim 1 and step (e) of claims 82 and 161 have been amended to recite—in reference to the individual dosage units formed—that "for…substantially equal sized individual dosage units…the amount of the active varies by no more than 10%." Claims 315-317 also recite the same language. Step (c) of newly proposed claim 318 recites that "for…substantially equal sized individual dosage units…the amount of said active varies by less than 5%." Newly proposed dependent claims 300-311 include the same recitations or require even narrower degrees of variation, *i.e.*, 2%, 1%, and 0.5%.

1. *Lack of clarity*

The recitations above require that individual dosage units vary from each other in the amount of active by no more than 10%, 5%, 2%, 1% or 0.5%. The clarity issue arises when Applicant attempts to broaden the meaning of these recitations in its Reply:

> …uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of a lot of the resulting film…
>
> Reply at p. 75, lines 7-11 (emphasis added).

The data presented in the Bogue Declaration reflect "the uniformity of content of active of individual dosage units within particular lots and across different lots." Bogue Decl. ¶ 8 (emphasis added) and Appendices A, B and C. But "lots" are not equated to "resulting films." And there is also no reference to a "lot," "lots," or "lots of resulting films" in any of the claims. While Applicant may act as its own lexicographer in drafting the specification, it may not do so after the application has been filed. The fact is, Applicant's "uniformity" data—presented in the Bogue Declaration—fails to demonstrate individual dosage units where the active varies by no more than 10%, 5%, 2%, 1% or 0.5% as claimed.

Moreover, Bogue's Appendix A, which conceals lot variation by dividing it by the lot average, does not negate Bogue's Appendix B, which clearly shows that even the lot data does not satisfy the 10% variance limitation. It only introduces confusion with respect to the meaning of the claims.

2. *Lack of enablement*

Applicant's arguments also create an enablement problem as to the claimed uniformity. Applicant argues that the prior art does not demonstrate its claimed uniformity because "physically observable properties of the resulting film product, for example, its appearance and weight…do not indicate that the amount of active in individual dosage units varies by no more than 10%..." Reply pp. 54-55. "Even if the film appears uniform, analytical chemical tests must then be conducted to verify uniformity of content at the prescribed level." Reply p. 59. In short, Applicant argues that uniformity may only be determined by analytical chemical testing of film,

not merely by physically observable properties of film. There is no indication or evidence in the '080 Patent that the disclosed methods result in a film with the claimed uniformity as determined by analytical chemical testing. In over 100 examples, the '080 Patent never demonstrates that any disclosed method results in a film that satisfies the recited active variation limitation as determined by analytical chemical testing. Applicant erroneously states that "analytical chemical testing is used in the '080 Patent to establish the actual amount of active in samples," citing Example M. Reply p. 59, last full ¶. The '080 Patent discloses no analytical chemical test for active with respect to Example M. '080 Patent 33:10-34:34. In fact, Example M contains no active. A red dye does not fall into the broadest reasonable interpretation of a bioactive or a pharmaceutical active.

Applicant now improperly attempts to remediate its enablement problem by providing the data in the Bogue Declaration. First, a declaration cannot be used to provide enablement after the fact. This is particularly true when the declaration methods are not well-described, and what is described does not match even a single claim. Second, and most importantly, the data does not even meets its own recited requirement. Appendix B of the Bogue Declaration shows that the active in the individual dosage units does vary by more than 10%. Indeed, Applicant admits in the Bogue Declaration that only 46 of the 73 lots (*i.e.,* only 63% of the lots) have active varying less than 5%, and only 1 lot (*i.e.*, only 1% of the lots) has active varying less than 2%. Finally, absolutely no lots have active varying less than 1% or 0.5%.

In short, none of these variation requirements are enabled in the '080 Patent specification. And the Bogue Declaration only serves to prove that its own commercial method—even if it were to fall within the claims—fails to produce films that meet the claimed variation requirements. By Applicant's own admission, without a demonstration of chemical tests, there is no indication that the disclosed methods met these requirements. Reply p. 67, lines 10-15. And physical tests are not enough, according to Applicant. *Id.*

D. Proposed rejection of independent claims 82, 315, and dependent claims 83-90, 92-94, 96-160, 261-271, 274, 276-278, 298, 304-307, and 313, under 35 USC § 112, first and second paragraphs - new recitation "varies by no more than 10% from desired amount of active".

In contrast to the maximum active variance limit recited in each of the independent claims and discussed directly above—step (f) of claims 82 and 315 includes the new recitation that "the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active."

1. *Lack of clarity*

Whereas the previously discussed new recitation allows a larger maximum variation of active content, this new recitation allows a maximum variation of 20% (± 10% around a target) in active content. Again, Applicant introduces clarity issues by attempting to amend its claims to match its new data. This new recitation in step (f) of claims 82 and 315 is particularly confusing because it appears to be broader than the uniformity recitation already present in step (e) of claims 82 and 315. The new language only appears to indicate that repeating the claimed method need not produce consistent films.

2. *Lack of written description*

The new language introduced into claims 82 and 315 allows a maximum variation of 20% (±10% around a desired amount or target) in the active content. Nowhere in the '080 Patent is this language found. Nor is this new definition of uniformity described or exemplified. Also there is absolutely no support for the idea that some uniformity is required within a resulting film and another is required between films. This language has been entirely fabricated in an attempt to retroactively support their claims with new data, but data in the specification does not support newly recited maximum variation of 20% in active content. As set forth in the MPEP: "If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from…the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.02. The claims lack written description because nowhere in the specification are these new limitation described.

3. *Lack of enablement*

Applicant's arguments also create the same enablement problem as to the maximum variation of active as discussed above. That is, there is no evidence in the '080 Patent that the

disclosed methods result in a film with the claimed uniformity—as determined by analytical chemical testing. And a declaration cannot be used to provide enablement after the fact.

E. Proposed rejection of all pending claims under 35 USC § 112, second paragraph – new recitation "rapidly increasing the viscosity of said flowable polymer matrix"

Step (d) of claim 1 and step (c) of claims 82 and 161 have been amended to include the vague and relative phrase "rapidly increasing the viscosity of said flowable polymer matrix." Each and every new independent claim recites the same language. First, the term "rapidly" is a relative term with no benchmark for assessment provided in the '080 Patent. Additionally, the term "rapidly" only refers to the timing at which a desired result is obtained. It does not refer to a well-defined manipulative step. Finally, there is no indication of the degree to which the viscosity must be increased. By its very nature, any drying process increases viscosity to some extent and may be deemed to do so "rapidly" by some benchmark. A person of ordinary skill in the art would not reasonably be apprised of what specific step or steps are required to "rapidly increase the viscosity." In short, introduction of this phrase into this claim creates ambiguity and indefiniteness.

F. Proposed rejection of all pending claims under 35 USC § 112, second paragraph – new recitation "during said drying said flowable polymer matrix temperature is 100 °C or less"

Claims 1, 82, and 161 have been amended to recite the phrase "during said drying said flowable polymer matrix temperature is 100 °C or less." New independent claims 315-318 recite the same language. This phrase introduces ambiguity into the claims. It is specifically noted that this temperature describes the flowable polymer matrix, not the visco-elastic film (*i.e.*, the matrix before it has been dried to a film). It appears that the limitation may be satisfied if the flowable polymer matrix began the drying at a temperature of 100 °C or less because this is "during said drying." Alternatively, it may require the temperature to be less than 100 °C throughout the drying step. It is unclear.

Also, the matrix comprises a solvent which "…may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof." '080 Patent 14:67 – 15:3. Since every single recited solvent has a boiling

point of 100 °C or less, it is not clear how the matrix would reach a temperature above the boiling point of the solvent contained therein. If the Applicant intended to recite that the visco-elastic film temperature is 100 °C or less, this has not been properly claimed. And even if it were, this recitation means nothing unless the oven temperature is above 100 °C. Since the oven temperatures utilized in the Examples of the '080 Patent are less than 100 °C ('080 Patent, Tables 7, 17, and 18), it is not clear what, if anything, this recitation might exclude. This is particularly significant with respect to claim 318, where the drying apparatus is "at a temperature of 60 °C." How would the matrix ever reach a temperature that is 40° hotter than the oven?

G. Proposed rejection of claim 318 under 35 USC § 112, first paragraph – lack of written description for combination of disparate concepts

There is absolutely no evidence in the '080 Patent specification that the Applicant had possession of the method recited in claim 318 at the time of filing.

> [T]o satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'
>
> MPEP 2163.02, *citing Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985) and *quoting In re Kaslow*, 707 F.2d 1366, 1375, (Fed. Cir. 1983).

Applicant has cobbled together unrelated elements in the '080 Patent specification. This lack of written description is evident, for example, in step (c):

> controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus at a temperature of about 60 °C and using air currents, which have forces below a yield value of the polymer matrix during drying… to form a visco-elastic film… within about the first 4 minutes …such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%.
>
> Claim 318, step (c).

There are only two instances in the '080 Patent where a temperature of "about 60 °C" appears. The first instance, Example CF, makes no reference whatsoever to: (i) the yield value of the film; (ii) control of air velocities; or (iii) visco-elasticity of film at 4 minutes. *See* '080 Patent 41:49-50. The second instance, Examples P1-P3 use a "second heater section" at 60 °C with no top air flow, but does not exemplify a method suitable for film formation. *See* '080 Patent 35:57-59 ("Composition P displayed a stringy elastic property. The wet film would not stay level, the coating was uneven, and the film did not dry.").

Moreover, the desired property relating to variation in active content—"[d]esirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight" (*see* '080 Patent 15:40-43)—cannot be attributed to any one of the 60 °C temperature, the air currents, or the formation of a visco-elastic film within 4 minutes. Indeed, there are no examples showing a variation of less than 5% in active content.

In short, this new combination of elements found in unconnected passages of the specification lacks written description. Even if some of the elements were connected in some way, the requirement of 5% or less variation in active content is not enabled.

H. Proposed rejection of all pending claims under 35 USC § 112, first and second paragraph – the large variety of alternative expressions relating to the desired uniformity

Instead of amending the claims to recite manipulative steps that distinguish the cited art, Applicant relies on its own newly concocted and varied expressions of its desired property of "substantially uniform distribution of active" to allegedly distinguish its methods. Indeed, as discussed above, what Applicant deems uniformity is really acceptable non-uniformity. This approach serves only to demonstrate how the amended claims lack certainty, enablement, and written description.

1. *Lack of clarity*

Applicant adds so many new and different recitations regarding variation limitations to its independent claims, with multiple distinct variation levels, even within the same claim, that the claims are mired in ambiguity and uncertainty.

Taking independent claim 82 as a representative claim, the problem with Applicant's approach is readily apparent. The preamble recites that the film must be suitable for regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the FDA relating to variation of an active in individual dosage units. Later in step (e), claim 82 requires that the film is suitable for FDA approval without connecting the suitability to analytical chemical tests or the standards of the FDA relating to variation of active content recited in the preamble. Are analytical chemical tests required to show the FDA standards are met? Must the film meet the FDA standards relating to variation of an active? Those limitations are not recited in the body of the claim. Then, to add more confusion, analytical chemical tests are required in a different part of step (e) to "indicate" that the active varies by no more than 10% in individual dosage units. First, this is not the FDA standard for approval. As discussed above, the standard is defined in USP General Chapter <905>. *See* Exhibit J. Second, what does it mean to "indicate" that the active varies by no more than 10%? Yet, there is one more layer of confusion. New step (f) requires that the amount of active varies no more than 10% from the desired amount of active. What is the desired active content? New step (f) also recites "said resulting film and said additional resulting films." How does a "resulting film" differ from "additional resulting films"? Where is that described in the specification? Or demonstrated for that matter? There is simply no discussion of ±10% from a target anywhere in the specification. And certainly not with respect to comparison of "resulting films." And why is the amount of variation so large? This new claim amendment, and the data presented in the Bogue Declaration, only serve to demonstrate that repeating the claimed method does not produce consistent films. The Applicant has neither described nor enabled the method it now seeks to claim.

Every single independent claim is similarly confusing, each with their own combination of the many shades of "uniformity" that individually and collectively create a hopeless morass of confusion.

2. *Lack of written description.*

As discussed above, there is absolutely no support for the recitation of "varying by no more an 10% from a desired target." And certainly none for this variation between "resulting

films" and "additional resulting films." In addition, if *Chen*'s disclosure is not enabling with respect to the various regulatory authority recitations, neither is its own. *See* Section above regarding the Lin Declaration.

3. *Lack of enablement*

Nowhere in any of the over 100 examples in the '080 Patent is any film demonstrated to meet any of the newly recited "uniformity" limitations. No analytical chemical tests are performed with respect to an active. No results of analytical chemical tests of active are provided. No demonstration is made that the active varies by no more than 10% in individual dosage units. No demonstration is made that "resulting films" and "additional resulting films" vary by no more than 10% from a desired target. It almost seems like Applicant is not familiar with the '080 Patent because every recitation added to distinguish claims from the cited art lacks written description and/or enablement in the '080 Patent specification.

V. MAINTAINED AND PROPOSED REJECTIONS OF ALL CLAIMS OVER CITED PRIOR ART

A. The Applicant has failed to establish that even one of the rejections of record is incorrect and should be withdrawn

In reply to the rejections of record, Applicant declines to explain how their claimed process differs from the processes of the cited references. Instead, Applicant applies five strategies that fail to advance prosecution. For the sake of brevity these strategies are addressed up front and individual rejections are further addressed as necessary directly below.

1. *Applicant argues that the prior art does not use the "same materials and method" as Applicant, "particularly as amended."*

Applicant's position that the cited art does not use the "same materials and method" and therefore cannot provide films with the same degree of uniformity appears to be based—in large part—on Applicant's position that the cited art does not disclose the newly-claimed steps of performing analytical chemical tests[2]. *See, e.g.*, Reply pp. 66-67. The newly-claimed steps are

[2] Secondary arguments, which are particular to *Staab*, *Le Person, and Horstmann*, are discussed with respect to each rejection below.

insignificant for at least three reasons. First, any alleged failure to disclose post-manufacturing analytical chemical tests does not change the fact that films of the cited prior art meet the claimed maximum variation of active. And the Office has made a proper *prima facie* case because the cited art teaches all of the manufacturing steps recited in the claims. It is now Applicant's burden to prove that the methods of the cited art do not necessarily produce film with the recited characteristics. *See* MPEP § 2112 (V). Second, as discussed above, adding a recitation of post-solution activity to a claimed process for manufacturing film cannot render the claimed manufacturing process patentable. Finally, the new steps—by Applicant's admission—are "conventional means for examining and testing" uniformity. *See* '080 Patent 29:33-39. In short, the new steps fail to distinguish the claimed methods for making films over prior art methods.

2. *Applicant relies on data that (i) does not correspond to any claimed method; and (ii) does not correspond to any claimed result.*

As discussed in the section devoted to the Bogue Declaration, the method recited in the Bogue Declaration does not match a single pending claim of the '080 Patent. And even if the process used to make the film lots in the Bogue Declaration were to match all of the steps recited in any of the '080 Patent claims—which has not been demonstrated—the resulting variance in active content fails to satisfy limits recited in the claims. To the extent that Applicant argues that "lots" of films would satisfy the active variance limits recited in the claims, this is completely unsupported in the specification. And none of the claims refers to "lots" of films. Finally, any unexpected results are irrelevant to anticipation by inherency. Indeed such results are referred to as "inherent."

3. *To the extent that the information in Chen is insufficient for FDA film product approval, the information in the '080 Patent is also insufficient.*

Applicant uses the Lin Declaration to support its argument that there is insufficient disclosure in *Chen* to allow the FDA to determine whether the drug product (*i.e.*, film) can be manufactured to the specification required for FDA approval. *See* Reply pp. 98-99 *citing* Lin Decl. ¶¶ 17-22. First and foremost, it is unreasonable to expect that a patent application would

have the level of information required for an FDA New Drug Application. These are two very different documents having two very different requirements and purposes. Clevenger Decl. ¶ 5. And, to the extent that *Chen* does not provide sufficient information to comply with all the information required in an NDA, neither does the "080 Patent. Clevenger Decl. ¶ 5.

4. *Applicant relies on an inherency case that has facts that support the Examiner's rejection.*

Applicant relies on the *Crown Operations International, Ltd. v. Solutia Inc.* decision in reply to every inherency rejection. But there was no genuine inherency issue in *Crown*. Indeed, the Federal Circuit merely affirmed the summary judgment Order of the court that there was no genuine issue of inherency. *See Crown*, 289 F.3d 1367, 1370 (Fed. Cir. 2002). And summary judgment is granted when, taking all facts in the light most favorable to the non-moving party, and with all doubts resolved in favor of the non-moving party, there is no genuine issue of material fact. *See* Fed. Rules Civ. Proc. Rule 56(c). *See also Anderson v. Liberty Lobby, Inc.*, 477 US 242, 255, 106 S. Ct. 2505 (1986).

The issue before the court was whether the safety/solar film assembly of the prior art inherently contributed no more than about 2% visible reflectance, as was recited in the patent claims. *See* Exhibit F, *Crown Operations International, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1371 (Fed. Cir. 2002). In the *Crown* case, there was no genuine issue of inherency because the examples in the prior art patent taught a glass thickness that, alone, would produce about 14% visible reflectance. *See* Exhibit G, *Crown Operations International, Ltd. V. Solutia Inc.*, 2000 WL 33906466 (W.D.Wis.) at 10. Based on the glass thickness alone—no matter what the patent taught about the rest of the safety/solar film—the film could not achieve the less than 2% reflectance. Attached are both opinions so that the Examiner can readily see for himself that the presentation of the facts of case to the Office was incomplete.

In short, the *Crown* case is the opposite of this reexamination, where the cited prior art references demonstrate uniformity to the same degree as the '080 Patent. The visual inspection and weight comparison employed to demonstrate uniformity in *Chen* are the very same methods for determining uniformity disclosed in the '080 Patent. *Compare Chen* 17:15 (demonstrating apparent uniform distribution by naked eye), p. 22 (Table 6 demonstrating uniform weight) and

Figure 5 (demonstrating dosages dissolved and "chemical" tested) *to* the '080 Patent 31:38-45 (demonstrating apparent uniform distribution by naked eye or slight magnification), 31:46-32:36 (demonstrating uniformity by uniform weight), 32:36-41 (proposing "an alternative method" by dissolution and "chemical" testing, but not actually testing its examples).

Unlike *Crown*, *Markman v. Westview Instruments, Inc.* is relevant to this reexamination. In *Markman*, the Supreme Court made clear that desired properties and scientific theories or explanations are not entitled to patentable weight. *See* 517 U.S. 370, 373 (1996) ("A claim covers and secures a process, a machine, a manufacture, a composition of matter, or a design, but never the function or result of either, nor the scientific explanation of their operation") (emphasis added). And, with respect to process claims, the Federal Circuit consistently held that, in a validity analysis, a "whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step...." *Minton v. Nat'l Ass'n of Securities Dealers*, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) citing *Texas Instruments v. USITC*, 988 F.3d 1165, 1172 (Fed. Cir. 1993); *see* also, *e.g.,* MPEP 2111.04. In the present claims, the process steps required to achieve the recited properties are not positively recited. The "elements" of a method claim are, and must be, acts or manipulative steps that are performed upon an article or chemical substance. Simply reciting desired features of a film, *e.g.,* substantial uniformity, and/or a scientific explanation of how uniformity is maintained, are of little patentable consequence in process claims. Rather, Applicant must properly recite the manipulative steps that necessarily produce the desired properties.

After *Markman*, the Federal Circuit decided a case with facts and issues strikingly similar to those presented here: *Bristol Myers Squibb Co. v. Ben Venue Labs, Inc.* In the *Bristol* case, the patentee failed to distinguish its process over the prior art by positively reciting method steps that were not in the prior art. Instead, the patent recited broad steps and relied on desired results rather than method steps to distinguish its methods over those of the prior art. The *Bristol* court found that the mere recitation of purpose and desired results does not patentably distinguish the claims over the same methods recited in the prior art. *See Bristol,* 246 F.3d 1368, 1376 (Fed. Cir. 2001) (Exhibit H) (desired results such as the anti-tumor effect "[do] not result in a manipulative difference in the steps of the claim."). Indeed, like the patentee in the *Bristol* case,

Applicant would like to retain its overly broad method claims even though the very same steps are in the prior art. Rather than positively reciting method steps that distinguish its claims over the prior art methods, Applicant relies on recitations of scientific theories and desired results. Applicant wishes to not only cover its own commercial product, but also to cover all methods of making films regardless of whether the methods falls within the prior art. As the Federal Circuit concluded in the *Bristol* case, Applicant "cannot have it both ways." *Id.*

5. *Applicant relies on cases that create a narrow exception from the established case law of Markman; but its own case does not fall within that exception.*

Applicant cites *Hoffer v. Microsoft Corp.*, 405 F.3d 1326 (Fed. Cir. 2005), for the proposition that their wherein clause "cannot be ignored in order to change the substance of the invention." Reply p. 73. Applicant's reliance on *Hoffer* is misplaced for at least three reasons. First, *Hoffer's* ruling—that a clause cannot be disregarded in determining patent infringement—does not address the question of whether a wherein clause should be given patentable weight during reexamination. Second, the wherein clause at issue in *Hoffer* was more than just a desired result. *Hoffer,* 405 F.3d at 1330 ("The whereby clause describes a network of users at multiple remote user terminals who are 'collectively able to concurrently engage in interactive data messaging.' This capability is more than the intended result of a process step; it is part of the process itself."). The relevant clauses in the present reexamination—clauses referring to the desired uniformity, desired regulatory approval, and other desired results—are not manipulative steps of the process itself, and are therefore not entitled to patentable weight. Third and finally, Applicant's argument that disregarding the '080 Patent's wherein clause would "change the substance of the invention" appears to be an admission that there are no manipulative steps recited in the claims that would provide the desired results. In short, *Hoffer* is not relevant to the facts and issues in this reexamination.

Applicant also points to *Griffin v. Bertina*, 285 F.3d. 1029 (Fed. Cir. 2002), as showing that a wherein clause is a claim limitation "because they relate back to and clarify what is required by the count." Like *Hoffer*, *Griffin* did not address whether a wherein clause should be given patentable weight during reexamination. Instead, *Griffin* addressed whether a wherein

clause should be disregarded during an interference. Also like *Hoffer*, *Griffin* found that the wherein clauses at issue in that case were part of the process itself.

B. Proper rejection of claims 1, 4, 5, 8-15, 17, 18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84, 87-90, 92-94, 96, 97, 99-111,113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-176, 178, 179, 181-193, 195, 197-201,205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-254, 256-262, 264, 265, 267-272, 274-280, 282, 283, 285-290, and 292-299 and proposed new rejection of new independent claims 315-318 under 35 USC 102(b) as anticipated by or, in the alternative, under 35 USC 103(a) as obvious over *Chen*

Applicant's Reply contends that the Examiner's rejection "is based on the belief that *Chen* uses the 'same materials and method as the Patentee,' but even if true, much more is required." Reply p. 67. This statement is incorrect on its face. If it is true that *Chen* uses the same materials and methods – which it does – then a *prima facie* case has been established and no more is required by the Office. Applicant criticizes *Chen* as being "so general and devoid of detail so as to provide no guidance other than that to dry, one places a film in a conventional hot air circulating oven at a temperature of from 40-100 °C and leaves it for a period of time." Reply p. 76. But Applicant fails to appreciate that, even if this statement were true, the method *Chen* describes would still anticipate the claims.

The suggestion—that Requester must show that "*Chen*'s process examples when followed exactly, with all the components exactly as listed, and all other conditions of *Chen* exactly met, will provide a process suitable for commercial manufacture, a process which produces products which are regulatory approvable by the FDA, and which exhibit the levels of uniformity of content in actual amount of active claimed by Patentee's processes" (Reply p. 66)—is simply incorrect. The burden is not on the Requester or the Office to prove that *Chen* inherently produces the desired results recited in the claim. The burden has been shifted to Applicant to show that *Chen* does not inherently produce these results. Applicant has not done so.

Turning to Applicant's contention that the Examiner's inherency rejection is "particularly incorrect in light of the claims as amended," none of the added recitations further distinguish the claims from *Chen*. Applicant, specifically discussing claim 317, asserts that *Chen* does not

disclose certain claim recitations found in claim 317, including "…a drying apparatus at a temperature of at least 60 °C … and further controlling drying through a process comprising drying at a temperature differential ranging from 5° C to 30 °C between polymer matrix inside temperature and outside exposure temperature." Reply p. 75. But claim 317 does not include any of these recitations.[3] And in fact, none of the claims include a recitation of the temperature differential.

To the extent that the newly added recitations in any of the proposed claims can be construed as limiting (*i.e.*, are neither admitted conventional prior art post-manufacturing steps nor intended results not entitled to patentable weight), *Chen* teaches them, as clearly evidenced by the Reitman Declaration and discussed below. Accordingly, there remains no distinction between the process of *Chen* and the presently claimed processes.

1. *New recitation: "said polymer matrix having a viscosity from about 400 to about 100,000 cps"*

Each and every independent claim recites that the polymer matrix has a viscosity from about 400 to about 100,000 cps. This range encompasses viscosities ranging from very thin castor oil to mincemeat. *See* Exhibit E. Thus, it is not clear how this would even limit the claim. In any event, *Chen* specifically teaches, at page 15, lines 24-26, that their coating solution has a viscosity of 500-15,000 cps. Additionally, Examples 4-8 in *Chen* all include 21% Methocel E5 HPMC in water. Attached as Exhibit I is an informational sheet showing the viscosity of various concentrations of Methocel E5 HPMC in water. Exhibit I, Figure 2, at p. 10. As demonstrated in this Exhibit, the coating solutions utilized in *Chen's* Examples 4-8 fall within the limitation of "about 400 to about 100,000 cps." Dr. Reitman confirms that the polymer mixture prepared in accordance with *Chen*'s Example 7 "exhibited the flow properties of honey (around 10,000 cps), as observed by my team." Reitman Decl. ¶8. In short, the addition of this viscosity range does not further distinguish from the teachings of *Chen* in any way.

2. *New recitation: "controlling drying."*

[3] To the extent that claim 318 includes some of these recitations, they are addressed below.

Each and every independent claim recites "controlling drying." Applicant alleges that *Chen* does not disclose "any controlled drying process whatsoever." Reply p. 76. But it has already been established that *Chen* teaches controlled drying. *See* Office Action p. 12, 2nd ¶. In particular, *Chen* discloses a drying apparatus in Fig. 2 that includes an "aeration controller" (11). It also discloses controlling the drying temperature. *See Chen*, p. 15, lines 28-29.

Also, it is not apparent whether "controlled" refers to time, temperature, airflow, atmosphere, etc. and there is nothing in the claims that provides any indication of how drying may be "controlled." Applicant argues that:

> [c]ontrolled drying includes methods that avoid, for example, the formation of bubbles, or uncontrolled air currents that may cause movement of particles within the visco-elastic film forming matrix. Controlled drying, as required by the invention as claimed, may be effectuated through evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100°C or less.
>
> Reply pp. 54-55.

To the extent that Applicant attempts to tie "controlled" to the idea of "evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying," this recitation is (1) already recited in the claim (so it is not clear what "controlled" would add to the claim) and (2) also inherent in *Chen*, as described immediately hereafter. And the argument is so circular that "controlled" adds no additional meaning to the claim. Arguing that the active is locked in by evaporating solvent to lock in the active amounts to nothing more than a desired result of the manipulative evaporating step. Once again, Applicant relies on what they want to obtain, rather than a manipulative step to get there – this is not proper in a method claim. And even if it were, it does not further distinguish *Chen*.

3. *New recitation: "conveying said polymer matrix through a drying apparatus..."*

Each and every independent claim in the proposed claims recites "conveying said polymer matrix through a drying apparatus." The claims do not recite the conditions imposed by the drying apparatus. To the extent that the word "conveying" represents any meaningful limitation whatsoever, *Chen* discloses, in Figure 2, a manufacturing process that would convey the matrix through the drying oven. Thus, addition of "conveying said polymer matrix" does not further distinguish from the teachings of *Chen* in any way.

4. *New recitation: "to form a visco-elastic film having said active uniformly distributed throughout within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying"*

Each and every proposed independent claim recites "to form a visco-elastic film having said active uniformly distributed throughout within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying." To the extent that this is deemed a process limitation at all, *Chen* also increases the viscosity of the polymer matrix upon initiation of drying to form a viscoelastic film within about the first 4 minutes. In the words of Dr. Reitman: "Within about 4 minutes after initiation of drying, the film was self-supporting, non-tacky, flexible and viscoelastic, as verified by my team." Reitman Decl. ¶ 8.

5. *New recitation: "wherein the polymer matrix temperature is 100°C or less."*

Each and every proposed independent claim recites that the polymer matrix temperature is 100° C or less. It is not clear how this recitation would even meaningfully limit the claims. In any event, *Chen* specifically teaches, at page 15, line 28, that the film is "dried under aeration at a temperature between 40 and 100° C." The polymer matrix temperature of *Chen* would meet the limitation of "100° C or less" because the oven temperature is less than 100° C. Additionally, Examples 4-8 in *Chen* all utilize an oven at 50° C, so the polymer matrix would never reach 100° C. Thus, this temperature range does not distinguish any claim from the teachings of *Chen*.

6. *New recitations: "performing analytical chemical tests"*

Each and every proposed independent claim recites the step of performing analytical chemical tests. To the extent that this post-solution step would be deemed worthy of consideration, it is taught by *Chen*. Applicant argues that *Chen* is deficient because it lacks the newly claimed "analytical chemical tests" for content uniformity, but actually it is the '080 Patent that lacks such analytical chemical tests. Not a single analytical chemical test was performed in over 100 examples of the '080 Patent to assess uniformity of active. Example M provides a fluorescence test for the amount of a red dye in the film. Red dye is not an active within the scope of the claims. Indeed, the only tests performed to assess uniformity of active in the '080 Patent are the physical tests that Applicant now argues (without support in the specification) are inferior to the "analytical chemical tests" of its new claims.

The new argument that the only effective way to determine uniformity of active is by analytical chemical testing is untenable. First, there is no requirement that the prior art even recognize an inherent property, much less test for it. Second, the '080 Patent specifically provides that films:

> …may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art.
>
> '080 Patent 29:34-39.

Applicant admits that *any conventional means* may be employed for testing uniformity of content. Applicant's new position that "[v]isual observation and physical measurements such as weight is insufficient to determine the active amount in equally sized dosage units" directly contradicts its own disclosure where these tests are described as alternatives to so-called "chemical tests." Compare *id.* to Reply p. 67. Similarly, Applicant's allegation—that "compositional uniformity or uniformity of content is not the same as having a surface that appears free of defects. Importantly, having a glossy surface does not equate to a uniform film..." (*see* Reply p. 55)—contradicts the specification at col. 31, lines 38-45. The specification states that "[t]he uniform distribution of the components within the film was apparent by examination

by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation…."

While Applicant may now dispute the uniformity criteria set forth in the '080 Patent, *Chen* not only teaches the same visual inspection method demonstrated in the '080 Patent, but also subjects samples of Examples 4-8 to "analytical chemical testing". *See Chen* Figure 5.

Applicant entirely misses the point when it states: "*Chen's* Figure 5 (Examples 5-8) clearly shows a lack of compositional uniformity of active". Reply at p. 77. Applicant's suggestion that the release profile over time indicates non-uniformity is ridiculous on its face. First, Applicant does not claim a uniform release profile—only a uniform amount of active per unit dosage. Second, there are many reasons by the different drugs may have different release profiles, the most important being different properties of the drugs. Finally, the error bars in Figure 5 cannot be interpreted to show a lack of active uniformity. As explained above in the discussion of the *Lin* Declaration, the fact that *Chen's* maximum release error bars decrease over time, indicates that the error noted in Lin is an artifact of the test method—not a characteristic of the film. In fact, even Dr. Lin concedes that the Figure 5 "data indicate that the test method used in the analysis is not reproducible." *See* Lin Decl. ¶ 22.

In short, adding the post-solution step of performing analytical chemical tests does not further distinguish the claims from *Chen*.

7. *New recitation: "suitable for commercialization and regulatory approval."*

The preamble of each independent claim recites that the films are suitable for commercialization and regulatory approval. To the extent that this recitation has any meaning, it is—at best—a desired result that is not entitled to patentable weight in a process claim. Moreover, as discussed in great detail in Section II.A regarding the Lin Declaration and the first § 112 rejection, to the extent that *Chen* lack sufficient data to allow for FDA approval, the '080 Patent is similarly lacking. In addition, Applicant clearly ties the recitation of "suitable for commercialization and regulatory approval" with the idea of obtaining a specific content uniformity and testing for that uniformity. As discussed in detail herein, *Chen* teaches the same

steps as presently claimed, would inherently produce the same desired uniformity, and further provides tests that show content uniformity. That is, in films produced by using the methods of *Chen* "…the active varies by less than 10%." Reitman Decl. ¶ 7.

8. New recitation: "such that uniformity of content in the amount of *said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%."*

Each independent claim except claim 318 recites that the amount of active in individual dosage units varies by no more than 10%. Claim 318 includes a similar recitation but specifies 5%. These recitations are desired results that are not entitled to patentable weight. In any event, *Chen* teaches the same manipulative steps for forming a film as presently claimed, and the resulting films would inherently have this desired property.

Furthermore, as confirmed by the Reitman Declaration, the sampling and "analytical chemical testing" of dosage units manufactured in accordance with *Chen* verified that "the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 10%." *See* Reitman Decl. ¶ 7 and Table 3. With respect to the recitation of active "vary[ing] no more than 5%" in claim 318, the data in the Bogue Declaration fails to support this desired result. That is, even if the Bogue method were commensurate in scope with any of the pending claims—which has not been demonstrated—only 46 of the 73 lots in the Bogue Declaration report active varying by 5% or less. Thus, the Bogue Declaration demonstrates that this desired result is not provided by Applicant's methods, and therefore this recitation cannot be properly added to the claims or relied upon to support patentability.

9. *New recitation: forming "additional resulting films, such that the uniformity of content of active in said resulting film and said additional resulting films varies no more than 10% from a desired amount."*

Amended claim 82 and proposed new claim 315 recite that additional films are formed having active that does not vary by more than 10% from a desired amount. Not only is this *another* desired result not entitled to patentable weight, the recitation of variation from a desired

amount is completely unsupported by the '080 Patent. In any event, to the extent that this recitation adds anything to the claims, *Chen* teaches the same manipulative steps for forming a film as presently claimed, and the resulting films would thus inherently have this desired property.

10. *New recitation: "at a temperature of about 60 °C."*

New claim 318 recites that the drying apparatus is at a temperature of about 60 °C. *Chen* teaches drying "under aeration at a temperature between 40-100 °C, which is inclusive of 60 °C. To the extent that *Chen* does not specifically call out 60 °C, a person of ordinary skill in the art could immediately envision this temperature based upon the teaching of *Chen*. In addition, *Chen's* Examples were performed at 50 °C and, as shown in the Reitman Declaration, were uniform. There is no reason to believe that the same process at about 60 °C would not also be uniform. Thus, this recitation does not further distinguish from the teachings of *Chen*.

11. *New recitation: "using air currents, which have forces below a yield value of the polymer matrix."*

Proposed new claim 318 recites that the drying uses "air currents, which have forces below a yield value of the polymer matrix." The '080 Patent states that "air velocities are desirably below the yield values of the film, *i.e.*, below any force level that can move the liquids in the film-forming compositions." *See* '080 Patent, 11:21-23. Moving liquids in the matrix during drying would produce defects in the film. *Chen*, however, produces a film that is glossy and substantially transparent. Contrary to Applicant's argument that "having a glossy surface does not equate to a uniform film, because the bottom side of a film product formed on a substrate will take the surface features of the substrate" (*see* Reply p. 55), *Chen* does not indicate that the film is glossy only on the bottom side, but a film that is glossy. Furthermore, *Chen*'s aeration controller (depicted in Figure 2) shows that little, if any, air is impinging on the surface of the film at the beginning of drying (*e.g.*, when it is still a flowable polymer matrix). Thus, air currents that do not exceed the yield value of the matrix do not further distinguish the claimed methods from the methods of *Chen*.

For at least the foregoing reasons, the rejection of claims listed in the section heading as anticipated by, or in the alternative, obvious over *Chen* should be maintained. And the rejection

should be extended to new independent claims 315-318 because—like amended claims 1, 82, and 161—they also fail to present any method recitations that patentably distinguish the claims over the methods of *Chen*.

C. Proposed rejection of new dependent claims 300-314 under 35 USC 102(b) as anticipated by or, in the alternative, under 35 USC 103(a) as obvious over *Chen*

Applicant has failed to separately argue any of the new dependent claims. Claims 300-311 recite "wherein said tests further indicate that the amount of active in said individual dosage units varies by less than 5%, 2%, 1% or 0.5%." First, these recitations are desired results and therefore not entitled to patentable weight. *See* Sections V(A) and V(A)5. In any event, *Chen's* processes include the same manipulative steps as Applicant's claims, and employ the same materials, and therefore this result is inherent. Claims 312-314 recite "wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof." These claims are anticipated because *Chen* teaches that its wet films are dried in a hot air (*i.e.*, air currents) circulating oven. *See* page 17, line 14. Because *Chen* anticipates, or discloses an obvious variation of, the claimed subject matter as set forth in detail in Table 1, Applicant requests the adoption of this proposed rejection.

D. Proper rejection of claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 85, 86, 98, 112, 114, 120-122, 127-129, 131,134-137, 139, 140, 167, 168, 180, 194, 196, 202-204, 209-211,213, 216-219, 221,222, 245, 248, 263, 266, 281, and 284 under 35 USC 103(a) as obvious over *Chen*

The claims listed in the section heading depend from claims 1, 82, and 161. As discussed above, amended claims 1, 82, and 161 are anticipated by, or in the alternative, obvious over *Chen*. Moreover, the limitations recited in these dependent claims are commonly known features and have already been deemed obvious to the Office Action. In any event, it would have been obvious to one of the ordinary skill in the art at the time of filing to incorporate these features into *Chen's* methods. Therefore, the rejection of these claims as obvious over *Chen* should be maintained.

E. Proper rejection of claims 2, 3, 32, 55, 72-81, 111,134, 151-160, 193, 216, and 233-242 under 35 USC 103(a) as obvious over the combined teachings of *Chen* and *Staab*

The claims listed in the section heading depend from claims 1, 82, and 161. As discussed above, amended claims 1, 82, and 161 are obvious over *Chen* in view of *Staab*. Moreover, the limitations recited in these dependent claims are commonly known features and have already been deemed obvious in the Office Action. In any event, it would have been obvious to one of the ordinary skill in the art at the time of filing to incorporate these features into *Chen's* methods. Therefore, the rejection of these claims as obvious over *Chen* in view of *Staab* should be maintained.

F. Proposed rejection of new independent claim 318 under 35 USC 103(a) as obvious over the combined teachings of *Chen* and *Arter*

As discussed in Section V(B), independent claim 318 should be rejected under 35 USC 102(b) as anticipated by or, in the alternative, under 35 USC § 103(a) as obvious over *Chen*. *Arter* (U.S. Patent No. 4,365,423, Exhibit L) also fully describes drying step (c) of claim 318, and does so in detail. *Arter* describes and exemplifies drying wet films in a two zone dryer, as shown in Figures 1-3. In the first zone, the film is rapidly dried while being protected by a shield that creates a quiescent zone above the top surface of the film in which there are no turbulent flow conditions and uniform drying is promoted. *See* Arter 12:10-20. Accordingly, *Arter* teaches "using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent," as required by step (c) of claim 318.

The first drying zone achieves the major portion of the drying. Thus, a visco-elastic film is formed by applying hot air currents to the bottom side and yet applying substantially no top air flow to maintain uniformity (*see* Arter 13:24-26). As can be seen, *e.g.*, in Figures 2 and 3, hot air flows, or is "applied", around the bottom side of the conveyor surface. Since the major portion of drying is accomplished in the first zone, the film would be visco-elastic at this point, and the active components locked in place as described in step (c).

Following the first zone, the film is further dried in a second zone to remove residual liquid medium from the film. *See* Arter 13:24-29 and Figures 1-3.

With respect to specific parameters recited in step (c), *Arter* exemplifies films that are dried in less than 3 seconds at 60 °C (Example 1, 15:45-55) and less than 6 seconds at 93°C (Example 2, 17:4-6) in the first drying zone. Thus, *Arter* discloses rapidly forming a visco-elastic film in less than 4.0 minutes "at a temperature of about 60 °C" in Examples 1-2. The films are further dried "to remove residual solvent" in a second step. *See* Arter Examples and Figures 1 and 4. *See also*, Arter 13:24-29, for a further description of (1) a first drying zone to remove a "major portion" of the solvent and (2) a second drying zone to remove "residual liquid medium."

The result of the drying process of *Arter* is that the films are dried with (a) substantially no top air flow, thus preventing flow migration (Arter 13:15-16), and (b) uniform heat transfer conditions to promote uniform drying (Arter 13:65-68). In other words, *Arter's* method prevents intermolecular forces from creating aggregates or conglomerates of components and maintains the compositional uniform distribution of components. A person of ordinary skill in the art would have been motivated to apply the commercial manufacturing methods of *Arter* to *Chen* in order to further increase the speed and efficiency of manufacture, and to further promote uniform drying.

G. Proposed rejection of new independent claim 318 under 35 USC 103(a) as obvious over the combined teachings of *Chen* and *Strobush*

Strobush (US Patent No. 5,881,476, Exhibit M) teaches a method for drying a coating on a substrate. *Strobush* discloses a drying apparatus depicted in Figure 23, wherein the first zone provides hot air currents to the underside of the conveyor and maintains airflow above the film only to the extent required for safe operation. The majority of the drying heat is provided by the backside airfoils in a first zone. Strobush 19:36-46.

In particular, *Strobush* teaches that "if desired, topside air bars (34) can be used such that no gas is supplied by the air bars when topside gas is not needed or desired.") (emphasis added). *See* Strobush 11:15-17 and 11:24-27. In other words, it teaches "using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent," as required by claim 318.

To the extent that the drying "at a temperature of about 60 °C" recited in step (c) of claim 318 is not obvious in view of *Chen*, *Strobush* describes drying temperatures in the range of 60-93.3 °C in the Examples. *See* Strobush 21:Tables 7 and Table 9. A person of ordinary skill in the art would have been motivated to combine *Chen* with *Strobush* to improve and scale-up efficient commercial manufacturing.

H. Proper rejection of claims 1-5, 10, 12-15, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78-84, 89, 92-94, 100, 103, 104, 111,123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171,173-176, 182, 185, 186, 193, 205-207, 215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 257-260, 267-270, 272, 275-278, 285-288, 290, and 293-299 and proposed new rejection of new independent claims 315-318 under 35 USC 102(b) as anticipated by, or in the alternative, under 35 USC 103(a) as obvious over *Staab*

Applicant neither rebuts the *prima facie* case of inherent anticipation by *Staab* nor clarifies its position. Again, rather than adding manipulative steps to overcome the rejection over *Staab* or presenting evidence that *Staab* does not inherently anticipate the claimed process, Applicant adds a large variety of desired results.

First, Applicant argues—with no evidence—that "absent statements based on testing to determine the actual uniformity of content in the amount of active present in the film, so as to meet FDA approval, *Staab* does not and cannot inherently disclose Patentee's resulting film having the claimed levels of uniformity of content...." Reply, p. 69. Not only is it unreasonable to say that a film must meet FDA approval to show a certain level of uniformity, but also it is well established that a reference need not recognize inherent properties of its films to anticipate the present claims. *See* MPEP §2112(II). Second, Applicant argues that "... *Staab* just states that there is 19 mg of benzalkonium chloride present in each sample weighing 190 mg, however *Staab* does not disclose testing to determine the amount of benzalkonium chloride present in the final film product." *Id.* Applicant classifies the 19 grams as a "perfect yield" and thus the data as "suspect." If Applicant is suggesting that *Staab* is not an enabling reference, under MPEP 2121, they have not met their burden of providing facts rebutting the presumption that *Staab* is operable – which has been established by *Staab*'s express statement that their dosage forms are uniform. The fact that *Staab* exhibits a uniformity that is better than Applicant's is not reason enough to doubt that *Staab*'s dosage forms each have 19 grams of active. And, to the extent that

Staab lacks information regarding analytical chemical tests, so also does the '080 Patent, since nowhere (including the Examples) in the '080 Patent does Applicant state how much active is in their dosage forms as determined by analytical chemical tests.

Applicant also discusses how *Staab* teaches the benefits of a gas-foamed film, which is "contraindicated in Patentee's invention." Reply pp. 80-81. In fact, Applicant specifically states that "the '080 Patent teaches the use of anti-foaming agents to prevent gas bubble formation." Reply p. 80 (emphasis in original). Yet not one of the pending claims recites the presence of an anti-foaming agent, or the formation of a film with no bubbles.

Applicant argues that *Staab* does not teach "controlled drying." Reply p. 79. But the Office Action already confirmed that *Staab* teaches the claimed drying methods. Office Action pp. 27-30. The addition of the word "controlled" does not distinguish the claims from *Staab*, at least because *Staab* also teaches controlled drying. For example, *Staab* states that the "drying/cooling tunnel of 126 ft. length is located immediately after the casting area. Heat is applied by underbelt current and overbelt hot air – both are adjustable." *See Staab* 10:31-34. *Staab* also specifies that that the polymer mixture is "passed through a drying oven at a controlled temperature, typically 130°-140°F." *See Staab* 11:4-6. With respect to forming a visco-elastic film within about 4 minutes, *Staab* teaches forming a viscoelastic film within about 4 minutes by increasing the viscosity of the polymer matrix upon initiation of drying because any drying process would increase viscosity upon initiation of drying. Even though *Staab* discloses drying its films in approximately 20 minutes (*See* col. 11, line 45), its films would be as viscoelastic as the films of the '080 Patent at 4 minutes, since they are produced by identical or substantially identical processes as claimed in the '080 Patent. With respect to the viscosity range, *Staab* teaches a pourable polymer matrix, which would necessarily have a viscosity of within about 400 to about 100,000 cps (which is a viscosity ranging from thin castor oil to mincemeat). The remainder of the recitations, *e.g.*, regarding active content variation and FDA compliance, are desired results not entitled to patentable weight.

Claim 318 recites "a drying apparatus at a temperature of at least 60° C and using air currents, which have forces below the yield value of the polymer matrix," but this recitation does not distinguish the claims from *Staab*. As noted above, *Staab* teaches that the drying oven is

typically at a temperature of 130°-140°F (which is 54.4°-60.0° C) and that overbelt hot air is adjustable.

For at least the foregoing reasons, the rejection of these claims as anticipated by, or in the alternative, obvious over *Staab* should be maintained. And the rejection should be extended to the new independent claims because—like amended claims 1, 82 and 161—they also fail to present any method recitations that patentably distinguish over the methods of *Staab*.

I. Proposed rejection of new dependent claims 300-314 under 35 USC 102(b) as anticipated by or, in the alternative, under 35 USC 103(a) as obvious over *Staab*

Applicant has failed to separately argue any of the above new dependent claims. Because *Staab* anticipates each of these claims, or discloses an obvious variation, as set forth in detail below, Applicant requests the adoption of this proposed rejection.

New claims 300-311 recite "wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%, 2%, 1%, or 0.5%". These recitations are desired results, not entitled to patentable weight. *See* Sections V(A)4 and V(A)5. In any event, *Staab*'s processes include the same manipulative steps as Applicant's process, and would thus inherently produce the same resulting film. *Staab* discloses a film with active material "evenly distributed throughout." *Staab*, 5:68 – 6:3. Claims 312-314 recite "wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof." These claims are anticipated because *Staab* teaches drying its films in an oven. *Staab* 11:45-46. In other words, *Staab* teaches using air currents/heat as the radiant energy.

J. Proper rejection of claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 under 35 USC 103(a) as obvious over *Staab*

The claims listed in the section heading depend from claims 1, 82, and 161. As discussed above, amended claims 1, 82, and 161 are anticipated by, or in the alternative, obvious over *Staab*. Moreover, the limitations recited in these dependent claims are commonly known features and have already been deemed obvious to the Office Action. In any event, it would

have been obvious to one of the ordinary skill in the art at the time of filing to incorporate these features into *Staab's* methods. Therefore, the rejection of these claims as obvious over *Staab* should be maintained.

K. Proper rejection of claims 82, 89, 90,161,171-173, 272, 274, 290, and 292 and proposed new rejection of new independent claim 315-318 under 35 USC 102(b) as anticipated by or, in the alternative, under 35 USC 103(a) as obvious over *Le Person*

As with *Chen* and *Staab*, Applicant fails to rebut *prima facie* case of inherent anticipation by *Le Person*. Applicant neither adds manipulative steps to their claims to overcome the rejection nor provides evidence that the process of *Le Person* would not inherently produce the same desired results. Instead, Applicant argues that "*Le Person* allows for materials which may have such a low molecular weight that forming a visco-elastic film may not be possible" and "lacks sufficient enabling disclosure to be an effective reference." Reply p. 70. But the claims do not require a high molecular weight. And again, Applicant has not met its burden of providing facts rebutting the presumption that *Le Person* is operable. *See* MPEP 2121. Indeed, for all *Le Person* allegedly "lacks," it still includes a teaching of each and every manipulative drying step recited in the pending claims.

Applicant also argues that *Le Person* "discloses methods that result in a non-uniform product prior to and at 10 minutes." Reply p. 82. Applicant argues:

> *Le Person* even states that "intense moisture removal through the exposed surface of the layer to the radiation, during the first 3 min of drying (*Le Person*, Fig. 7) produces a stress on the polymer skeleton ... and as a result the acrylic polymer becomes more and more dense in the upper part of the layer (exposed surface)." (*Le Person*, p. 261). As a result, this "intense" shrinkage results in displacement of the active phase.
>
> Reply page 83.

But what *Le Person* actually says is that "[t]his intense shrinkage coupled with the polymer compaction causes a displacement of the active phase towards the bottom of the layer." *Le Person* p. 26, col. 2, last ¶ (emphasis added). Changes in density in the upper and lower part of

the layer and displacement of the active to the bottom of the film would have no effect on dose-to-dose variability.

Again, as with *Staab*, Applicant presents the basically identical conclusory argument that *Le Person* does not teach the claimed drying methods. Reply pp. 81-82. But the Office Action already confirmed that *Le Person* teaches the claimed drying methods. Office Action, pp. 36-39. The addition of the word "controlled" does not distinguish the claims from *Le Person*, at least because *Le Person* teaches "a conventional drying rig where temperature ($T_{\infty db}$),velocity (U_{∞}),and humidity (Y_{∞}), of air are controlled." *See Le Person*, p. 258, col. 2 and Fig. 1. Additionally, *Le Person* teaches a polymer matrix having a viscosity of from about 400 to about 100,000 cps, at least because this viscosity range encompasses any conceivable polymer solution that is capable of being cast. And *Le Person* teaches forming a viscoelastic film within about 4 minutes by increasing the viscosity of the polymer matrix upon initiation of drying. *See Le Person*, Figure 2, illustrating that, at 4 minutes (or 240 s – approximately 15 $s^{0.5}$), water content is less than 20% by weight in films dried by MIR and SIR and less than about 35% by weight in all dried films[4]. The remainder of the recitations are desired results not entitled to patentable weight as discussed several times above.

Applicant argues a number of limitations for claim 317 that do not appear in the claims, *i.e.*, temperature differential. *See* Reply p. 82. To the extent that claim 318 recites "a drying apparatus at a temperature of at least 60° C and using air currents, which have forces below the yield value of the polymer matrix," this recitation does not distinguish the claims from *Le Person*, which teaches drying with an air velocity of 4 m/s and a heated slab at a temperature of 60° C (T_c). *See Le Person*, p. 259, Table 2.

For at least the foregoing reasons, the rejection of claims 82, 89-91,161,171-173, 272-274 and 290-292 and proposed new rejection of new independent claim 55-61, 89 and 226 as anticipated by, or in the alternative, obvious over *Le Person* should be maintained and/or adopted. And the rejection should be extended to new independent claims 315-318 because—

[4] "[E]ach point of a curve corresponds to a separate drying experiment carried out at least twice." *Le Person* p. 250, col. 2.

like amended claim 82—they also fail to present any method recitations that patentably distinguish the claims over the methods of *Le Person*.

L. Proposed rejection of new dependent claims 300-314 under 35 USC 102(b) as anticipated by or, in the alternative, under 35 USC 103(a) as obvious over *Le Person*

Applicant has failed separately argue that any of the above new dependent claims would distinguish the claims from *Le Person*. Because *Le Person* anticipates each of these claims, or in alternative, renders these claims obvious as set forth below, Applicant requests the adoption of this proposed rejection.

Claims 300-311 recite "wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%, 2%, 1%, or 0.5%." These recitations are desired results, not entitled to patentable weight. In any event, *Le Person*'s processes include the same manipulative steps as Applicant's process, and would thus inherently produce the same resulting film. Claims 312-314 recite "wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof." These claims are obvious at least because *Le Person* teaches using different drying modes including convection (*i.e.,* heat), medium and short infra-red. *See* p.258, col. 1, last four lines.

M. Proper rejection of claims 92 and 174 under 35 USC 103(a) as obvious over *Le Person*

The claims listed in the section heading depend from claims 1, 82, and 161. As discussed above, amended claims 1, 82, and 161 are anticipated by, or in the alternative, obvious over *Le Person*. Moreover, the limitations recited in these dependent claims are commonly known features and have already been deemed obvious to the Office Action. In any event, it would have been obvious to one of the ordinary skill in the art at the time of filing to incorporate these features into *Le Person's* methods. Therefore, the rejection of these claims as obvious over *Le Person* should be maintained.

N. Proper rejection of claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 92, 93, 102, 142, 143, 161,166,168-171,173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 and proposed new rejection of new independent claims 315-317 under 35 USC 102(b) as anticipated by, or in the alternative, under 35 USC 103(a) as obvious over *Horstmann*

Applicant fails to rebut the *prima facie* case of inherent anticipation by *Horstmann*, or to clarify its position. Again, rather than adding manipulative steps to overcome the rejection over *Horstmann* or presenting evidence that *Horstmann* does not inherently anticipate the claimed process, Applicant instead contends that "*Horstmann* forms a gel, rather than a solid film as in the present invention. Thus the gel rheological properties of *Horstmann* are very different than a solid visco-elastic film having a water content of 10% or less." Reply p. 71 and 72, the bridging paragraph. But gels are not excluded by the claims.

Applicant then concludes – with no evidence – that "absent statements based on testing for the amount of active present in the film. . . *Horstmann* does not and cannot inherently disclose Patentee's resulting film claiming the specified levels of uniformity in the amount of active." Reply, p. 72. But this is irrelevant because it is well established that prior art need not recognize its inherent property to render a claim unpatentable. *See* MPEP §2112(II).

Moreover, the Office has already determined that *Horstmann* teaches the claimed method steps. In reply, Applicant bears the burden of identifying which, if any, method step is not in the prior art. Yet Applicant fails to do so by vaguely asserting that it "has added several additional process steps not in the prior art". Reply p. 72.

For at least the foregoing reasons, this rejection should be maintained. And the rejection should be extended to new independent claims 315-317, because—like amended claims 1, 82, and 161—they also fail to present any method recitations that patentably distinguish the claims over the methods of *Horstmann*.

O. Proposed rejection of new dependent claims 300-314 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Horstmann*

Applicant has failed to separately argue how any of the new dependent claims would further distinguish their claims from *Horstmann*. Because *Horstmann* anticipates each of these claims, or in alternative, renders these claims obvious as set forth in detail below, Applicant requests the adoption of this proposed rejection. Claims 300-311 recite "wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%, 2%, 1% or 0.5%." These recitations are desired results, not entitled to patentable weight. However, to the extent that this represents any limitation whatsoever, *Horstmann's* processes include the same manipulative steps as Applicant's process, and would thus inherently produce the same resulting film. Claims 312-314 recite "wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof." *Hortsmann* teaches the use of "heat" by drying at 80 ºC. *Hortsmann* 5:52-53.

P. Proposed rejection of new independent claim 318 under 35 USC 103(a) as obvious over the combined teachings of *Hortsmann* and *Arter*

To the extent that *Horstmann* does not specifically recite drying the flowable polymer matrix in "a drying apparatus at a temperature of about 60 ^{o}C" and "using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent," *Arter* teaches these recitations as discussed above in Section V.F. A person of ordinary skill in the art would have been motivated to combine the teachings of these two references, to improve and scale-up efficient commercial manufacturing. All of the recited features were known in the prior art and one skilled in the art could have combined them by known methods with no change in their respective functions, and the combination would yield predictable results. MPEP § 2143(A).

Q. Proposed rejection of new independent claim 318 under 35 USC 103(a) as obvious over the combined teachings of *Hortsmann* and *Strobush*

To the extent that *Horstmann* does not specifically recite drying the flowable polymer matrix in "a drying apparatus at a temperature of about 60 ^{o}C" and "using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent...", *Strobush* teaches these recitations as discussed above in Section V.G.

A person of ordinary skill in the art would have been motivated to combine the teachings of these two references, to improve and scale-up efficient commercial manufacturing. All of the recited features were known in the prior art and one skilled in the art could have combined them by known methods with no change in their respective functions, and the combination would yield predictable results. MPEP § 2143(A).

VI. CONCLUSION

Instead of providing clarifying and narrow amendments in response to the carefully reasoned rejections, Applicant chose to introduce claim language that is broadening, unclear, and unsupported in the specification. Applicant's remarks also fail to clarify and distinguish the invention, relying, heavily, on recitations not entitled to patentable weight rather than manipulative process steps in the claims.

In view of the foregoing comments, Requester respectfully requests that the rejections of record be maintained, the new and amended claims be rejected as proposed, and an Action Closing Prosecution be issued.

Respectfully submitted,
McCarter & English LLP

Dated: April 12, 2013

By: /Danielle L. Herritt/

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Attorneys for Requester, BioDelivery Sciences International, Inc.

LIST OF EXHIBITS

Electronic Acknowledgement Receipt

EFS ID:	15510157
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	12-APR-2013
Filing Date:	10-SEP-2012
Time Stamp:	21:57:47
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_A_Claim_Comparison_v2.PDF	101415 6a3cf31bc7b0706f045026d662fbbf0f67823b88	no	9

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
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2	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_C_Clevenger_Declaration.PDF	497093 3befc6ad8991d5e3beadb7f3e4d688832dd2e291	no	7
Warnings:					
Information:					
3	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_D_Merriam_Webster_uniform.PDF	259585 7df93e3407de0a1b172c7ee906e2a8f6f2d31642	no	5
Warnings:					
Information:					
4	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_E_Common_Viscosities.PDF	131816 586a668592041872a069a39cfe9c88d9d4f3f317	no	5
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5	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_F_Crown_v_Solutia_FedCirc_2002_080.PDF	65623 ac09778279577e40a1862aad4a27233824b4dc32	no	11
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6	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_G_Crown_v_Solutia_2000_WL33906466_080.PDF	169600 a2b230ce4080841d0966c410bef1d5194f9a8c2c	no	16
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7	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_H_BMS_v_BenVenue_FedCir_2001_080.PDF	61078 8c003e1ab7547b8b2be23dd61aac7cc9807541e6	no	10
Warnings:					
Information:					
8	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_I_Viscosity_of_Methocel_E5_at_varied_concentrations_080.PDF	1762536 de3109237253997f6b0b8929ab13e00f5e5f85a3	no	33
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Information:					
9	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_J_USP_905_Uniformity_2011.PDF	144379 3111ff63374ffc1ea4176f63b3bd58fb11fa1c57	no	4

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10	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_K_USP_905_Uniformity_2007.PDF	496996 fb3e115d20c218bca83b67fdbff984ab4490d27d	no	8
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11	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_L_Arter_US_4365423.PDF	1402781 e7524f416141cd77432881ab2ae65b8b6e473ca7	no	15
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12	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_M_Strobush_US_5881476.PDF	1841302 c2f8d3187243c2b704f4bd3f94d94eb152833d28	no	30
Warnings:					
Information:					
13	Reexam Certificate of Service	Ex_N_Certificate_of_Service.PDF	6196 9f6b20247e031483980e0d221bb747df7bcd7dfa	no	2
Warnings:					
Information:					
14	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Ex_B_Reitman_Decl--.PDF	593570 4988f54efb0c09a7575be0c11eefc3a8d72dea4a	no	11
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Information:					
15	Third Party Requester Comments after Non-final Action	117744_00023_Comments-.PDF	280572 1ea4336aaa187ffcf6210216756cd03896f4ee1b	no	54
Warnings:					
Information:					
			Total Files Size (in bytes):	7814542	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 04/11/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	
ART UNIT	**PAPER NUMBER**
3991	

MAIL DATE	DELIVERY MODE
04/11/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DRL - EXHIBIT 1007
DRL1484

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HOFFMAN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791

(For Patent Owner)

Danielle L. Herritt
McCARTER AND ENGLISH LLP
265 Franklin Street
Boston, Massachusetts 022110

(For Third Party Requester)

In re: Yang et al.
Inter Partes: Reexamination Proceeding
Control No.: 95/002,170
For: U.S. Patent No.: 7,897,080

DECISION ON PETITION

This is a decision on the petition filed by the Third Party Requester: a petition filed March 22, 2013 entitled "PETITION TO DENY ENTRY OF PATENT OWNER'S SUPPLEMENTAL RESPONSE UNDER 37 CFR §1.182". The decision also addresses Patent Owner's petition filed March 22, 2013 entitled "PETION TO EXPEDITE UNDER 37 CFR §1.182"

In the petition, Third Party Requester requests that Patentee's March 13, 2013 response to the February 26, 2013 Notice re Defective Paper in Inter Partes Reexamination be denied entry under 37 CFR 1.945 and 1.939(a).

As a procedural matter, the petition is treated as a petition under 37 CFR § 1.181. It is noted that the petition under 37 CFR 1.182 is not proper because the petition address issues that are properly raised under 37 CFR 1.181.

The petition is before the Director of the Central Reexamination Unit.

The petition is **DISMISSED.**

REVIEW OF RELEVANT FACTS

- U.S. Patent No. 7,897,080 issued on March 1, 2011.
- A Request for *inter partes* reexamination was filed by third party requester on September 10, 2012 and assigned control no. 95/002,170.
- *Inter-Partes* reexamination was ordered on October 22, 2012.
- A Non-Final Office Action was mailed on October 22, 2012.
- David J. Kappos, Director of the United States Patent & Trademark Office issued a memorandum entitled *Emergency Notice of Relief Available to Patent and Trademark Applicant's, Patentees and Trademark Owners Affected by Hurricane Sandy* on November 21, 2012.
- Patent Owner filed the above identified petition on November 26, 2012 requesting that the October 22, 2012 Office Action be reissued.
- A decision granting the October 22, 2013 petition was mailed on November 28, 2012.
- The Non-Final Office Action was re-mailed on November 29, 2012.
- Patent Owner filed a response to the Non-Final Office Action on January 29, 2013.
- A Notice Re Defective Paper in Inter Partes Reexamination was mailed on February 26, 2013.
- Third Party Requester filed Comments to the Office Action and Patent Owner's amendment on February 28, 2013.
- Patent Owner filed a response to the Notice of Defective Paper on March 13, 2013.
- Third Party Requester filed the instant petitions to (1) have Patent Owner's response to the Notice of Defective paper denied entry and to (2) have expedited the answering of the petition on March 22, 2013.

STATUTES, REGULATIONS, AND PATENT EXAMINING PROCEDURES

M.P.E.P 2666.60 Response by Patent Owner/Third Party to Notice of Defective Paper

Any submission correcting the defect which provides a discussion of the merits should (A) set forth that discussion separately from the portion of the response that corrects the defect, and (B) clearly identify the additional discussion as going to the merits. The additional discussion going to the merits must, in and of itself, have an entry right, or the entire submission will be returned to the party that submitted it, and one additional opportunity (30-days or one month, whichever is longer) will be provided, to correct the defect without a discussion of the merits. If the portion directed to the merits is not clearly delineated and identified, the entire submission may be returned to the party that submitted it, and one additional opportunity (30-days or one month, whichever is longer) is then given for that party to correct the defect without intermixed discussion of the merits. The examiner may, however, choose to permit entry of such a paper.

37 CFR 1.945 Response to Office action by patent owner in inter partes reexamination.

(b) Any supplemental response to the Office action will be entered only where the supplemental response is accompanied by a showing of sufficient cause why the supplemental response should be entered. The showing of sufficient cause must include:

(1) An explanation of how the requirements of § 1.111(a)(2)(i) are satisfied;

(2) An explanation of why the supplemental response was not presented together with the original response to the Office action; and

(3) A compelling reason to enter the supplemental response.

DECISION

In the above identified petition, Third Party Requester (Petitioner) asserts that the Patent Owner's corrected response to the Notice of Defective Paper is improper and should be denied entry as required by 37 CFR 1.945(b). In particular, Third Party Requester asserts that in response to the February 26, 2013 Notice Re Defective Paper in in *Inter Partes* Reexamination, Patent Owner's submission was not limited to solely correcting the defect, but rather incorporated new arguments, new data and a new declaration. Third Party Requester points to

MPEP 2666.60 which states that that "any additional discussion on the merits must, in and of itself have an entry right". Thus, Third Party Requester argues that because the response contains additional arguments and evidence, it should be deemed a supplemental response, and that the supplemental response does not comply with 37 CFR 1.945(b), which requires a showing of sufficient cause as to why the supplemental response should be entered.

A review the record indicates that Office has not issued any communication in response to Patent Owner's March 13, 2013 response to the Notice Re Defective Paper. Thus, the Office has made no determination as of yet as to whether Patent Owner's response contains any additional information that need have a separate entry right. Absent any determination or communication by the Office that Patent Owner's March 13, 2013 response is compliant with Office rules and procedures, the proceeding is not ripe for such a petition.

Accordingly, Third Party Requester's petition is premature since there is no been decision by the Office as to whether the submission by Patent Owner is in compliance with Office rules and procedures.

In conclusion, the petition by Third Party Requester is **dismissed** as being premature.

CONCLUSION

1. The petition filed by Patent Owner on March 22, 2012, is **dismissed.**

2. Telephone inquiries related to this decision should be directed to Stephen Stein, Supervisory Patent Reexamination Specialist, at (571) 272-1544 or in his absence to the undersigned at (571) 272-0700.

Irem Yucel
Director, Central Reexamination Unit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	
	)	
Issued: March 1, 2011	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
	)	
Control No.: 95/002,170	)	Examiner: Alan D. Diamond
	)	
Request Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	)	H&B Docket: 1199-26 RCE/ CON/ REX
	)	
Date: March 22, 2013	)	

Mail Stop *Petition*
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION TO EXPEDITE UNDER 37 CFR § 1.182

Dear Sir or Madam:

Pursuant to 37 CFR 1.182, Petitioner hereby requests that the Office ***expedite*** the handling of the "PETITION TO DENY ENTRY OF PATENT OWNER'S SUPPLEMENTAL RESPONSE UNDER 37 CFR § 1.182" filed concurrently herewith.

Due to the shortened response periods in *inter partes* reexamination, it is respectfully submitted that expedited handling of the attached Petition is appropriate in order to ensure that all involved parties are apprised of the status of the Supplemental Response in a timely manner. Additionally, a prompt decision would avoid placing unnecessary burden on the Examiner, and thus be beneficial to the Office in the present situation.

In accordance with 37 CFR 1.182, Petitioner submits herewith the surcharge set forth in 37 CFR 1.17(f).

If any additional charges are required with this Petition, Petitioner authorizes the Commissioner to charge any fee deficiency to Deposit Account No. 50-4876, under Reference Number 117744-00023.

Respectfully submitted,
McCarter & English LLP

Dated: March 22, 2013

By: /Danielle L. Herritt/

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Attorneys for Petitioner, BioDelivery Sciences International, Inc.

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this Petition to Expedite, the Petition to Deny Entry of Patent Owner's Supplemental Response (together with the associated Exhibits A-C), and this certificate of first class service have been served, by first class mail, on March 22, 2013, in their entirety on the Patent Owner in accordance with 37 C.F.R. §§ 1.903 and 1.248. The name and address of the party served is:

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(Attn: Daniel A. Scola, Jr.)
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SYOSSET, NY 11791

By: /Danielle L. Herritt/

Danielle L. Herritt
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Boston, MA 02110

Direct Dial: 617-449-6513
Email: dherritt@mccarter.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of:	)	
	)	
US Patent No. 7,897,080	)	
	)	
Issued: March 1, 2011	)	Confirmation No.: 6418
	)	
Named Inventor: Robert K. Yang *et al.*	)	Group Art Unit: 3991
	)	
Control No.: 95/002,170	)	Examiner: Alan D. Diamond
	)	
Request Filed: September 10, 2012	)	M&E Docket: 117744-00023
	)	
Title: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	)	H&B Docket: 1199-26 RCE/ CON/ REX
	)	
Date: March 22, 2013	)	

Mail Stop Petition
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P.O. Box 1450
Alexandria, VA 22313-1450

PETITION TO DENY ENTRY OF PATENT OWNER'S SUPPLEMENTAL RESPONSE UNDER 37 CFR § 1.182

On February 26, 2013, in the *inter partes* reexamination of US Patent No. 7,897,080, the Office issued a Notice re Defective Paper, PTOL-2069. The only defect discussed in the Notice is that Patentee's January 29, 2013 reply exceeds the maximum page limit under 37 CFR 1.943(b) by 6 pages. In reply, Patentee did not file a "submission directed to solely correcting the defect" as directed by MPEP 2666.60, *i.e.,* reducing the page length of the original reply by either re-drafting to remove passages or by redaction as directed by the Office. On the contrary, Patentee filed a response improperly incorporating new claim amendments, new claims, new arguments, new data, and a new declaration by a new declarant. Third Party Requestor requests that this unauthorized and supplemental response be denied entry as required by 37 CFR 1.945(b) and 37 CFR 1.939(a).

Statement of Facts:

1. On January 29, 2013, Patentee filed an amendment and response (the "Reply") to a first Office action dated November 29, 2012. The Reply included claim amendments, attorney arguments and two supporting declarations: the declaration of Dr. Fuller ("Fuller Declaration") and the declaration by Dr. Bogue ("Bogue Declaration"). The January 29, 2013 Reply is attached as Exhibit A.

2. On February 26, 2013, the Office mailed a Notice re Defective Paper in *Inter Partes* Reexamination (the "Notice") because the Reply exceeded the 50-page limit under 37 CFR 1.943 by 6 pages. It was specifically noted that the claims and the Bogue Declaration did not count toward the page limit. The Notice directed Patentee to correct the defect by either re-drafting or redacting the original Reply to meet 37 CFR 1.943.

3. On February 28, 2013, Third Party Requestor ("TPR") filed its Comments, unaware of the Notice that crossed in the mail.

4. On March 13, 2013, instead of properly replying to the Notice by simply reducing the page length of the original Reply as directed by the Office, Patentee filed a supplemental response ("Supplemental Response"). The Supplemental Response was not accompanied by a showing under 37 CFR 1.945 as to why the Supplemental Response should be entered. The March 13, 2013 Supplemental Response is attached as Exhibit B.

Issue to be considered:

Whether Patentee should benefit from its failure to comply with the page limits imposed by 37 CFR 1.943 by gaining an extension of time to consider the Office Action and an opportunity to file a second, new response thereto—without being required to comply with 37 CFR 1.945(b) (prohibiting a supplemental response without a showing of sufficient cause) and 37 CFR 1.939(a) (prohibiting consideration of an unauthorized paper during an inter partes reexamination proceeding).

On February 26, 2013, the Office issued a Notice re Defective Paper in *Inter Partes* Reexamination. The only defect discussed in the Notice is that Patentee's original Reply exceeded the maximum page limit under 37 CFR 1.943(b) by 6 pages. The Office also directed the Patentee to correct the defect by redrafting or by redacting to reduce the original Reply to the required 50-page limit. *See* Notice at p. 3. Patentee, however, did not file a "submission directed to solely correcting the defect" as directed by MPEP 2666.60. On the contrary, in comparison to the original defective Reply, Patentee improperly added new amendments, new claims, new attorney argument, new data, and a new declaration. Further, the remainder of the Supplemental Response is substantially revised and altered as compared to the attorney argument submitted with the original Reply. By way of example, the Supplemental Response is substantively different from the original defective Reply in at least the following ways:

1. New Claim Amendments. The Supplemental Response amends, for example, original independent claims 1, 82 and 161 in a way entirely different from that presented in the original Reply. *See* Comparison of Supplemental Response filed March 13, 2013, Exhibit C at pp. 2-3, 12-14, and 22-24.

2. New Independent Claims. The Supplemental Response presents 4 new independent claims not in the original Reply. *See* Exhibit C at pp. 41-48. These claims recite new limitations found neither in any original claim nor

in any amended claim in the original Reply, for example, reciting an oven temperature of 60° C in new claim 318. The Patentee also removes over 300 claims presented in the original Reply. This is not an amendment directly solely to correcting the defect because (i) deleting claims does not to reduce page count, and (ii) the Patentee never argued a single dependent claim in its original Reply.

3. New Description of "The Patented Invention." The Supplemental Response presents an entirely new description of "The Patented Invention." *See* Exhibit C at pp. 90-93.

4. New Discussion of "Patentee's Claims." The Supplemental Response presents an entirely new a discussion of the claimed subject matter. *See* Exhibit C at pp. 93-103.

5. New Attorney Arguments. The Supplemental Response presents entirely new arguments, for example, regarding TPR's alleged burden (which is actually Patentee's burden) to reproduce the method of the *Chen* reference to rebut the Office's *prima facie* case of inherency and Patentee's new theory about Figure 5 of Chen with extensive "support" from the new Lin Declaration. *See* Exhibit C at pp. 113-114 and 129.

6. New Declarant and Declaration. The Supplemental Response presents an entirely NEW declaration by a different declarant (the "Lin Declaration"). *See* Exhibit B, Lin Declaration. The Lin Declaration is directed to a new line of attorney argument. The Patentee has removed its original Fuller Declaration (*See* Exhibit A, Fuller Declaration). This removal is not directed to reducing page count because the Fuller Declaration (4 pages) is replaced by the much ***longer*** Lin Declaration (6 pages).

7. New Data and New Arguments in an Expanded Bogue Declaration. The Supplemental Response includes several pages of new data, as well as new calculations and discussions of claims limitations that were not in the

> original Bogue Declaration. Indeed, except for the introductory paragraphs and the original Exhibit, the entire Bogue Declaration is either new or substantially revised to include new arguments and new data. See Bogue Declaration in Exhibit B at ¶¶ 4-11 and its new Exhibits A and C.

None of the new claim amendments, new claims, new arguments, new data, and new declaration was present in the original Reply. Further, it appears that the Patentee improperly and substantially revised their arguments in order to address substantive responses made in TPR's Comments filed after the original Reply, but before TPR was aware of the Notice. This creates a further burden on the Office as it would have to study the original Reply and TPR's Comments to the original Reply in order to understand the Supplemental Response.

None of the new claims, new arguments, and new theories found in the Supplemental Response properly falls within the scope of the changes authorized by the Notice. Yet, the Patentee made no effort to indicate that its new Reply is a *bona fide* effort to comply with the Notice. In addition, none of these additions is authorized under 37 CFR 1.945(b) or 37 CFR 1.939(a). Rule 1.945(b) requires that a showing be made to justify an entry right:

> § 1.945 Response to Office Action by Patent Owner in *Inter Partes* Reexamination
> …
> (b) Any supplemental response to the Office action will be entered only where the supplemental response is accompanied by a showing of sufficient cause why the supplemental response should be entered. The showing of sufficient cause must include:
> (1) An explanation of how the requirements of § 1.111(a)(2)(i) are satisfied;
> (2) An explanation of why the supplemental response was not presented together with the original response to the Office action; and
> (3) A compelling reason to enter the supplemental response.
>
> 37 CFR § 1.945(b).

Patentee did not even attempt to make such a showing.

Rule 1.939(a) states that such unauthorized papers will not be considered by the Office.

> § 1.939 Unauthorized Papers in *Inter Partes* Reexamination.
>
> (a) If an unauthorized paper is filed by any party at any time during the *inter partes* reexamination proceeding it will not be considered and may be returned.
>
> ...
>
> 37 CFR § 1.939(a)

As the MPEP provides in its section regarding response to Notice of Defective Paper: "[Any] additional discussion of the merits must, in and of itself, have an entry right, or the entire submission will be returned to the party that submitted it...." MPEP 2666.60. In short, the Supplemental Response is an unauthorized paper and the Rules and the direction of the Office require that the paper be denied entry.

The Office may, of course, provide the Patentee one more opportunity to appropriately respond to the Notice, as discussed in MPEP 2666.60. Alternatively, the Office may regard the Supplemental Response as a failure to file a timely and appropriate response and terminate prosecution under 37 CFR 1.957(b). This is also discussed in the first paragraph of MPEP 2666.60. But to take no action and permit entry in this particular case is not only counter to the clear direction of 37 CFR 1.945 and 37 CFR 1.939, but also counter to the requirement of 35 USC 314(c) for special dispatch. Allowing Patentee to effectively take an extension and file a completely new response, without even offering any justification for doing so, is counter to the statute and merely prolongs prosecution. In other words, if Patentee's action were permitted, every defective response would essentially be a request for extension of time with the unlimited right to enter any new amendments, data, evidence or attorney argument. The statutory requirement for special dispatch and the Patent Rules setting deadlines and limiting supplemental responses would thereby be rendered meaningless.

Action Requested:

There is no doubt that Patentee's most recent filing is an unauthorized supplemental submission rather than a proper response to the Notice of Defective Paper, which simply requires Patentee to reduce the length of its original Reply to meet the 50 page limit. The Supplemental Submission is replete with new amendments, new claims, new arguments, new data and a new declarant, but lacks any showing under 37 CFR 1.945(b) why the submission may be entitled to entry. Accordingly, TPR requests that the Supplemental Submission be denied entry as required by 37 CFR 1.945(b) and 37 CFR 1.939(a). Additionally, since the new matter is inextricably intermixed with original matter in the Supplemental Response, and to avoid any further delay and burden on the Office, TPR requests that the Office direct Patentee to file a copy of the original January 29, 2013 Reply with pages redacted to satisfy the 37 CFR 1.943 page limit requirement.

The petition fee set forth in 37 CFR 1.17(f) is included with this petition. If any additional charges are required with this Petition, Petitioner authorizes the Commissioner to charge any fee deficiency to Deposit Account No. 50-4876, under Reference Number 117744-00023.

Respectfully submitted,

Dated: March 22, 2013

By: /Danielle L. Herritt/

Danielle L. Herritt Reg. 43,670

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Exhibits A-C

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this Petition by the Third Party Requester, the associated Exhibits A-C, and this certificate of first class service have been served, by first class mail, on March 22, 2013, in their entirety on the Patent Owner in accordance with 37 C.F.R. §§ 1.903 and 1.248. The name and address of the party served is:

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EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	January 29, 2013	M&E Docket:	117744-00023

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Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on January 29, 2013.
Signed: /Michael I. Chakansky /Michael I Chakansky/

REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111

Madame:

In response to an Office Action in the above-identified *Inter Partes* Reexamination, dated November 29, 2012 ("Office Action"), a reply to which is due January 29, 2013, please amend U.S. Patent No. 7,897,080 ("the '080 Patent") in reexamination as set forth hereinbelow. The present amendments are being made in accordance with 37 C.F.R. §1.530(d)–(j). If there are any fees due in connection with this submission, authorization to charge such fees to Deposit Account No. 08-2461 is hereby provided.

Amendment to the Claims begins on page 2 of this paper.

Remarks begin on page 79 of this paper.

Amendment to the Claims

1. (Amended) A process for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval said [making a]film having a substantially uniform distribution of a pharmaceutical active[of components], comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]a pharmaceutical active to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent [from said flowable polymer matrix]to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying within about the first [10]4 minutes [or fewer]to maintain said substantially uniform distribution of said pharmaceutical active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform

distribution of pharmaceutical active by said locking-in or substantially preventing migration of said pharmaceutical active is maintained;

(f) forming a plurality of individual dosage unit samples of substantially the same size from said resulting pharmaceutical film; and

(g) performing analytical chemical tests for content uniformity on said plurality of individual dosage unit samples from said resulting pharmaceutical film, said tests indicating said substantially uniform distribution of the pharmaceutical active, in that the amount of the pharmaceutical active in the individual dosage unit samples varies by no more than 10%.

2. (Original) The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids,

polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (Original) The process of claim 1, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management

agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,] cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15. (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Cancelled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group

consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (Original) The process of claim 1, wherein said active is an anti-diarrhea.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H_2-antagonist.

35. (Original) The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough

suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (Amended) The process of claim 72, wherein said second film layer is coated onto said resulting pharmaceutical film.

74. (Amended) The process of claim 72, wherein said second film layer is spread onto said resulting pharmaceutical film.

75. (Amended) The process of claim 72, wherein said second film layer is cast onto said resulting pharmaceutical film.

76. (Amended) The process of claim 72, wherein said second film layer is extruded onto said resulting pharmaceutical film.

77. (Amended) The process of claim 72, wherein said second film layer is sprayed onto said resulting pharmaceutical film.

78. (Amended) The process of claim 72, wherein said second film layer is laminated onto said resulting pharmaceutical film.

79. (Amended) The process of claim 72, further comprising laminating said resulting pharmaceutical film to another film.

80. (Amended) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim 72, wherein said active in said second film layer is different than said active in said resulting pharmaceutical film.

82. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval said [making a]film having a substantially uniform distribution of an active[of components], comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent [from said flowable polymer matrix]to rapidly form a visco-elastic film having said active uniformly distributed throughout by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying within about the first [10]4 minutes [or fewer]to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less, wherein content uniformity of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]the resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) forming a plurality of individual dosage unit samples of substantially the same size from said resulting film; and

(f) performing analytical chemical tests for content uniformity on said plurality of individual dosage unit samples from said resulting film, said tests indicating said substantially uniform distribution of the active, in that the amount of the active in the individual dosage unit samples varies by no more than 10%.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Cancelled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular

drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Cancelled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (Original) The process of claim 82, wherein said active is an anti-diarrhea.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (Original) The process of claim 82, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step of providing a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said

resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (Amended) The process of claim 151, wherein said second film layer comprises an active.

160. (Amended) The process of claim 151, wherein said active in said second film layer is different than said active in said resulting film.

161. (Amended) A process for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval said [making a]film capable of being administered to

a body surface having a substantially uniform distribution of a pharmaceutical active[components], comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a[n] pharmaceutical active, said matrix having a substantially uniform distribution of said pharmaceutical active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) conveying said flowable polymer matrix through a drying appsratus and evaporating at least a portion of said solvent [from said flowable polymer matrix]to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying within about the first [10]4 minutes [or fewer]to maintain said substantially uniform distribution of said pharmaceutical active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming [a]the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of pharmaceutical active by said locking-in or substantially preventing migration of said pharmaceutical active is maintained; [and]

(e) [administering said resulting pharmaceutical film to a body surface.]forming a plurality of individual dosage unit samples of substantially the same size from said resulting pharmaceutical film;

(f) performing analytical chemical tests for content uniformity on said plurality of individual dosage unit samples from said resulting pharmaceutical film, said tests indicating said substantially uniform distribution of the pharmaceutical active, in that the amount of the pharmaceutical active in the individual dosage unit samples varies by no more than 10%; and

(g) administering said resulting pharmaceutical film to a body surface.

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl

cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (Original) The process of claim 161, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion

exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Cancelled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (Original) The process of claim 161, wherein said active is an anti-diarrhea.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H_2-antagonist.

196. (Original) The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition provides a sustained release.

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step of providing a second film layer.

234. (Amended) The process of claim 233, wherein said second film layer is coated onto said resulting pharmaceutical film.

235. (Amended) The process of claim 233, wherein said second film layer is spread onto said resulting pharmaceutical film.

236. (Amended) The process of claim 233, wherein said second film layer is cast onto said resulting pharmaceutical film.

237. (Amended) The process of claim 233, wherein said second film layer is extruded onto said resulting pharmaceutical film.

238. (Amended) The process of claim 233, wherein said second film layer is sprayed onto said resulting pharmaceutical film.

239. (Amended) The process of claim 233, wherein said second film layer is laminated onto said resulting pharmaceutical film.

240. (Amended) The process of claim 233, further comprising laminating said resulting pharmaceutical film to another film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim 233, wherein said active in said second film is different than said active in said resulting pharmaceutical film.

243. (Amended) The process of claim 1, wherein said active is an anti-nauseant.

244. (Amended) The process of claim 1, wherein said active is an erectile dysfunction therapy.

245. (Amended) The process of claim 1, wherein said active is a vasoconstrictor.

246. (Amended) The process of claim 1, wherein said active is a stimulant.

247. (Amended) The process of claim 1, wherein said active is a migraine treatment.

248. (Amended) The process of claim 1, wherein said active is granisetron hydrochloride.

249. (Amended) The process of claim 1, wherein said resulting pharmaceutical film provides administration of said active to an individual through the buccal cavity of said individual.

250. (Amended) The process of claim 1, wherein said resulting pharmaceutical film provides administration of said active through gingival application to an[of said] individual.

251. (Amended) The process of claim 1, wherein said resulting pharmaceutical film provides administration of said active through sublingual application to an[of said] individual.

252. (Amended) The process of claim 1, wherein said resulting pharmaceutical film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (Amended) The process of claim 1, wherein said resulting pharmaceutical film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. (Amended) The process of claim 1, wherein said resulting pharmaceutical film has a variation of the amount of the pharmaceutical active [content]of less than [10%]5% per [film unit] individual dosage unit.

255. (Cancelled)

256. (Amended) The method of claim 1, wherein said pharmaceutical resulting film contains less than about 6% by weight solvent.

257. (Original) The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

258. (Amended) The method of claim 1, wherein said resulting pharmaceutical film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Orignal) The method of claim 1, wherein said matrix comprises a dispersion.

261. (Amended) The process of claim 82, wherein said active is an anti-nauseant.

262. (Amended) The process of claim 82, wherein said active is an erectile dysfunction therapy.

263. (Amended) The process of claim 82, wherein said active is a vasoconstrictor.

264. (Amended) The process of claim 82, wherein said active is a stimulant.

265. (Amended) The process of claim 82, wherein said active is a migraine treatment.

266. (Amended) The process of claim 82, wherein said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (Amended) The process of claim 82, wherein said resulting film provides administration of said active through gingival application to an[of said] individual.

269. (Amended) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application to an[of said] individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (Amended) The process of claim 82, wherein in step (c) the active varies less than 5% and in step (f) said resulting film has a variation of the amount of active [content]of less than 5%[10%] per [film unit] individual dosage unit.

273. (Cancelled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (Original) The method of claim 82, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (Amended) The process of claim 161, wherein said active is an anti-nauseant.

280. (Amended) The process of claim 161, wherein said active is an erectile dysfunction therapy.

281. (Amended) The process of claim 161, wherein said active is a vasoconstrictor.

282. (Amended) The process of claim 161, wherein said active is a stimulant.

283. (Amended) The process of claim 161, wherein said active is a migraine treatment.

284. (Amended) The process of claim 161, wherein said active is granisetron hydrochloride.

285. (Amended) The process of claim 161, wherein said resulting pharmaceutical film provides administration of said active to an individual through the buccal cavity of said individual.

286. (Amended) The process of claim 161, wherein said resulting pharmaceutical film provides administration of said active through gingival application to an[of said] individual.

287. (Amended) The process of claim 161, wherein said resulting pharmaceutical film provides administration of said active through sublingual application to an[of said] individual.

288. (Amended) The process of claim 161, wherein said resulting pharmaceutical film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (Amended) The process of claim 161, wherein said resulting pharmaceutical film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (Amended) The process of claim 161, wherein said resulting pharmaceutical film has a variation of in the amount of pharmaceutical active [content]of less than [10%]5% per [film unit] individual dosage unit.

291. (Cancelled)

292. (Amended) The method of claim 161, wherein said resulting pharmaceutical film contains less than about 6% by weight solvent.

293. (Original) The method of claim 161, wherein said at least one edible polymer, said active,

and said at least one polar solvent are each ingestible materials.

294. (Amended) The method of claim 161, wherein said resulting pharmaceutical film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) The process of claim 1, wherein the forming of a plurality of individual dosage unit samples and performing analytical chemical tests comprises:

(a) cutting the substantially equally sized individual dosage unit samples from the different locations of the resulting film;

(b) dissolving at least a portion of said dosage unit samples; and

(c) testing for the amount of the pharmaceutical active present in each dosage unit sample.

301. (New) The process of claim 1, wherein regulatory approval is provided by the U.S. Food and Drug Administration.

302. (New) The process of claim 1, wherein the amount of the pharmaceutical active in of individual dosage units has a variance of less than 5%.

303. (New) The process of claim 1, wherein the amount of the pharmaceutical active in of individual dosage units has a variance of less than 2%.

304. (New) The process of claim 1, wherein the amount of the pharmaceutical active in of individual dosage units has a variance of less than 1%.

305. (New) The process of claim 1, wherein the amount of the pharmaceutical active in of individual dosage units has a variance of less than 0.5%.

306. (New) The process of claim 82, wherein the forming of a plurality of individual dosage unit samples and performing analytical chemical tests comprises:

(a) cutting the substantially equally sized individual dosage unit samples from the different locations of the resulting film;

(b) dissolving at least a portion of said dosage unit samples; and

(c) testing for the amount of the active present in each dosage unit sample.

307. (New) The process of claim 82, wherein regulatory approval is provided by the U.S. Food and Drug Administration.

308. (New) The process of claim 82, wherein the amount of the active in of individual dosage units has a variance of less than 5%.

309. (New) The process of claim 82, wherein the amount of the active in of individual dosage units has a variance of less than 2%.

310. (New) The process of claim 82, wherein the amount of the active in of individual dosage units has a variance of less than 1%.

311. (New) The process of claim 82, wherein the amount of the active in of individual dosage units has a variance of less than 0.5%.

312. (New) The process of claim 161, wherein the forming of a plurality of individual dosage unit samples and performing analytical chemical tests comprises:

(a) cutting the substantially equally sized individual dosage unit samples from the different locations of the resulting film;

(b) dissolving at least a portion of said dosage unit samples; and

(c) testing for the amount of the pharmaceutical active present in each dosage unit sample.

313. (New) The process of claim 161, wherein regulatory approval is provided by the U.S. Food and Drug Administration.

314. (New) The process of claim 161, wherein the amount of the pharmaceutical active in of individual dosage units has a variance of less than 5%.

315. (New) The process of claim 161, wherein the amount of the pharmaceutical active in of individual dosage units has a variance of less than 2%.

316. (New) The process of claim 161, wherein the amount of the pharmaceutical active in of individual dosage units has a variance of less than 1%.

317. (New) The process of claim 161, wherein the amount of the pharmaceutical active in of individual dosage units has a variance of less than 0.5%.

318. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

319. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

320. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

321. (New) A process for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval said film having a substantially uniform distribution of an active, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said active uniformly distributed throughout by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying within about the first 4 minutes to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(e) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(f) forming a plurality of individual dosage units of substantially the same size from said resulting pharmaceutical film; and

(g) performing analytical chemical tests for content uniformity on said plurality of individual dosage units from said resulting pharmaceutical film, said tests indicating said substantially uniform distribution of the active, in that the amount of the active in individual dosage units varies by no more than 10%.

322. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval said film capable of being administered to a body surface having a substantially uniform distribution of an active, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said active uniformly distributed throughout by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying within about the first 4 minutes to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) forming a plurality of individual dosage units of substantially the same size from said resulting film;

(f) performing analytical chemical tests for content uniformity on said plurality of individual dosage units from said resulting film, said tests indicating said substantially uniform distribution of the active, in that the amount of the active in individual dosage units varies by no more than 10%; and

(g) administering said resulting film to a body surface.

323. (New) A process for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval said film having a substantially uniform distribution of a desired amount of an active in individual doses of the resulting pharmaceutical film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 minutes to maintain said uniform distribution of said pharmaceutical active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said uniform distribution of pharmaceutical active by said locking-in or substantially preventing migration of said pharmaceutical active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies no more than 10% from the desired amount of the active; and

(e) performing analytical chemical tests for content uniformity of said pharmaceutical active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies no more than 10% from the desired amount of the active.

324. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval said film having a substantially uniform distribution of an active, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said active uniformly distributed throughout by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying within about the first 4 minutes to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less, wherein content uniformity of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming the resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(e) forming a plurality of individual dosage unit samples of substantially the same size from said resulting film, wherein the amount of the active in the individual dosage unit samples varies by no more than 10%.

325. (New) The process of claim 321, wherein said water-soluble polymer comprises polyethylene oxide.

326. (New) The process of claim 321, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

327. (New) The process of claim 326, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

328. (New) The process of claim 326, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic

acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

329. (New) The process of claim 326, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

330. (New) The process of claim 326, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

331. (New) The process of claim 321, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

332. (New) The process of claim 331, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

333. (New) The process of claim 321, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-congulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

334. (New) The process of claim 321, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and

combinations thereof.

335. (New) The process of claim 321, wherein said active is a bioactive active.

336. (New) The process of claim 321, wherein said active is an opiate or opiate-derivative.

337. (New) The process of claim 321, wherein said active is an anti-emetic.

338. (New) The process of claim 321, wherein said active is an amino acid preparation.

339. (New) The process of claim 321, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

340. (New) The process of claim 321, wherein said active is a protein.

341. (New) The process of claim 321, wherein said active is insulin.

342. (New) The process of claim 321, wherein said active is an anti-diabetic.

343. (New) The process of claim 321, wherein said active is an antihistamine.

344. (New) The process of claim 321, wherein said active is an anti-tussive.

345. (New) The process of claim 321, wherein said active is a non-steroidal anti-inflammatory.

346. (New) The process of claim 321, wherein said active is an anti-asthmatics.

347. (New) The process of claim 321, wherein said active is an anti-diarrhea.

348. (New) The process of claim 321, wherein said active is an alkaloid.

349. (New) The process of claim 321, wherein said active is an anti-psychotic.

350. (New) The process of claim 321, wherein said active is an anti-spasmodic.

351. (New) The process of claim 321, wherein said active is a biological response modifier.

352. (New) The process of claim 321, wherein said active is an anti-obesity drug.

353. (New) The process of claim 321, wherein said active is an H_2-antagonist.

354. (New) The process of claim 321, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

355. (New) The process of claim 321, wherein said active is a smoking cessation aid.

356. (New) The process of claim 321, wherein said active is an anti-parkinsonian agent.

357. (New) The process of claim 321, wherein said active is an anti-depressant.

358. (New) The process of claim 321, wherein said active is an anti-migraine.

359. (New) The process of claim 321, wherein said active is an anti-Alzheimer's agents.

360. (New) The process of claim 321, wherein said active is a dopamine receptor agonist.

361. (New) The process of claim 321, wherein said active is a cerebral dilator.

362. (New) The process of claim 321, wherein said active is a psychotherapeutic agent.

363. (New) The process of claim 321, wherein said active is an antibiotic.

364. (New) The process of claim 321, wherein said active is an anesthetic.

365. (New) The process of claim 321, wherein said active is a contraceptive.

366. (New) The process of claim 321, wherein said active is an anti-thrombotic drug.

367. (New) The process of claim 324, wherein said active is an analgesic.

368. (New) The process of claim 324, wherein said active is a hormone.

369. (New) The process of claim 324, wherein said active is a decongestant.

370. (New) The process of claim 324, wherein said active is a loratadine.

371. (New) The process of claim 324, wherein said active is dextromethorphan.

372. (New) The process of claim 324, wherein said active is chlorpheniramine maleate.

373. (New) The process of claim 324, wherein said active is selected from the group

consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

374. (New) The process of claim 324, wherein said active is an appetite stimulant.

375. (New) The process of claim 324, wherein said active is a gastrointestinal agent.

376. (New) The process of claim 324, wherein said active is a hypnotic.

377. (New) The process of claim 321, wherein said active is diphenhydramine.

378. (New) The process of claim 321, wherein said active is nabilone.

379. (New) The process of claim 321, wherein said active is albuterol sulfate.

380. (New) The process of claim 321, wherein said active is an anti-tumor drug.

381. (New) The process of claim 321, wherein said active is a glycoprotein.

382. (New) The process of claim 321, wherein said active is an analgesic.

383. (New) The process of claim 321, wherein said active is a hormone.

384. (New) The process of claim 321, wherein said active is a decongestant.

385. (New) The process of claim 321, wherein said active is a loratadine.

386. (New) The process of claim 321, wherein said active is dextromethorphan.

387. (New) The process of claim 321, wherein said active is chlorpheniramine maleate.

388. (New) The process of claim 321, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

389. (New) The process of claim 321, wherein said active is an appetite stimulant.

390. (New) The process of claim 321, wherein said active is a gastrointestinal agent.

391. (New) The process of claim 321, wherein said active is a hypnotic.

392. (New) The process of claim 321, wherein said active is taste-masked.

393. (New) The process of claim 321, wherein said active is taste-masked using a flavor.

394. (New) The process of claim 321, wherein said active is coated with a controlled release composition.

395. (New) The process of claim 394, wherein said controlled release composition provides an immediate release.

396. (New) The process of claim 394, wherein said controlled release composition provides a delayed release.

397. (New) The process of claim 394, wherein said controlled release composition provides a sustained release.

398. (New) The process of claim 394, wherein said controlled release composition provides a sequential release.

399. (New) The process of claim 321, wherein said active is a particulate.

400. (New) The process of claim 321, further comprising adding a degassing agent to said flowable polymer matrix.

401. (New) The process of claim 321, further comprising a step of providing a second film layer.

402. (New) The process of claim 401, wherein said second film layer is coated onto said resulting pharmaceutical film.

403. (New) The process of claim 401, wherein said second film layer is spread onto said resulting pharmaceutical film.

404. (New) The process of claim 401, wherein said second film layer is cast onto said resulting pharmaceutical film.

405. (New) The process of claim 401, wherein said second film layer is extruded onto said resulting pharmaceutical film.

406. (New) The process of claim 401, wherein said second film layer is sprayed onto said resulting pharmaceutical film.

407. (New) The process of claim 401, wherein said second film layer is laminated onto said

resulting pharmaceutical film.

408. (New) The process of claim 401, further comprising laminating said resulting pharmaceutical film to another film.

409. (New) The process of claim 401, wherein said second film layer comprises an active.

410. (New) The process of claim 401, wherein said active in said second film layer is different than said active in said resulting pharmaceutical film.

411. (New) The process of claim 322, wherein said water-soluble polymer comprises polyethylene oxide.

412. (New) The process of claim 322, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

413. (New) The process of claim 412, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

414. (New) The process of claim 412, wherein said polymer further comprises a polymer

selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

415. (New) The process of claim 412, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

416. (New) The process of claim 412, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

417. (New) The process of claim 322, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

418. (New) The process of claim 417, wherein said solvent is selected from the group

consisting of ethanol, isopropanol, acetone, and combinations thereof.

419. (New) The process of claim 322, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

420. (New) The process of claim 322, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.

421. (New) The process of claim 322, wherein said active is a bioactive active.

422. (New) The process of claim 322, wherein said active is an opiate or opiate-derivative.

423. (New) The process of claim 322, wherein said active is an anti-emetic.

424. (New) The process of claim 322, wherein said active is an amino acid preparation.

425. (New) The process of claim 322, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

426. (New) The process of claim 322, wherein said active is a protein.

427. (New) The process of claim 322, wherein said active is insulin.

428. (New) The process of claim 322, wherein said active is an anti-diabetic.

429. (New) The process of claim 322, wherein said active is an antihistamine.

430. (New) The process of claim 322, wherein said active is an anti-tussive.

431. (New) The process of claim 322, wherein said active is a non-steroidal anti-inflammatory.

432. (New) The process of claim 322, wherein said active is an anti-asthmatics.

433. (New) The process of claim 322, wherein said active is an anti-diarrhea.

434. (New) The process of claim 322, wherein said active is an alkaloid.

435. (New) The process of claim 322, wherein said active is an anti-psychotic.

436. (New) The process of claim 322, wherein said active is an anti-spasmodic.

437. (New) The process of claim 322, wherein said active is a biological response modifier.

438. (New) The process of claim 322, wherein said active is an anti-obesity drug.

439. (New) The process of claim 322, wherein said active is an H_2-antagonist.

440. (New) The process of claim 322, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

441. (New) The process of claim 322, wherein said active is a smoking cessation aid.

442. (New) The process of claim 322, wherein said active is an anti-parkinsonian agent.

443. (New) The process of claim 322, wherein said active is an anti-depressant.

444. (New) The process of claim 322, wherein said active is an anti-migraine.

445. (New) The process of claim 322, wherein said active is an anti-Alzheimer's agents.

446. (New) The process of claim 322, wherein said active is a dopamine receptor agonist.

447. (New) The process of claim 322, wherein said active is a cerebral dilator.

448. (New) The process of claim 322, wherein said active is a psychotherapeutic agent.

449. (New) The process of claim 322, wherein said active is an antibiotic.

450. (New) The process of claim 322, wherein said active is an anesthetic.

451. (New) The process of claim 322, wherein said active is a contraceptive.

452. (New) The process of claim 322, wherein said active is an anti-thrombotic drug.

453. (New) The process of claim 322, wherein said active is diphenhydramine.

454. (New) The process of claim 322, wherein said active is nabilone.

455. (New) The process of claim 322, wherein said active is albuterol sulfate.

456. (New) The process of claim 322, wherein said active is an anti-tumor drug.

457. (New) The process of claim 322, wherein said active is a glycoprotein.

458. (New) The process of claim 322, wherein said active is an analgesic.

459. (New) The process of claim 322, wherein said active is a hormone.

460. (New) The process of claim 322, wherein said active is a decongestant.

461. (New) The process of claim 322, wherein said active is a loratadine.

462. (New) The process of claim 322, wherein said active is dextromethorphan.

463. (New) The process of claim 322, wherein said active is chlorpheniramine maleate.

464. (New) The process of claim 322, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

465. (New) The process of claim 322, wherein said active is an appetite stimulant.

466. (New) The process of claim 322, wherein said active is a gastrointestinal agent.

467. (New) The process of claim 322, wherein said active is a hypnotic.

468. (New) The process of claim 322, wherein said active is taste-masked.

469. (New) The process of claim 322, wherein said active is taste-masked using a flavor.

470. (New) The process of claim 322, wherein said active is coated with a controlled release composition.

471. (New) The process of claim 470, wherein said controlled release composition provides an immediate release.

472 (New) The process of claim 470, wherein said controlled release composition provides a delayed release.

473. (New) The process of claim 470, wherein said controlled release composition provides a sustained release.

474. (New) The process of claim 470, wherein said controlled release composition provides a sequential release.

475. (New) The process of claim 322, wherein said active is a particulate.

476. (New) The process of claim 322, further comprising adding a degassing agent to said flowable polymer matrix.

477. (New) The process of claim 322, further comprising a step of providing a second film layer.

478. (New) The process of claim 477, wherein said second film layer is coated onto said resulting film.

479. (New) The process of claim 477, wherein said second film layer is spread onto said resulting film.

480. (New) The process of claim 477, wherein said second film layer is cast onto said resulting film.

481. (New) The process of claim 477, wherein said second film layer is extruded onto said resulting film.

482. (New) The process of claim 477, wherein said second film layer is sprayed onto said resulting film.

483. (New) The process of claim 477, wherein said second film layer is laminated onto said resulting film.

484. (New) The process of claim 477, further comprising laminating said resulting film to another film.

485. (New) The process of claim 477, wherein said second film layer comprises an active.

486. (New) The process of claim 477, wherein said active in said second film layer is different than said active in said resulting film.

487. (New) The process of claim 323, wherein said water-soluble polymer comprises polyethylene oxide.

488. (New) The process of claim 323, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

489. (New) The process of claim 488, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

490. (New) The process of claim 488, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

491. (New) The process of claim 488, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

492. (New) The process of claim 488, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids,

polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

493. (New) The process of claim 323, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

494. (New) The process of claim 493, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

495. (New) The process of claim 323, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer

agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

496. (New) The process of claim 323, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.

497. (New) The process of claim 323, wherein said active is a bioactive active.

498. (New) The process of claim 323, wherein said active is an opiate or opiate-derivative.

499. (New) The process of claim 323, wherein said active is an anti-emetic.

500. (New) The process of claim 323, wherein said active is an amino acid preparation.

501. (New) The process of claim 323, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

502. (New) The process of claim 323, wherein said active is a protein.

503. (New) The process of claim 323, wherein said active is insulin.

504. (New) The process of claim 323, wherein said active is an anti-diabetic.

505. (New) The process of claim 323, wherein said active is an antihistamine.

506. (New) The process of claim 323, wherein said active is an anti-tussive.

507. (New) The process of claim 323, wherein said active is a non-steroidal anti-inflammatory.

508. (New) The process of claim 323, wherein said active is an anti-asthmatics.

509. (New) The process of claim 323, wherein said active is an anti-diarrhea.

510. (New) The process of claim 323, wherein said active is an alkaloid.

511. (New) The process of claim 323, wherein said active is an anti-psychotic.

512. (New) The process of claim 323, wherein said active is an anti-spasmodic.

513. (New) The process of claim 323, wherein said active is a biological response modifier.

514. (New) The process of claim 323, wherein said active is an anti-obesity drug.

515. (New) The process of claim 323, wherein said active is an H_2-antagonist.

516. (New) The process of claim 323, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

517. (New) The process of claim 323, wherein said active is a smoking cessation aid.

518. (New) The process of claim 323, wherein said active is an anti-parkinsonian agent.

519. (New) The process of claim 323, wherein said active is an anti-depressant.

520. (New) The process of claim 323, wherein said active is an anti-migraine.

521. (New) The process of claim 323, wherein said active is an anti-Alzheimer's agents.

522. (New) The process of claim 323, wherein said active is a dopamine receptor agonist.

523. (New) The process of claim 323, wherein said active is a cerebral dilator.

524. (New) The process of claim 323, wherein said active is a psychotherapeutic agent.

525. (New) The process of claim 323, wherein said active is an antibiotic.

526. (New) The process of claim 323, wherein said active is an anesthetic.

527. (New) The process of claim 323, wherein said active is a contraceptive.

528. (New) The process of claim 323, wherein said active is an anti-thrombotic drug.

529. (New) The process of claim 323, wherein said active is diphenhydramine.

530. (New) The process of claim 323, wherein said active is nabilone.

531. (New) The process of claim 323, wherein said active is albuterol sulfate.

532. (New) The process of claim 323, wherein said active is an anti-tumor drug.

533. (New) The process of claim 323, wherein said active is a glycoprotein.

534. (New) The process of claim 323, wherein said active is an analgesic.

535. (New) The process of claim 323, wherein said active is a hormone.

536. (New) The process of claim 323, wherein said active is a decongestant.

537. (New) The process of claim 323, wherein said active is a loratadine.

538. (New) The process of claim 323, wherein said active is dextromethorphan.

539. (New) The process of claim 323, wherein said active is chlorpheniramine maleate.

540. (New) The process of claim 323, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

541. (New) The process of claim 323, wherein said active is an appetite stimulant.

542. (New) The process of claim 323, wherein said active is a gastrointestinal agent.

543. (New) The process of claim 323, wherein said active is a hypnotic.

544. (New) The process of claim 323, wherein said active is taste-masked.

545. (New) The process of claim 323, wherein said active is taste-masked using a flavor.

546. (New) The process of claim 323, wherein said active is coated with a controlled release composition.

547. (New) The process of claim 546, wherein said controlled release composition provides an immediate release.

548. (New) The process of claim 546, wherein said controlled release composition provides a delayed release.

549. (New) The process of claim 546, wherein said controlled release composition provides a sustained release.

550. (New) The process of claim 546, wherein said controlled release composition provides a sequential release.

551. (New) The process of claim 323, wherein said active is a particulate.

552. (New) The process of claim 323, further comprising adding a degassing agent to said flowable polymer matrix.

553. (New) The process of claim 323, further comprising a step of providing a second film layer.

554. (New) The process of claim 553, wherein said second film layer is coated onto said resulting pharmaceutical film.

555. (New) The process of claim 553, wherein said second film layer is spread onto said resulting pharmaceutical film.

556. (New) The process of claim 553, wherein said second film layer is cast onto said resulting pharmaceutical film.

557. (New) The process of claim 553, wherein said second film layer is extruded onto said resulting pharmaceutical film.

558. (New) The process of claim 553, wherein said second film layer is sprayed onto said resulting pharmaceutical film.

559. (New) The process of claim 553, wherein said second film layer is laminated onto said resulting pharmaceutical film.

560. (New) The process of claim 553, further comprising laminating said resulting pharmaceutical film to another film.

561. (New) The process of claim 553, wherein said second film layer comprises an active.

562. (New) The process of claim 553, wherein said active in said second film layer is different than said active in said resulting pharmaceutical film.

563. (New) The process of claim 324, wherein said water-soluble polymer comprises polyethylene oxide.

564. (New) The process of claim 324, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

565. (New) The process of claim 564, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

566. (New) The process of claim 564, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

567. (New) The process of claim 564, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carrageenan, locust bean gum, dextran, gellan gum and combinations thereof.

568. (New) The process of claim 564, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

569. (New) The process of claim 324, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

570. (New) The process of claim 569, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

571. (New) The process of claim 324, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements,

dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

572. (New) The process of claim 324, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.

573. (New) The process of claim 324, wherein said active is a bioactive active.

574. (New) The process of claim 324, wherein said active is an opiate or opiate-derivative.

575. (New) The process of claim 324, wherein said active is an anti-emetic.

576. (New) The process of claim 324, wherein said active is an amino acid preparation.

577. (New) The process of claim 324, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

578. (New) The process of claim 324, wherein said active is a protein.

579. (New) The process of claim 324, wherein said active is insulin.

580. (New) The process of claim 324, wherein said active is an anti-diabetic.

581. (New) The process of claim 324, wherein said active is an antihistamine.

582. (New) The process of claim 324, wherein said active is an anti-tussive.

583. (New) The process of claim 324, wherein said active is a non-steroidal anti-inflammatory.

584. (New) The process of claim 324, wherein said active is an anti-asthmatics.

585. (New) The process of claim 324, wherein said active is an anti-diarrhea.

586. (New) The process of claim 324, wherein said active is an alkaloid.

587. (New) The process of claim 324, wherein said active is an anti-psychotic.

588. (New) The process of claim 324, wherein said active is an anti-spasmodic.

589. (New) The process of claim 324, wherein said active is a biological response modifier.

590. (New) The process of claim 324, wherein said active is an anti-obesity drug.

591. (New) The process of claim 324, wherein said active is an H_2-antagonist.

592. (New) The process of claim 324, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

593. (New) The process of claim 324, wherein said active is a smoking cessation aid.

594. (New) The process of claim 324, wherein said active is an anti-parkinsonian agent.

595. (New) The process of claim 324, wherein said active is an anti-depressant.

596. (New) The process of claim 324, wherein said active is an anti-migraine.

597. (New) The process of claim 324, wherein said active is an anti-Alzheimer's agents.

598. (New) The process of claim 324, wherein said active is a dopamine receptor agonist.

599. (New) The process of claim 324, wherein said active is a cerebral dilator.

600. (New) The process of claim 324, wherein said active is a psychotherapeutic agent.

601. (New) The process of claim 324, wherein said active is an antibiotic.

602. (New) The process of claim 324, wherein said active is an anesthetic.

603. (New) The process of claim 324, wherein said active is a contraceptive.

604. (New) The process of claim 324, wherein said active is an anti-thrombotic drug.

605. (New) The process of claim 324, wherein said active is diphenhydramine.

606. (New) The process of claim 324, wherein said active is nabilone.

607. (New) The process of claim 324, wherein said active is albuterol sulfate.

608. (New) The process of claim 324, wherein said active is an anti-tumor drug.

609. (New) The process of claim 324, wherein said active is a glycoprotein.

610. (New) The process of claim 324, wherein said active is taste-masked.

611. (New) The process of claim 324, wherein said active is taste-masked using a flavor.

612. (New) The process of claim 324, wherein said active is coated with a controlled release composition.

613. (New) The process of claim 612, wherein said controlled release composition provides an immediate release.

614. (New) The process of claim 612, wherein said controlled release composition provides a delayed release.

615. (New) The process of claim 612, wherein said controlled release composition provides a sustained release.

616. (New) The process of claim 612, wherein said controlled release composition provides a sequential release.

617. (New) The process of claim 324, wherein said active is a particulate.

618. (New) The process of claim 324, further comprising adding a degassing agent to said flowable polymer matrix.

619. (New) The process of claim 324, further comprising a step of providing a second film layer.

620. (New) The process of claim 619, wherein said second film layer is coated onto said resulting film.

621. (New) The process of claim 619, wherein said second film layer is spread onto said resulting film.

622. (New) The process of claim 619, wherein said second film layer is cast onto said resulting film.

623. (New) The process of claim 619, wherein said second film layer is extruded onto said resulting film.

624. (New) The process of claim 619, wherein said second film layer is sprayed onto said resulting film.

625. (New) The process of claim 619, wherein said second film layer is laminated onto said resulting film.

626. (New) The process of claim 619, further comprising laminating said resulting film to another film.

627. (New) The process of claim 619, wherein said second film layer comprises an active.

628. (New) The process of claim 619, wherein said active in said second film layer is different than said active in said resulting film.

REMARKS

I. Description of the Patent and the Applicant's Reply

The above-identified U.S. Patent No. 7,897,080 (" '080 Patent") is presently under reexamination. Claims 1-299 were issued in the '080 Patent. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 16, 95 and 177, have been canceled herein as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. . Claims 91, 255, 273 and 291 have also been canceled. Claims 300 through 628 are new.

While the Examiner's rejection of the claims is respectfully traversed, claims 1, 82 and 161 of the '080 Patent have been amended in an effort to expedite prosecution of the present reexamination. Claims 1, 82 and 161are hereby amended in accordance with 37 C.F.R. §1.530(d) (2) and (f). In accordance with 35 U.S.C. § 314(a), the amendments to claims 1, 82 and 161, new independent claims 321-324, and new dependent claims 300-320 and claims 325-628, do not enlarge the scope of the claims of the '080 Patent. Explanation of the support for these claims appears below. Entry of this amendment and reconsideration is respectfully requested.

II. Status of Claims and Support for Claim Changes Pursuant to 37 C.F.R. §1.530(e)

The status of the claims as of the date of this amendment is as follows: Claims 1-299 were issued in the '080 Patent and are subject to reexamination. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 300 through 628 are new and are subject to examination. Please cancel claims 16, 95 and 177, as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Please cancel claims 91, 255, 273 and 291.

In compliance with 37 C.F.R. § 1.530(j), the amendments to claims 1, 82 and 161 do not enlarge their scope or the scope of the original claims or introduce new matter, nor do the amendments adding new claims 300 through 628 enlarge the scope of the original claims or introduce new matter.

Support for the amendments to claims 1, 82 and 161 and new claims 300 through 628 may be found throughout the '080 Patent, including, the Abstract, Specification, Figures and Claims, for example, at col. 28, l. 66 through col. 29, l. 6; col. 29, ll. 20-35; col. 32, ll. 34-39; col. 2, ll. 27-46; col. 15, ll. 28-40 and the Abstract; quoted in detail below; and col. 2, l. 57, col. 3, ll. 5-60 ("the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval"); col. 19, l. 30 through col. 21, l. 30 (actives including pharmaceutical actives); col. 6, ll. 49-52 ("These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process."); Figures 6, 7, 8, 35 and 36 and col. 14, ll. 20-25 ("drying" and "drying apparatus"); col. 13, ll. 36-37 ("After mechanical mixing, the film may be placed on a conveyor"); col. 29, ll. 11-13 ("As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus"); col. 10, ll. 47-48 ("The film . . . is finally formed on the substrate"); col. 26, l. 33 through col. 27, l. 10 ("the coating is then deposited onto the substrate"); col. 44, 11. 9-13 ("the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the 'locking-in' of uniformity of content throughout the film"); col. 58, claim 28 ("wherein the visco-elastic film is formed within about 4 minutes"); col. 4, l. 8; col. 6, ll. 46-52; col. 13, ll. 36-43; col. 26, ll. 9-27; col. 28, ll. 24-58; col. 29, ll. 8-10; col. 18, ll. 53-58; col. 29, l. 63 through col. 30, l.2; support for new claims may also be found throughout the '337 Patent, including, the Figures and Claims, for example at col. 19, ll. 10-25, col. 19, l. 30 through col. 22, l. 28, col. 25, ll. 53-65, col. 28, ll. 53-58, col. 18, ll. 54-59, col. 22, ll. 24-28; Figures 6-8 and 35.

"Temperatures that approach 100° C. will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of 70° C. for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature.

"Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component."

'080 Patent. col. 12, ll. 20-36.

"The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process."

'080 Patent, col. 16, l. 62 through col. 17, l. 3 (emphasis supplied).

"It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and overall appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."

'080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

"The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s). . . . After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples."

'080 Patent, col. 29, ll. 20 through 35 (emphasis supplied).

"An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."

'080 Patent, col. 32, ll. 36-41 (emphasis supplied).

"The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present."

'080 Patent, col. 2, ll. 27-46 (emphasis supplied).

"Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the

matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. "

'080 Patent, col. 15, ll. 28-43 (emphasis supplied).

III. Declarations Submitted With This Reply

Along with this Reply, the Patentee is submitting the Declarations of Dr. B. Arlie Bogue (Exhibit A) and Dr. Gerald Fuller (Exhibit B) both under 37 C.F.R. §1.132. The Declarations provide no legal arguments, but rather provides technical opinions and factual statements, and thus should not count toward the page limit of 37 C.F.R. §1.943.

IV. Background of the '080 Patent

The '080 Patent is a continuation of U.S. application Ser. No. 10/856,176, filed May 28, 2004 now U.S. Pat. No. 7,666,337 (" '337 Patent"), which claims the benefit of U.S. Provisional Application No. 60/473,902, filed May 28, 2003 and is a continuation-in-part of U.S. application Ser. No. 10/768,809, filed Jan. 30, 2004 now U.S. Pat. No. 7,357,891 (" '891 Patent"), which claims benefit to U.S. Provisional Application No. 60/443,741 filed Jan. 30, 2003 and is a continuation-in-part of:

(a) PCT/US02/32575 filed Oct. 11, 2002, which claims priority to: (1) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002 which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (2) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002;

(b) PCT/US02/32594, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and

(c) PCT/US02/32542, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002.

The '080 Patent has not been and is not currently involved in litigation.

The '891 Patent is involved in a U.S. litigation wherein Patentee has alleged that the Third Party Requester, BioDelivery Sciences International, Inc. ("BDSI") has infringed its '891 Patent. The litigation is Civil Action No. 10-cv-5695 in the U.S. District Court in the District of New Jersey. In the litigation, Patentee also alleged that the Third Party Requester infringed two other of Patentee's patents, U.S. 7,425,292 (" '292 Patent") and U.S. 7,824,588 (" '588 Patent").

Third Party Requester requested reexamination of the '891 Patent (90/012,098), the '292 Patent (90/012,097) and the '588 Patent (95/001,753) as well. Both the '292 and the '891 Patent successfully exited reexamination. The Examiner on January 23, 2013 issued a Right of Appeal Notice ("RAN") for the '588 Patent reexamination. Finally, Third Party Requester requested reexamination of the '080 Patent and another of Patentee's related patents U.S. Pat. No. 7,666,337 (Control No. 95/002,171), reexamination was ordered, an Office Action issued and Patentee is preparing a response thereto.

'080 Patent Office Action Statements

In connection with the Order Granting Request for Inter Partes Reexamination of the '080 Patent, Control No. 95/002,170 ("Order Granting IPR Request '080 Patent"), noted above, certain comments were made by the Examiner with respect to Claim 25 of the '337 Patent. The statements were made when the Examiner addressed Third Party Requester's request to find that claim 82 of the '080 Patent should be rejected under 35 U.S.C. § 101 double patenting over claim 25 of the '337 Patent. Patentee supports the Examiner's finding that the Third Party Requester had failed to demonstrate a reasonable likelihood of success, in that respect, with at least one claim of the '080 Patent. However, Patentee respectfully disagrees with the Examiner's statements interpreting "uniform" and "substantially uniform" therein. In particular, Patentee disagrees that "the active is uniformly distributed (i.e. no variance of active)" in the matrix. Certainly a uniform distribution does not require a state of "no variance". See pages 21 and 22 of the Order Granting IPR Request '080 Patent:

The concept of "no variance" of anything has little practical value in the real physical world and in the '337 Patent, where the phrase does not appear. The '337 Patent makes no claim to some form of absolute 100% uniformity, it discloses, *inter alia*, uniformity of active and substantial uniformity of active both with no more than 10% variance. As used in the '337 Patent, while a "uniform distribution of active" has little variance in active, and in particular, less variance in active than a "substantially uniform distribution of active", Patentee does not claim its processes involve obtaining absolute uniformity of composition or content uniformity of no variance. The variance in uniformity may be very small but that is not the same as saying that a uniform distribution has no variance in the distribution. As the Examiner can appreciate, manufacturing processes never result in "no variance" in the quantitative compositional makeup of products made therefrom. In short, "uniform" and "substantially uniform" are indeed different, but "uniform" from a practical standpoint,. Must of necessity allow for some variance, albeit less than "substantially uniform".

V. The Patented Invention

The present invention is directed to a novel and non-obvious method of manufacturing an ingestible therapeutic active delivery system and uses thereof. The patented invention, as explicitly claimed, covers a process for manufacturing a resulting film suitable for commercialization and regulatory approval said film having a substantially uniform distribution of a pharmaceutical active components, wherein substantially uniform distribution of the pharmaceutical active is indicated through analytical chemical tests for active content of substantially equal sized individual dosage units sampled from the resulting film varies by no more than 10%. Hence the commercially manufactured '337 Patent film is both a commercially viable product as well as a product which can and does meet, for example, FDA regulations, including assaying requirements.

This should be compared to the laboratory produced films described in the prior art relied on by the Examiner. In the cited prior art, terms such as uniformity, substantial uniformity, homogeneity, are all accepted without real support. They cannot be relied upon. What is missing is the support for the statements, that is, having had the amount of active tested by analytical chemical testing, including assaying. Patentee uses the '337 Patent invention to manufacture commercially acceptable pharmaceutical products for which Patentee must establish the content uniformity of active in its products by such analytical chemical testing as required by regulatory agencies, such as the FDA. Dr. Bogue's Declaration describes such testing on Patentee's products produced in accordance with the invention and the results which are consistent with the '337 Patent's claims for active content of substantially equal sized individual dosage units sampled from the resulting film varies by no more than 10%. Bogue Declaration, ¶¶ 5-13.

Patentee's instant claims recited additional detail about its processes for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval. Some of the details include: forming a flowable polymer matrix; said matrix having a uniform distribution of said pharmaceutical active; casting said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps and conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 minutes to maintain said uniform distribution of said pharmaceutical active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film, wherein the polymer matrix temperature is 100 °C or less; forming the resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said uniform distribution of pharmaceutical active by said locking-in or substantially preventing migration of said pharmaceutical active is maintained, wherein said resulting film is suitable for commercialization and regulatory approval; sampling the resulting film at different locations of the resulting film in

order to perform the analytical chemical tests for content uniformity of said pharmaceutical active and thus establish for commercialization and regulatory purposes the substantially uniform distribution of the pharmaceutical active throughout the film product at a desired/required degree of uniformity, i.e., vary by more than 10%.

Of particular relevance to the Office Action, the patented invention relates to film products and film-containing products, wherein controlling the viscosity of the polymer matrix and controlling the drying process, among other things, ensures that the active components maintain their uniform distribution throughout the film product so that the desired uniformity is found in the resulting product as indicated and/or verified by testing, such as the steps of cutting samples from the resulting film product, dissolving at least portions of the samples and then testing each sample for the actual amount of actives present using analytical equipment.

As used throughout the '080 Patent, the resulting visco-elastic product is defined as a product that has maintained the desired uniformity of content of the active after being subjected to a coating/deposition step (i.e., casting) and drying. For example, the '080 Patent, at col. 8, lines 64-66, discloses that the stability is important "in the wet film stage until sufficient drying has occurred to lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained." The '080 Patent, at col. 13, lines 53-54 clearly discloses that: "The resulting dried film 1 is a visco-elastic solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film."

Thus, as defined in the application as filed and present in the issued claims, a visco-elastic solid is one that has been controllably dried to lock its components into a substantially uniform distribution throughout the film while avoiding problems associated with conventional drying methods. By providing a visco-elastic film product having this compositional uniformity, the user can be assured that the product includes the proper amount of components, such as an active contained therein. Thus, a visco-elastic product is one in which the active contained

therein is present in an amount that is substantially uniform in the visco-elastic product. Further, when the process is used to make large-scale film products, such as large rolls of film from which smaller films are cut, the user can feel confident that no matter where the large roll of film is cut, the resulting pieces (e.g., unit dosages) will have a substantially uniform composition. The need for providing a process for obtaining the desired uniformity of content of the desired amount of active in the resulting product is critically important, particularly for regulated products, such as pharmaceuticals.

Prior to the present invention, it was known to prepare film products. However, in many cases the end product was assumed to be homogeneous, either because the initial components were blended together or because after the blending step the physically observable properties of the resulting film product, for example, its appearance or weight, were satisfactory. However, these physical properties do not indicate that the amount of the active in individual dosage units varies by no more than 10%. The only way to actually test for the amount of the active present in individual dosage unit samples, is to use analytical chemical testing and actually test for the presence of the desired amount of active.

Importantly, the process of forming a proper film product does not end at the mixing stage. Patentee has discovered that the various steps post-mixing also play an important role in the resulting product composition. For example, one key step in the formation of a film product is the drying step, particularly when heat and/or radiation is used to dry the film. Patentee has discovered that controlled drying methods may be used to prepare a compositionally uniform film product. Controlled drying includes methods that do not include, for example, the formation of bubbles, or uncontrolled air currents that may cause movement of particles within the visco-elastic film forming matrix.

It is important to understand that compositional uniformity or uniformity of content is not the same as uniform thickness, nor is it the same as having a surface that appears free of defects.

Importantly, having a glossy surface does not equate to a uniform film, since the bottom side of a film product formed on a substrate will take the surface features of the substrate. If the substrate is smooth, the resulting bottom surface will also be smooth and possibly glossy. A product that has a surface that appears free of defects may have experienced significant non-uniformity below the surface, for example due to agglomeration of components, movement due to the Soret effect, etc. It is important to note that just because the surface of a resulting product looks glossy or free of defects does not inherently mean that the actives within the film product are uniform so as to satisfy regulatory requirements and/or deliver the desired amount to the patient. See Fuller Declaration, ¶ 11-13.

The '080 Patent discloses in a section entitled "Testing Films for Uniformity" (col. 28, l. 65 through col. 29, l. 53) that "[i]t may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process". '080 Patent, col. 28, l. 66 through col. 29, l. 1. In particular:

> "It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and over all appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."
>
> '080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

Thus disclosed are two general types of testing, one for physical uniformity, and one for chemical uniformity. The disclosure goes on to provide different ways to test for each.

> "After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art. If the testing results show non-uniformity between film samples, the manufacturing process

> may be altered. This can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions, mixing conditions, compositional components and/or film viscosity may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others."
>
> '080 Patent, col. 29, ll. 33-38 (emphasis supplied).

In this way the '080 Patent provides multiple tests for non-uniformity, which are extremely useful in the commercial manufacture of films. For example, manufacturing runs of films which appear to exhibit "non-uniformity" may be adjusted early in the run with less waste of materials, thus saving time and expense associated with the possibility of a non-uniform film. Physical tests, such as observational tests, are insufficient to determine the degree of uniformity. However, especially in the case of individual doses of actives, for example, pharmaceutical actives, the actual uniformity of content in the amount of active is essential and must be quantified through analytical chemical testing. For example, testing to determine the appropriate degree of content uniformity of the resulting film for commercial scale and regulatory compliance may involve sampling substantially equal sized individual dosage units of the resulting film, dissolving at least a portion of the sampled resulting film, and testing for the amount of active present in the sampled resulting film. Thus, the '080 Patent discloses that uniformity of the active is demonstrated through testing.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar sizes cut from different locations on the same film contain substantially the same amount of active."
>
> '080 Patent, col. 32, ll. 36-41 (emphasis supplied).

In this respect the Examiner, in his Scope of Claims section has mistakenly included physical uniformity type tests, used to quickly suggest non-uniformity, with chemical uniformity

type tests involving analytic equipment, that is, the actual testing of the uniformity of content for the amount of active. In the Scope of Claims section of the Office Action (pp. 3-7), the Examiner refers to two different portions of the '080 Patent's "EXAMPLES" section as follows:

> "An alternative means for evaluating uniformity is to cut the films into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39)."
>
> Office Action, p. 7.

Unfortunately the two sentences are not related to each other, other than that both deal with examples and with cutting the film into dosage forms. The first is from a physical test, the second, relating to actives, is from an analytical chemical test for uniformity of content of active.

> First is the physical test which refers to uniformity in mass.
>
> "Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:
>
> [Table omitted.]
>
> "The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. **Therefore,** when the components of different densities are combined in a uniform manner in a film, as in the present invention, **individual dosages forms from the same film of substantially equal dimensions, will contain the same mass.**"
>
> '080 Patent, col. 31, l. 46 through col. 32, l. 34 (emphasis supplied).

In accordance with this test, if the masses are unequal that would be an indication of mass non-uniformity.

Immediately after the above quoted disclosure, the '080 Patent discloses essentially that to demonstrate uniformity of content for active, the amount of active in each substantially similarly sized sample must be determined.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. **The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active.**"
>
> '080 Patent, col. 32, ll. 35-40 (emphasis supplied).

The Examiner also relies on the paragraph at '080 Patent, col. 31, ll. 38-45 for support that physical type tests, in this case observational tests, are sufficient to establish uniformity of content of active.

> "The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film."
>
> '080 Patent, col. 31, ll. 38-45

However, it is one thing to have films which appear to be substantially free of aggregation and rely on that to say there is substantially no disparity among the amount of active in any portion of the film, and it is a totally different thing to demonstrate by testing for the active that its

distribution among film samples of the same size establishes a uniformity of content within a desired range.

This paragraph, again, from the '080 Patent's section on "EXAMPLES", sets the stage for disclosing both the physical and chemical type tests referred to above at '080 Patent, col. 31, l. 46 through col. 32, l. 40, which follows this paragraph (see citation). Moreover, this paragraph itself follows the manufacture of the film of Examples A-I and starts with what would be a expected quick and inexpensive procedure of right after making the film taking a look at it, to see if it appears non-uniform. That is, look at the film and see if it looks like everything is uniform and, if it does, then test the film to make sure it is. Such an observational test is at a macro level and does not indicate the degree of uniformity. What followed next were the two other tests discussed above.

Importantly, the first test obviously a physical type test needed to rely on assumptions to reach its conclusion of substantially no disparity among the amount of active found in any portion of the film. Namely, by "viewing the films it was apparent that they were substantially free of aggregation . . . . Therefore, there was substantially no disparity among the amount of active found in any portion of the film." Based on physical observations a conclusion was drawn. The second, another physical test, concluded "individual dosages forms from the same film of substantially equal dimensions will contain the same mass;" again, referring to mass not uniformity of content of active. Again, no simple declarative statement, that the amount of active in each sample was substantially the same. [If we modify the independent claim to include test for the active, we should refer to that here.]

It was only the third test, the chemical type test that could directly establish that "films of substantially similar size cut from different locations on the same film contain substantially the same amount of active". This is to be expected as only the chemical based tests could provide the necessary assurance for the statement that substantially the same amount of active was

present in each dose. Thus, it is wrong to rely on physical tests in prior art disclosures to "establish" that the prior art films actually possessed the uniformity of active required by the '080 Patent as determined by actual analytical chemical testing for the active. In fact, such physical tests would not result in the type of quantitative assay which would yield the percent (%) variance as recited in the claims.

The resulting product of the present invention is a useful, active-containing, visco-elastic film product that has a substantially uniform distribution of active components after formation, such that uniformity of content of the resulting film varies no more than 10% with respect to the desired amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film. Importantly, in accordance with the invention the patented processes can be used in the manufacture of commercial products.

VI. Arriving at the Invention

The inventors of the '337 Patent are the first to not only identify the problems associated with manufacturing commercially and pharmaceutically viable active containing film dosage forms, but also to solve those problems. Although many prior publications discussed the use of film as a dosage form for drugs, none of the publications identified nor solved the problems and complications associated with their manufacture. These early publications focused on the compositional and qualitative aspects of the films only and merely treated the manufacturing, if mentioned at all, as being simple, such as exposing the cast wet film to a conventional hot air circulating oven. However, especially in a commercial manufacturing setting, drying an active-containing cast wet film (even if the wet film is homogenous), in a conventional hot air circulating oven does not necessarily produce a film that is commercially viable, or deliver a film with the prescribed degree of uniformity of content in said setting. The '337 Patent does. See Bogue Declaration, ¶¶ 5-13.

A. Recognition of the Problem

The inventors have discovered that it is not commercially viable to manufacture therapeutic–active-containing films using conventional drying methods. Even when a wet film matrix is properly formed so as to have a uniform distribution of active within it, there are numerous factors which can destroy that uniformity of content during later processing such as casting and drying. The present specification describes many of these problems, which include (i) self-aggregation and agglomeration of active; (ii) skinning of the surface (a barrier through which remaining solvent must penetrate) before the thickness of the film is sufficiently dried, resulting in ripping and re-forming of the surface; (iii) forming of ripples on the surface; (iv) formation of air bubbles, which result in voids or air spaces within the film product; (v) maintaining the active in a substantially stable and uniformly dispersed state; or (vi) movement of active particles due to uncontrolled air currents during drying. See, for example, col. 3, l. 33 through col. 4, l. 6, the '080 Patent.

B. Solving the Problem

The inventors not only were the first to identify all the problems described above, but the first to solve them. Failure to solve one or more of these problems results in a film product that lacks the desired degree of uniformity of content of active per unit dose of film and therefore when equal dosage sizes are cut from the bulk film product, the desired amount of active per dosage lacks the desired and/or required degree of uniformity of content of active. The inventive methods and processes of the '080 Patent maintain the desired uniformity of content of active by, *inter alia*, controlling polymer matrix viscosity and controlling the drying processes so as to avoid the aforementioned problems. Thereby forming a visco-elastic film that locks-in the substantially uniform distribution of active(s) during the drying steps. As described in the specification and claims, the present invention substantially maintains the uniformity of active

from the formation of the initial matrix through the final drying process, such that the pharmaceutical active varies by no more than 10%.

The Examiner has cited several references, which will be discussed in further detail below. For ease of understanding, the Patentee will briefly discuss the primary cited references herein. During the discussion, it is important to keep in mind that statements from these sources regarding uniformity of content of components, especially actives, are not based on analytical chemical testing for the amount of active present in equally sized samples, but are assumptions.

The below discussion is supported by the Bogue Declaration and the Fuller Declaration.

VIII. The Claim Rejections.

The Examiner's rejection of the claims begins on page 7 of the Office Action.

A. Claims 1-299 were improperly rejected.

Claims 1-299 were rejected as allegedly anticipated under 35 U.S.C. §102(b), or, in the alternative under 35 U.S.C. § 103(a), as obvious over, each of the following references: Chen (WO 00/42992) ("Chen"), Staab (U.S. 5,393,528) ("Staab"), Le Person (*Chemical Engineering and Processing*, Vol. 37, pp. 257-263 (1998)) ("Le Person") and Horstmann (U.S. 5,629,003) ("Horstmann") or some combination thereof as set forth in the Office Action. These rejections relied on the Examiner's findings that material claim elements of the '080 Patent's only independent claims in reexamination, Claims 1, 82 and 161, were inherent in the cited references. Two limitations were of paramount importance, namely the limitations of "uniform distribution of components" and of "locking-in or substantially preventing migration of" active component.

Patentee maintains that the foregoing claim limitations are sufficent in themselves to establish patentability. Nevertheless, independent claims 1, 82 and 161, as amended, and all the new independent claims, claims 321-324, are not explictly, implicitly or inherently disclosed or suggested in the cited prior art. In particular, the prior art of recod does not disclose, forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a uniform distribution of said pharmaceutical active, casting said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps and conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 minutes to maintain said uniform distribution of said pharmaceutical active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less, forming the resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said uniform distribution of pharmaceutical active by said locking-in or substantially preventing migration of said pharmaceutical active is maintained, wherein said resulting film is suitable for commercialization and regulatory approval, sampling the resulting film at different locations of the resulting film, in order to perform the analytical chemical tests for content uniformity of said pharmaceutical active, and thus establish for commercialization and regulatory purposes the substantially uniform distribution of the pharmaceutical active throughout the film product, and/or where the required degree of uniformity is such that the amount of active does not vary by more than 10%.

The Examiner basically relies on the Declaration of Edward D. Cohen, Ph.D. under 37 C.F.R. § 1.132, dated September 6, 2012 ("Cohen Declaration) for his assumption that it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active. Office Action, pp. 14 and 43. However, Dr. Cohen's assumption is dead wrong on its face or does not apply to the '080 Patent. Importantly, Dr. Cohen does not discuss

the degree of uniformity of content. He refers generally to "substantial uniformity of content of active" and "uniform content of active" per unit dosage. Cohen Declaration, ¶¶ 8-10. Dr. Cohen's statement about uniform content of active, without providing the degree of uniformity of content cannot be applied to the '080 Patent's invention. Especially now that the '080 Patent expressly claims a degree of uniformity of content, namely, that uniformity of content of the resulting film varies no more than 10% with respect to the desired amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film.

Moreover, the Declaration of Dr. Fuller on the other hand provides, at paragraphs 6-10, a basis and opinion for a conclusion much different from that provided by Dr. Cohen.

> "6. It is my opinion that the film process as described by Chen at commercial scale would not inherently result in a film having a uniform distribution of active in the film. In particular, it is also my opinion that the film process of Chen would not inherently result in a film having a uniformity of content of active in substantially equal sized individual dosage units sampled from Chen's resultant film, where the active in the dosage units varies no more than 10%.
>
> "7. The process described by Chen does not describe how to dry in a manner that would avoid redistribution and inhomogeneity of a dissolved solute or suspended actives due to well-known thermodiffusive effects. The effects, also referred to as the Soret effect, can drive inhomogeneities during the drying of a previously homogeneous mixture. In other words, even if a solution containing a solute or suspended actives is spatially homogeneous in that constituent, the act of drying the solution to create a solid film can cause redistribution of the solute or suspended actives through the creation of temperature variations. This is the result of temperature gradients within the polymer film matrix causing the solute or suspended actives in the film to migrate and accumulate in different locations even if the solute or suspended actives were initially uniformly distributed. The Soret effect, which was described in 1800's, is a classical phenomenon, and is well-known to the chemical process industry. (see Appendix II)
>
> "8. Dr. Cohen's assumption that Chen's process will lead to films that are spatially homogeneous in composition is flawed because it does not recognize

that thermodiffusive effects can result in spatial redistribution of constituents even if they were initially homogeneous prior to the application of heating during the process of film formation. Because Chen does not describe the film drying process, it cannot be assumed that any resulting temperature gradients within the polymer film matrix during the drying process will not lead to thermodiffusion and spatial inhomogeneity.

"9. Chen does not discuss the development of viscoelasticity in the film during the drying process. Chen discloses the use of hydrocolloids and it is well-established that these materials can increase viscosity but will not necessarily enhance viscoelasticity. It is well known that viscosity is only one property within the general description of viscoelasticity. Even though these materials, such as Carbopol®, can lead to shear thinning materials, they are often inelastic and purely viscous. Chen does not recognize the mechanism of viscoelasticity of a film undergoing drying needs to be effectuated to retain the spatial uniformity of the constituents of that film. The development of viscoelasticity has the ability of arresting processes such as the Soret effect that can induce inhomogeneities. The Monosol process that creates a viscoelastic film within the first four (4) minutes of drying has the important benefit of locking in a spatially homogeneous distribution of components by inhibiting the effects of thermodiffusion to obtain active uniformity that does not vary more than 10% in the amount of active present in substantially equal sized individual dosage units.

"10. Dr. Cohen is incorrect in his assumption that simply increasing the viscosity of a hydrocolloid material through film drying will retain spatial uniformity of the constituents of a film. In the absence of conditions which rapidly build viscoelasticity, components can diffuse spatially in a viscous media in response to thermodiffusive effects. The development of a rapid viscoelastic network formation is able to spatially constrain the diffusion of components and inhibit thermodiffusivity and retain spatial uniformity to the desired degree."

Moreover, as set forth in the Bogue Declaration, ¶¶ 10-14, 730 samples of individual dosage units, ten each from 73 separate manufacturing lots of resulting films produced in accordance with Patentee's invention, were tested for active content. The results were that the active content of each individual dosage unit remained well within the control limits of 90% to 110%.

> "It can be seen from Appendix A that the active content of each individual dosage unit remains well within the control limits of 90% to 110%. The target or desired amount is 8.00 mg of active per individual dosage unit. The range of analytical chemical testing results among those 730 individual dosage units was 93.50% (7.48 mg) to 105.80% (8.47 mg) of the target or desired amount of active. This uniformity of content level is consistent with that described in the '337 Patent."
>
> Bogue Declaration, ¶ 12.

As noted, the FDA requires that the amount of active vary from dose to dose by no more than a prescribed percentage from the desired amount of active, essentially prescribing a degree of content uniformity of active which must be met. Dr. Cohen provides no support for any prescribed degree of uniformity, and certainly not for the prescribed degree of uniformity of content explicitly recited by Patentee's claims under examination to meet commercial and/or regulatory requirements, or the degree of uniformity present in resulting films manufactured in accordance with Patentee's invention, as clearly demonstrated by the Bogue Declaration.

As held by the Court of Appeals for the Federal Circuit ("Federal Circuit") inherency requires much more than probabilities, possibilities, or for that matter assumptions, such as, that by starting with so-called "uniform" mix of materials, stirring them, then casting and drying inherently results in the processes claimed in the '080 Patent. In *Crown Operations Intern., Ltd. V. Solutia Inc.*, 289 F.3d 1367 (Fed.Cir. 2002) ("*Crown*"), the patents at issue related to layered films used to create safety and solar control glass. The multi-layer film added properties to the glass assembly, such as impact resistance. An inner layer had solar control properties to reflect, absorb (and thus convert to heat), or transmit defined percentages of certain wavelengths of light. *Crown*, at 1370. The district court had held the only relevant independent claim of one of the patents, the '511 patent, not invalid on the grounds of anticipation and obviousness. It claimed a composite solar/safety film, comprised of a solar control film "wherein said solar control film contributes no more than about 2% visible reflectance". *Crown*, at 1372.

> "Crown [the declaratory judgment plaintiff] argued that U.S. Patent No. 4,017,661 to Gillery (the "Gillery patent") anticipates the '511 patent. The district court held otherwise, because, while the Gillery patent discloses the first three limitations of claim 1 of the '511 patent, it does not disclose the two percent visible reflectance limitation. The court found that neither the Gillery patent claims nor its description expressly disclose a two percent limit on reflectance contribution from the solar control film layer. Crown argued that the two percent limitation was inherently present in the Gillery patent's teachings because the Gillery patent disclosed an assembly with PVB layers, substrate layer, and substrate metal-coating ---- arguably of the same composition and thickness of the films disclosed by the '511 patent. Thus, Crown argued, because the structure, thickness and materials of the assembly were the same or within the same range(s), the Gillery patent must inherently disclose a two percent limitation. The district court rejected this argument because it found that none of the embodiments disclosed by the Gillery patent meet the two percent visible light reflectance limit."
>
> *Crown*, at 1372.

The Federal Circuit, in upholding the decision of the District Court as well as the validity of the '511 patent, discussed the application of inherency to validity that is most relevant here.

> "Regarding alleged anticipation by the Gillery patent, on its face the Gillery patent does not disclose or discuss a two percent limitation for the reflectance contribution of the solar control film. Crown maintains that the '511 patent merely claims a preexisting property inherent in the structure disclosed in the prior art. Crown urges us to accept the proposition that if a prior art reference discloses the same structure as claimed by a patent, the resulting property, in this case, two percent solar control film reflectance, should be assumed. We decline to adopt this approach because this proposition is not in accordance with our cases on inherency. If the two percent reflectance limitation is inherently disclosed by the Gillery patent, it must be necessarily present and a person of ordinary skill in the art would recognize its presence. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed.Cir.1999); *Continental Can*, 948 F.2d at 1268, 20 USPQ2d at 1749. **Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient**." *Id.* at 1269, 20 USPQ2d at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)) (emphasis supplied)."

The alleged inherency of the art cited by the Examiner and discussed below has not been established other than by statements of probabilities and/or possibilities and/or just statements that things are uniform without providing any degree of uniformity that must be present. Again, inherency requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. Importantly, the mere possibility that some of the films produced as disclosed by the art cited might result in some type of "uniform" film is not sufficent.

1. Chen's alleged inherency.

> "The claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" of the active in independent claims 1, 82 and 161, and the variation of active content of 10% or less in dependent claims 254-255,272-273 and 290-291, are inherent in Chen's exemplified films and process. Inherency is based on the following: As discussed above, Chen uses the same materials and method as here claimed. Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection."
>
> Office Action, p. 13.

The criteria used by Chen as cited by the Examiner for evaluation of "substantial uniform distribution" are physical observations. Such "observations" cannot be used, either inherently or otherwise, to establish the uniformity of content in the actual amount of active in equally sized samples in Chen's examples. Absent, statements or data based on analytical chemical testing, not weighing or visual inspection, for the amount of active present in the film, Chen does not and cannot inherently disclose Patentee's resulting film having uniformity of content, with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, which varies by no more than 10% from the desired amount of the active. Moreover, even if Chen disclosed, which it does not, the use of the same

materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra*, at 1378.

The Examiner states that the films made in accordance with the claims as issued are inherent in Chen. This conclusion is based on the belief that Chen uses the "same materials and method" as the Patentee. Patentee respectfully submits that this conclusion is incorrect, and particularly incorrect with the amended claims. The examiner erroneously states that Chen "uses the same criteria" as the '080 Patent that issued in evaluating substantial uniform distribution, i.e. weights of dosages and visual inspection." Although, a number of ways to test films in the patent are disclosed, in order to test content uniformity of an FDA regulated film product, it is necessary to assay using analytical chemical tests for drug or therapeutic active content of unit film doses. This is necessary to ensure the amount of active is within acceptable guidelines. Visual observation and physical measurements such as weight is insufficient to determine the active amount in equally sized dosage units. Almost all of Patentees' amended claims require analytical chemical testing and/or that the films have uniformity in the amount of active which varies by no more than 10% variance. The Examiner's assumption that visual inspection and weight measurements provide this information is therefore incorrect.

Fuller Declaration, especially at ¶¶ 6-14, provides further reasoning regarding this incorrect assumption and lack of inherency. According to Dr. Fuller, "the film process as described by Chen would not inherently result in a film having a uniform distribution of active in the film. . . [or] a uniformity of content of active in substantially equal sized individual dosage units sampled from Chen's resultant film, where the active in the dosage units varies no more than 10%." Fuller Declaration, ¶ 6. Moreover, Chen disclosure exhibits a lack of understanding and more importantly any teaching "to describe the drying operation that would cause it to avoid redistribution and inhomogeneity of a dissolved solute or suspended actives due to well-known thermodiffusive effects. The effects, also referred to as the Soret effect can drive inhomogeneities during the drying of a previously homogeneous mixture. In other words, even if

a solution containing an active ingredient is spatially homogeneous in that constituent, the act of drying the solution to create a solid film can cause redistribution of the solute through the creation of temperature variations." Fuller Declaration, ¶ 7.

"Chen does not recognize that the mechanism of viscoelasticity of a film undergoing drying to retain the spatial uniformity of the constituents of that film. The development of viscoelasticity has the ability of arresting processes such as the Soret effect that can induce inhomogeneities. The Monosol process that creates a viscoelastic film within the first four minutes of drying has the important benefit of locking in a spatially homogeneous distribution of components by inhibiting the effects of thermodiffusion." Fuller Declaration, ¶ 9.

Finally, Dr. Fuller's Declaration addresses the misplaced reliance on the physical terms "glossy" and "transparent" in the Office Action, which the Examiner use to establish the presence of "uniformity" in Chen's films. However, as Dr. Fuller declares, the "term 'glossy' is not interchangeable with nor equivalent to the uniformity of content of components of a film, nor the content uniformity of an active in the film. It is also not interchangeable with a specific variation of active content in unit dosage samples taken from a film. . . . The term 'transparent' . . is also a visual appearance characteristic that is neither indicative nor suggestive of the uniformity of content of the film. In particular, this term does not necessarily provide any indication or suggestion of a specific variance of active per unit dose of film sampled therefrom." Fuller Declaration, ¶¶ 12-13. As such the Chen's films can neither inherently anticipate nor make obvious the '337 Patent claims.

2. Staab's alleged inherency.

"Staab also discloses that "[t]he device of the invention thus is composed of a biologically-compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Accordingly, Staab's films inherently have the instantly claimed substantially uniform distribution of components and active.

> Also, in view of the fact that each film contains 19 mg of benzalkonium chloride and in view of said homogeneous blending, the variation of active in the dosage units is 0% (*sic* 10%), as per claims 254, 255, 272, 273, 290 and 291."
>
> Office Action, p. 29.
>
> "In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. Accordingly, Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, after drying for about 10 minutes, a viscoelastic film having less water that before drying is formed."
>
> Office Action, p. 30.
>
> "While Staab does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process."
>
> Office Action, p. 31.

Again, as with Chen, absent statements based on testing and/or a determination of the actual amount of active present in the film, Staab does not and cannot inherently disclose Patentee's resulting film having uniformity of content, with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, which varies no more than 10% from the desired amount of the active. Staab does not and cannot inherently form a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content within this recited 10% variance.

Moreover, even if Staab disclosed, which it does not, the use of the same materials and methods as the '337 Patent, the mere fact that a certain thing may result from a given set of

circumstances is not sufficient to support inherency. *Crown, supra*, at 1378. Moreover, Staab just states that there is 19 mg of benzalkonium chloride present in each sample weighing 190 mg, however Staab does not disclose testing to determine the amount of benzalkonium chloride present in the final film product. Staab, col. 11, l. 35 through col. 12, l. 3. Staab's resulting structure is a foam rather than a substantially solid visco-elastic structure formed within 4 minutes and Staab also would not inherently have the recited degree of uniformity of amount of active in substantially equal sized dosage units. Moreover, Staab starts with a composition having 10% by weight of benzalkonium chloride (50% aqueous). Yet allegedly obtains a resulting film with 19 mg benzalkonium chloride in a 190 mg film, to once again obtain a 10% benzalkonium chloride resulting composition.

3. Le Person's alleged inherency.

> "Le Person discloses that after 5 min of the drying, 'the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates.' (See p. 262, col. 2, third full paragraph.) Le Person also teaches that '[b]etween the 5th and 10th min of drying the heavy solvent migrates... active substance, slowed down in its migration, stays in the bottom of the layer.' (See the last four lines at page 262, col. 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that, inherently, a substantial uniform distribution of the active is locked-in and migration is substantially prevented within the film, as here claimed. The active material homogenizes and a quasi-equilibrium is obtained for the components of the Page 38 active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13), and thus, there is a variation of active content of less than 10%, as per claims 272, 273, 290 and 291.
>
> Office Action, pp. 37-38.
>
> "While Le Person does not discuss viscoelasticity or that the films in its process have a 'substantially uniform distribution of components' or disclose 'locking-in or substantially preventing migration' of the active, Le Person, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 82, 89-91,161,171-173, 272-274 and 290-292, if not anticipated under 35 USC

102(b), would be obvious under 35 USC 103(a)."

Office Action, p. 38.

Le Person is entirely devoid of any details with respect to its process and materials. For example, nowhere does Le Person discuss what type of acrylic polymer he uses, nor the molecular weight of the polymer. Thus, Le Person allows for materials which may have such a low molecular weight that forming a visco-elastic film may not be possible. Moreover, Le Person lacks sufficient enabling disclosure to be an effective reference as applied in view of the amended claims. Such deficiencies cannot be used in support of an inherency argument.

Again, absent statements and data based on testing for the amount of active present in the film with results establishing a substantial uniformity of content, which active varies by no more than 10%, Le Person does not and cannot inherently disclose Patentee's resulting film, having uniformity of content, with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, varying by no more than 10% from the desired amount of the active. Le Person does not and cannot inherently form a viscoelastic film in about 4 minutes which locks-in the uniformity of content within this recited 10% variance.

Moreover, Le Person discloses very little about the acrylic polymer, such as the molecular weight. If the molecular weight was low enough it may not become a viscoelastic material. Patentee asks, how could Le Person anticipate and/or make obvious the '080 Patent which is directed to the commercial manufacture of a resulting film with a specified content uniformity of active, where Le Person's goal, as noted in its abstract was devoted determining "cases of maldistribution of the active substance," in connection with different drying methods, and not to providing a process for manufacturing films with active uniformity of the desired amount. Importantly, Patentee has added several additional process steps not in the prior art. These new process steps present in the amended independent claim, as well as the new

independent claims, further distance Patentee's patent from the prior art, by negating any anticipation and obviousness assertions.

4. Horstmann's alleged inherency.

> "The claimed substantially uniform distribution of components and active, and locking-in or substantially preventing migration of active, and the variance of active content of 10% or less in dependent claims 254, 272 and 290 are also inherent in Horstmann's Examples 1, 3 and 4. In particular, Horstmann's films before drying are described as being uniform and homogeneous (see col. .3, line 11-19, 29-34 and 37-41; col. 5, lines 1 and 50), and as noted above, Horstmann uses the same components and process steps as here claimed. The '080 patent notes that Horstmann addressed the problem of self-aggregation and nonuniformity by increasing the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film (see col. 2, line 60 through col. 3, line 1).
>
> Office Acton, p. 43.
>
> "While Horstmann does not discuss viscoelasticity, water content of its dried films or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the, active, Horstmann, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1, 5,7-10,12-1423,63,64,82,84,86-89,91-93,102,142,143,161, 166, 168-171, 173-175, 184,224,225,249,254,267,272,285 and 290, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, pp. 43-44.

Horstmann forms a gel, rather than a solid film as in the present invention. Thus the gel rheological properties of Horstmann are very different than a solid visco-elastic film having a water content of 10% or less. Moreover, Horstmann specifically teaches protecting the gels from drying up by placing the cut out gel shapes in a water vapor impermeable sealing material. See Horstmann, col. 5, ll. 11-13. This is a direct teaching away from drying to a water content of 10% or less. Moreover, Horstmann at col. 2, ll. 25-29, suggests drying may not be necessary.

Again, absent statements based on testing for the amount of active present in the film with results establishing a substantial uniformity of content, with no more than 10% variation from a desired amount of the active, Horstmann does not and cannot inherently disclose Patentee's resulting film having said uniformity of content which varies no more than 10% with respect to the desired amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film.

Additionally, as the Examiner admits, Horstmann discloses only that its film is alleged to be uniform at a point prior to drying. Horstmann, col. 3, ll. 37-41. Horstmann says nothing about the uniformity of the product during or after drying. Again, *Crown* holds that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* A disclosure of some unspecified degree of uniformity of a film prior to drying in Horstmann does not establish that the product after drying is uniform, let alone the degree of uniformity as claimed by the '080 Patent. As noted throughout the '080 Patent, controlled drying is required for ensuring, among other things, [that uniformity of content of the resulting film varies no more than 10% with respect to the desired amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film].

Importantly, Patentee has added several addition process steps not in the prior art. These new process steps present in the amended independent claims, as well as the new independent claims, further distance Patentee's patent from the prior art, by negating any anticipation and obviousness assertions. Even without the process steps, even if it were possible that a resulting film with the proper uniformity of content might possibly result from some manipulations of the disclosures given in any of Chen, Staab, Le Person and/or Horstmann, it is incorrect to rely on these references in an attempt to show they inherently disclosed Patentee's resulting film. See *Crown*, at 1377-1378, *supra*.

As the absence of inherency in and of itself removes Chen, Staab, Le Person and Horstmann as viable prior art for rejecting Patentee's claims under either 35 U.S.C. § 102, the Examiner should withdraw his rejections of Patentee's claims claims 1, 82 and 161 based on same. For the same reasons new independent claims 321-324 are allowable. Moreover, these references for the same reasons discussed above, as well as the reason discussed below, do not support any finding of obviousness, and thus the claims 1, 82 and 161 rejections based on 35 U.S.C. § 103 should be withdrawn as well. For the same reasons new independent claims 321-324 are not obvious in light of the prior art. Finally, Patentee's claims 2 through 81, 83 through 160, 163 through 299 and 300 through 320 and 325 through 628 as they depend from independent claims 1, 82, 161, and 321-324 should all be allowed as well, with any rejections withdrawn.

B. Third Part Requester's Wherein Argument is Wrong

Patentee finds it necessary to address Third Party Requester's attempt to vitiate the '080 Patent's claim language beginning with "wherein". Third Party Requester cites to the Federal Circuit for the premise that "a whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed.Cir.2003). Third Party Requester's Request for Inter Partes Reexamination ("The Request"), p. 16.

However, the Federal Circuit has also strongly held that "when the 'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F. 3d 1326, 1329 (Fed. Cir. 2005). Essentially, Requester proposes that with elimination of the "whereby" clauses, the claims 1, 82 and 161 (before the amendments herein) would not require "wherein said resulting film has a water

content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained." The Request, p. 20.

Patentee's fundamental invention concerns among other things making a film having a substantially uniform distribution of components or, as now claimed a uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film is such that uniformity of content of the resulting film varies no more than 10% with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film.

As noted above, "when the whereby clause states a condition that is material to patentability, it cannot be ignored to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326 (Fed. Cir. 2005); *see also Fantasy Sports Properties, Inc. v. Sportsline.com, Inc.*, 287 F.3d 1108, 1111-16 (Fed. Cir. 2002); *Griffin v. Bertina*, 285 F.3d 1029, 1034 (Fed. Cir. 2002). In *Griffin*, for example, the court found that "wherein" clauses were claim limitations "because they relate back to and clarify what is required by the count. Each 'wherein' clause ... expresses the inventive discovery [and] ... elaborates the meaning of the preamble." *Griffin*, 285 F. 3d at 1033-34. Further, "the allegedly inherent properties of the 'wherein clauses' provide the necessary purpose to the steps." *Id.* See also, MPEP, § 2111.04.

The original '080 Patent independent claims' wherein clause limitations cannot be disregarded. The '080 Patent claims processes for manufacturing pharmaceutical films with a substantial uniform distribution of components suitable for commercialization and regulatory approval. The ability to make such films with the required amount of uniformity in distribution of active is the essence of Patentee's invention. Thus any wherein clause which expresses the inventive discovery and elaborates the meaning of the preamble, for example, that the uniformity of content of the resulting film varies by no more than 10% with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different

locations of the resulting film, or that such uniformity must be determined by analytical chemical testing in compliance with regulations, cannot be ignored for purposes of patentability.

Finally, Third Party Requester has made many allegations about the '080 Patent and its specifications and claims, and the prior art in The Request. Patent owner believes the amendment to claim 25 herein clarifying the scope of same, obviates the need to address Third Party Requester's allegations or the Examiner's statements made without the benefit of the amendments, nevertheless, to the extent that any are not explicitly addressed herein, Patentee hereby asserts they are wrong and unsupported in either fact or law.

C. **Claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84,87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen.**
Claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Chen, WO 00/42992 ("Chen") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Chen. Patentee incorporates its previous discussions in sections A. and B. above. Chen is a primary reference relied upon by the Examiner in the Office Action.

Patentee respectfully traverses the rejection on the basis, among others, that Chen does not disclose the claimed: particular drying methods; resulting visco-elastic product; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing

the viscosity of the polymer matrix upon initiation of drying within about 4 minutes to maintain said uniform distribution of pharmaceutical active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film and is in compliance with regulations governing same.

Chen discloses two methods of forming a film product, a solvent casting method and an extrusion method. The extrusion method does not rely upon putting a hydrocolloid in a solvent, nor does the extrusion method use a drying oven and is apparently preferred by Chen over the solvent method. Chen, page 15, lines 9-21. In the solvent casting method, Chen states that a hydrocolloid is dissolved or dispersed in water, and mixed to form a homogeneous solution. The active agent and other ingredients may be added and dispersed or dissolved uniformly in the hydrocolloid solution. The coating solution with a solid content of 5-50% and a viscosity of 500-15000cps is degassed and coated onto a polyester film and "dried under aeration" at a temperature between 40-100°C to avoid destabilizing the agents. Chen, p. 15, ll. 19- 29. The dry film formed by this process is described to be a "glossy, stand alone, self supporting, non-tacky and flexible film". Chen, p. 15, ll. 30-31. These very general statements are all that are given by Chen as to the formation and drying of Chen's film product. These statements cannot support either anticipation nor obviousness rejections. See, e.g., Fuller Declaration, ¶¶ 6-13.

Chen's drying process is so general and devoid of detail so as to provide no guidance other than that to dry, one places a film in a conventional hot air circulating oven at temperatures of from 40-100°C and leaves it for a period of time. As shown in Patentee's photographs (Figures 9-16), drying in a hot air oven does not produce uniform films through the locking in of the active in a substantially uniform distribution throughout the visco-elastic film.

Again, it is important to note that while physical testing and observations such as Patentee's photographs (Figures 9-16) may be generally relied on to show non-uniformity, direct

establishment of the uniformity of content for the amount of active is by testing for the active needed to demonstrate that the amount of active is substantially uniform throughout the film. Importantly, Chen's "tests" for uniformity, except perhaps for water content, are for physical uniformity, that is, appearance (glossy, transparent), weight, density, thickness and not the relevant testing of the active itself to demonstrate the desired uniformity of content of the desired amount of active per unit dosage as required by the claims in reexamination. Fuller Declaration, ¶ 11-13.

Chen does not disclose any other drying methods beyond drying "under aeration", nor does Chen disclose any controlled drying processes whatsoever. Chen showed no recognition of the complexities involved in the commercial manufacturing of films, as Chen's focus relates solely to the ingredients, not the process. Without any recognition of the problems, and without any appreciation of the difficulties in preventing the settling, migration and/or aggregation or agglomeration of active(s) in the cast flowable mass, Chen neither sought nor found the solution to creating commercial scale films having substantial uniformity of active(s) per unit dose or per unit of film. Chen lacks substantial disclosure in view of the '337 Patent. Among its deficiencies, Chen lacks any disclosure as to specific processing means (beyond generally drying in a generic oven) or the formation of a visco-elastic film state. Chen only discloses the apparent homogeneity of a blended matrix, and this is prior to the addition of actives. There is no disclosure or suggestion as to how to create a uniform distribution of the pharmaceutical or biological active active in the blended matrix and then cast that matrix to maintain uniformity, and then convey said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 to maintain said uniform distribution of said pharmaceutical or biological active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film and then test it to establish the substantially uniform distribution of pharmaceutical or biological active content.

Thus, among other things, the '337 Patent claims are directed to locking-in the pharmaceutical or biological active within the first 4 minutes. The Examiner has stated in the Reexamination, Reasons for Patentability/ Confirmation ("RFP/C"), in connection with both the '292 Patent and the '891 Patent reexaminations that "Chen does not discuss what happens within the first 4 minutes of drying." Moreover, in the '891 Patent RFP/C the Examiner goes on to state that: "Chen does not discuss uniformity of pharmaceutical or biological active components in its doses. Table 4 of Chen gives the grams per unit dosage film and density for Example 1 with standard deviation based on three or four measurements, but does not give compositional uniformity." Additionally, Chen's Example 1 contains only food flavorings and a sweetener.

Chen does not disclose that the resulting products are compositionally uniform, but only that they are "glossy". Glossy does not imply or establish compositionally uniform. Fuller Declaration, ¶¶ 11-13. In fact, Chen's Figure 5 (Examples 5-8) clearly shows a lack of compositional uniformity of active. While statistics are not defined in the text, the error bars represent either high or low values, standard deviation or some measure of variation. Given that the compositions of Examples 5-8 are the same, except for the amount of active, it is reasonable to assume that the active is not uniformly present in the individual films due to the wide variation of release of active from the same film compositions. For example, with regard to the release of nicotine in the same film compositions, release reaches in excess of 100%. It is reasonable to conclude that a major reason for these release differences is that the amount of active in each film tested varies by more than the claimed 10%, despite the identical film-forming compositions.

Patentee's claims are directed to the formation of a suitable visco-elastic product, prepared through the methods of the invention. As used throughout the application, the formation of a suitable commercial and regulatory compliant product is the desired goal, and a suitable product is one that is substantially uniform in active content to the extent required by

said commercial and regulatory concerns. For example, those regulations and directions provided by the FDA for pharmaceuticals and biologic actives.

As used throughout the application, the resulting visco-elastic product is defined as a product that has maintained the desired compositional uniformity after being subjected to a coating/deposition step and drying. For example, the '080 Patent at col. 8, ll. 64-66 states that the stability is important "in the wet film stage until sufficient drying has occurred to lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained." The '080 Patent at col. 13, ll. 53-59 even more clearly states that: "The resulting dried film 1 is a visco-elastic solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film."

Thus, as defined in the specification for the '337 Patent as filed, a visco-elastic solid is one that has been sufficiently dried to lock its active components into a substantially uniform distribution throughout the film. The '337 Patent claims require that this be done within the first 4 minutes or less. The Examiner has previously stated that Chen does not disclose that the resulting film product has any compositional uniformity of pharmaceutical or biological active at that point in time. See '891 Patent RFP/C. The Examiner cannot point to any portion of Chen, or the other references, that teaches this step.

As explained throughout the '080 Patent and as summarized above, the present invention is based upon the discovery that certain process parameters, such as, viscosity and controlled drying methods must be employed to provide a commercially viable film product. Chen does not disclose such a resulting product. Chen discloses that various components (absent the active) are combined and that the mixture is blended to form a "uniform" solution. (Chen, p. 20, ll. 19-20). While even the formation of a uniform solution in a blender is beneficial, it is not the end of the process by any means. Chen's initial blend (without the active) may be mixed to be homogeneous, but there is absolutely no disclosure whatsoever of forming a homogeneous

mixture containing an active and casting and drying to maintain such uniformity in the resulting film. Further, as explained above, conventional drying methods do not inherently provide uniform films and, in fact, would not be expected to provide resultant films having compositional uniformity or uniformity of content of active. See Fuller Declaration, ¶¶ 6-10.

In addition, use of non-controlled drying methods such as described in the '080 Patent specification can lead to compositional non-uniformity, as explained above, due to the number of problems associated with conventional drying, see col. 3, ll. 13-57 of the '080 Patent. In fact, as explained in the '080 Patent, depending upon the drying methods used, various "hot spots" can form due to uneven air flow and temperatures, which destroy the compositional uniformity of the resulting product. See the '080 Patent, col. 13, ll. 6-16, as well as, Figs. 9-16. Chen's drying methods, such as the use of uncontrolled hot air circulating ovens, do not inherently provide compositionally uniform films. In fact, the Patentee has demonstrated quite the contrary occurs. See also, Fuller Declaration, ¶¶ 6-10.

Patentee's claimed process is not present in Chen, either literally or inherently, and it cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Chen does not render obvious the pending claims of this rejection.

D. Claims 2, 3, 16, 32, 55, 72-81, 95, 111, 134, 151-160, 177, 193, 216 and 233-242 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

The Office Action rejected the above claims under 35 U.S.C. § 103(a), as being unpatentable over the combined teaching of Chen and Staab, U.S. 5,393,528 ("Staab").

Patentee incorporates its previous discussions in sections A., B. and C., above, and D., below. As all the above claims depend from one of the independent claims, claims 1, 82 and 161, they are allowable for all the reasons provided in the sections dealing with Chen, above, and Staab, below.

E. Claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78- 84, 89, 91-95, 100, 103, 104,111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171,173-177,182,185,186,193,205-207,215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Staab.
Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 were rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Staab, or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Staab. Patentee incorporates its previous discussions in sections A., B., C. and D., above,

Patentee respectfully traverses the rejection on the basis, among others, that Staab does not disclose the claimed: particular drying methods; resulting visco-elastic product; substantially uniform distribution of components; casting a flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; or locking-in or substantially preventing migration of the active; or said uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the polymer matrix upon initiation of drying within about 4 minutes to maintain said uniform distribution of pharmaceutical active, such that uniformity of content of the resulting film vary by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film is in compliance with regulations governing same.

Staab teaches the benefits of using a "gas foamed film" or films. Staab, col. 5, ll.33-35; col. 8, ll. 33. Staab also teaches away from the '337 Patent by teaching that air bubbles are necessary, which are contraindicated in Patentee's invention requiring the uniform distribution of active. Staab instead teaches that gas bubbles must be added to the polymer/drug mixture prior to casting. .

> "It should be noted that heretofore, the significance of the addition of gases in the formation of the film to alter the texture and solubility of the film has not been recognized."
>
> Staab, col. 3, ll. 15-20.
>
> "The fine tuning of dissolution rates and delivery of agent material, by the addition of gases and by altering the grades or mixtures of polymer materials or layers, is an important aspect of the present invention.
>
> "On addition of the gas, preferably nitrogen, a web is formed of the final formulation and the gas. The resultant structure can be described as a foam with various sized air bubbles trapped in the matrix. There is a dual benefit that has been surprisingly observed in this connection, namely that not only can the size of the bubbles in the foam alter the dissolution rates and correct what is a serious flaw in standard polymer films, it also offers to the user a perceptible softness to the film which enables the delivery of many types of drugs to tender mucosal tissues. It has been observed that the formation of this web of the polymer/drug formulation and the gas must be made just prior to casting on the glass or steel plates. This offers precise control over the microbubbles and resultant control over the dissolution,
>
> "Without this web formation, the quick release of drug was heretofore not possible. This frothy foam mixture or web can also be added to a mold to provide a formed device such as a barrier delivery system which completely dissolves upon use in a body cavity, e.g. the vagina.
>
> "The gases, for example, air or nitrogen are introduced near the point of application of the liquid polymer material to the stainless steel casting sheet. The gases are added in a closed system by mixing with whipping blades or a motor driven homogenizer to homogenize the mixture of polymer, active material and gas to form a frothy foam. The final mixture then sets up or gels

> as a foam. It is also possible to pour the frothy foam mixture into a mold. The mold is then deformed and the formed device such as a diaphragm, is removed."
>
> Staab, col. 8, ll. 29-64 (emphasis supplied).

In direct conflict with Staab's teaching, the '080 Patent teaches the use of anti-foaming agents to **prevent** gas bubble formation.

> "Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films. . . . **Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product."**
>
> '080 Patent, col. 4, ll. 5-21 (emphasis supplied).

> "A number of techniques may be employed in the mixing stage to **prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed.** Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film."
>
> '080 Patent, col. 9, ll. 56-65 (emphasis supplied).

See also section of '080 Patent entitled "Anti-foaming and De-foaming Compositions" ('080 Patent, col. 22, l. 47 through col. 23, l. 53).

Staab addresses the fine tuning of dissolution rates and delivery of active agent, by teaching the addition of gases as an important aspect of his invention (Staab, col. 8, ll. 30-34). Staab is silent with respect to the claimed uniformity of content, the essence of the '080 Patent.

The '080 Patent in connection with achieving said uniformity of content teaches the removal of such gases and bubbles ('080 Patent, col. 9, ll. 56-65). Moreover, Staab uses conventional drying (Staab, col. 11, ll. 64-65) rather than the particular drying methods used to ensure the uniformity of content claimed by the '080 Patent.

Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that contains the recited level of active uniformity. Similar to the discussion of Chen above, Staab teaches general drying methods that would be expected to subject the material to similar air forces as in Chen's air drying oven, but does not teach the formation of and maintenance of a film having a substantially uniform active content. Again, as explained above, Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that includes the claimed content uniformity. Similar to the discussion of Chen above, Staab teaches general drying methods that are likely to subject the material to similar air forces as in a conventional air drying oven, but does not teach the formation of and maintenance of a film having a substantially uniform active content.

The presently claimed process is not present in Staab, either literally or inherently, and it cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Staab does not render obvious the pending claims of this rejection. Patentee respectfully traverses the rejection on the basis, among others, that Staab does not disclose the claimed: particular drying methods; resulting visco-elastic product; substantially uniform distribution of components; casting a flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; or locking-in or substantially preventing migration of the active; or said uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidily increasing the viscosity of the polymer matrix upon initiation of drying within about 4 minutes to maintain said uniform distribution of pharmaceutical active, such that uniformity of

content of the resulting film's variation in amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film is in compliance with regulations governing same.

Staab teaches the benefits of using a "gas foamed film" or films. Staab, col. 5, ll.33-35; col. 8, ll. 33. Staab also teaches away from the '337 Patent teaching that air bubbles are contraindicated for the patented uniform compositional distribution. Staab instead teaches that gas bubbles must be added to the polymer/drug mixture prior to casting. .

> "It should be noted that heretofore, the significance of the addition of gases in the formation of the mm to alter the texture and solubility of the film has not been recognized."
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> Staab, col. 3, ll. 15-20.
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> "**The fine tuning of dissolution rates and delivery of agent material, by the addition of gases and by altering the grades or mixtures of polymer materials or layers, is an important aspect of the present invention.**
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> "On addition of the gas, preferably nitrogen, a web is formed of the final formulation and the gas. The resultant structure can be described as a foam with various sized air bubbles trapped in the matrix. There is a dual benefit that has been surprisingly observed in this connection, namely that not only can the size of the bubbles in the foam alter the dissolution rates and correct what is a serious flaw in standard polymer films, it also offers to the user a perceptible softness to the film which enables the delivery of many types of drugs to tender mucosal tissues. It has been observed that the formation of this web of the polymer/drug formulation and the gas must be made just prior to casting on the glass or steel plates. This offers precise control over the microbubbles and resultant control over the dissolution,
>
> "Without this web formation, the quick release of drug was heretofore not possible. This frothy foam mixture or web can also be added to a mold to provide a formed device such as a barrier delivery system which completely dissolves upon use in a body cavity, e.g. the vagina.

> "The gases, for example, air or nitrogen are introduced near the point of application of the liquid polymer material to the stainless steel casting sheet. The gases are added in a closed system by mixing with whipping blades or a motor driven homogenizer to homogenize the mixture of polymer, active material and gas to form a frothy foam. The final mixture then sets up or gels as a foam. It is also possible to pour the frothy foam mixture into a mold. The mold is then deformed and the formed device such as a diaphragm, is removed."
>
> Staab, col. 8, ll. 29-64 (emphasis supplied).

In direct conflict with Staab's teaching, the '337 Patent teaches the use of anti-foaming agents to **prevent** gas bubble formation.

> "Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films. . . . **Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product."**
>
> '337 Patent, col. 4, ll. 5-21 (emphasis supplied).

> "A number of techniques may be employed in the mixing stage to **prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed.** Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film."
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> '337 Patent, col. 9, ll. 56-65 (emphasis supplied).

See also section of '337 Patent entitled "Anti-foaming and De-foaming Compositions" ('337 Patent, col. 22, l. 47 through col. 23, l. 53).

Staab addresses the fine tuning of dissolution rates and delivery of agent material, by teaching the addition of gases as an important aspect of his invention (Staab, col. 8, ll. 30-34). Staab is silent with respect to the claimed uniformity of content, the essence of the '337 Patent. The '337 Patent in connection with achieving said uniformity of content teaches the removal of such gases and bubbles ('337 Patent, col. 9, ll. 56-65). Moreover, Staab uses conventional drying (Staab, col. 11, ll. 64-65) rather than the particular drying methods used to ensure the uniformity of content claimed by the '337 Patent.

Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that contains the recited level of active uniformity. Similar to the discussion of Chen above, Staab teaches general drying methods that would be expected to subject the material to similar air forces as in Chen's air drying oven, but does not teach the formation of and maintenance of a film having a substantially uniform active content. Again, as explained above, Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that includes the claimed content uniformity. Similar to the discussion of Chen above, Staab teaches general drying methods that are likely to subject the material to similar air forces as in a conventional air drying oven, but does not teach the formation of and maintenance of a film having a substantially uniform active content.

The presently claimed process is not present in Staab, either literally or inherently, and it cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Staab does not render obvious the pending claims of this rejection.

F. Claims 82, 89-91, 161, 171-173, 272-274 and 290-292 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Le Person.

Claims 92 and 174 were rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Le Person, Chemical Engineering and Processing, Vol. 37, pp. 257-263 (1998) ("Le Person") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Le Person. Patentee incorporates its previous discussions in sections A., B., C., D. and E., above,

Patentee respectfully traverses the rejection on the basis, among others, that Le Person does not disclose the claimed: particular drying methods to provide a substantially uniform distribution of components; resulting visco-elastic product; substantially uniform distribution of components; casting a flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; or locking-in or substantially preventing migration of the active; or said uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the polymer matrix upon initiation of drying within about 4 minutes to maintain said uniform distribution of pharmaceutical active, such that uniformity of content of the resulting films vary by no more than 10% in the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film is in compliance with regulations governing same. Le Person discloses that the drying step used plays a role in the final product, but fails to disclose or suggest how to achieve a uniform final product. In fact, Le Person discloses methods that result in a non-uniform product prior to and at 10 minutes. According to Le Person, the resulting product dried in 9 minutes would not have claimed uniformity of content of active.

Le Person's goal was to determine "cases of maldistribution of the actives substance," in connection with different drying methods, said maldistribution having consequences on storage and delivery of a drug and proposes the use of Laser Scanning Confocal Microscopy on the

active substance and the heavy solvent to determine same. (Le Person, Abstract). Le Person acknowledges that in the formation of a film product, "drying is the essential unit operation necessary to form the final product." (Le Person, p. 257). In Le Person's experiment, a coating mixture includes a polymer, three light solvents, a heavy solvent, and a pharmaceutical active substance. Le Person stated that the drying process used must evacuate the light solvent and preserve the heavy solvent. Le Person's experimental set-up was composed of two parts, "the drying cell and the wind tunnel. . . . [wherein] the wind tunnel is a conventional drying rig. . . ." Le Person, p. 258, col. 2 & Fig. 1. Le Person's disclosure of the use of a wind tunnel further negates any argument that Le Place inherently anticipates or makes obvious Patentee's invention.

Le Person conducted experiments on drying conditions. At the 5 minute mark, Le Person noted that intense moisture removal through the exposed surface of the layer to radiation during the first three minutes of drying produced a stress on the polymer and caused "displacement of the active phase towards the bottom of the layer." (Le Person, p. 261). Le Person noted that, initially, the constituents of the active phase are apparantly homogeneously distributed, but during a drying process, the active substance separated and sunk to the bottom. (Le Person, p. 262). Le Person noted that, between 5 and 10 minutes of drying, the heavy solvent migrates towards the top surface and the active substance stays in the bottom layer. (Le Person, p. 262). After 15 minutes, Le Person notes that the active substance crystallizes, due to the lack of solvent contained therein. (Le Person, p. 263). Eventually, the active substance homogenizes, and only after 15 minutes a quasi equilibrium is obtained for the active phase, taking into account the evaporation of heavy solvent. (Le Person, p. 263). Thus, Le Person acknowledged that the drying step of a film formation is critical, and noted the non-homogeneity of the film product it produced during drying.

It is important to note that Le Person simply recognized the overall, general difficulty in obtaining films with a substantially uniform distribution of active. However, Le Person did not recognize the specific reasons therefor, nor did Le Person recognize the solutions needed to

overcome this difficulty. Le Person's goal was to find ways to best determine whether or not there was homogeneity of film product. Le Person uses water with a heavy solvent (see abstract and Table 1), and does not complete its drying, and in particular removal of the heavy solvent, until after 15 minutes (see Le Person, pp. 261-263). After 10 minutes, Le Person's heavy solvent has migrated to the exposed surface; and after 15 minutes, a quasi-equilibrium is obtained for the components of the active phase, taking into account the evaporation of the heavy solvent (see Le Person, p. 263).

However, the point of Le Person is that, in the time period (i.e., less than 10 minutes), there is non-uniformity of the product. Le Person even states that "intense moisture removal through the exposed surface of the layer to the radiation, during the first 3 min of drying (Le Person, Fig. 7) produces a stress on the polymer skeleton … and as a result the acrylic polymer becomes more and more dense in the upper part of the layer (exposed surface)." (Le Person, p. 261). As a result, this "intense" shrinkage results in displacement of the active phase. As such, Le Person's disclosure is not directed towards achievement of a substantially uniform film through drying, and in fact, if anything, teaches away from achieving such content uniformity. The presently claimed process is not present in Le Person, either literally or inherently, and it cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Le Person does not render obvious the pending claims of this rejection.

G. Claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hortsmann.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Horstman, et al. U.S. 5,629,003 ("Horstmann") or, in the alternative under 35 U.S.C.

§ 103(a), as obvious over Horstmann. Patentee incorporates its previous discussions in sections A., B., C., D., E. and F., above,

Patentee respectfully traverses the rejection on the basis, among others, that Horstmann does not disclose the claimed: particular drying methods to provide a substantially uniform distribution of components; resulting visco-elastic product; substantially uniform distribution of components; casting a flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; or locking-in or substantially preventing migration of the active; or said uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the polymer matrix upon initiation of drying within about 4 minutes to maintain said uniform distribution of pharmaceutical active, such that uniformity of content of the resulting films vary by no more than 10% in the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film is in compliance with regulations governing same.

Moreover, the '080 Patent's description of the differences between Horstmann and Patentee's invention claimed in the '080 Patent is relevant to the Examiner's current rejections as well. For example:

> "In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann . . . incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. "
>
> '080 Patent, col. 2, l. 63 to col. 3, l. 9.

Horstmann's use of conventional drying methods and need for gel formers teaches away from obtaining a resulting film with the desired uniformity of content of active of no more than 10% variation. Horstmann does not disclose the degree of uniformity of content, merely, for example, in Example 2, referring to film sections containing "approximately" 3 mg of active and a weight of "approximately" 80 mg. Horstmann, col. 5, ll. 15-36. Horstmann does not disclose that these amounts are based on any testing, or for that matter what they are based upon. The presently claimed process is not present in Horstmann, either literally or inherently, and it cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Horstmann does not render obvious the pending claims of this rejection.

IX. Conclusion

No reference, either alone or in combination with other references, teaches the processes claimed by the '080 Patent. Entry of the amendments herein is respectfully requested. For at least the reasons set forth above, independent claims 1, 82, 161, and 321-324 are allowable. Claims 2 - 81, 83 - 160, 162 - 320, and 325-628 are allowable at least based on their dependencies, whether direct or indirect, from independent Claims 1, 82, 161, 321 and 322. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections to same. Fees for addition of 4 new independent claims and 324 new dependent claims are due with this submission, and the Commissioner is authorized to charge this fee to Deposit Account No. 08-2461. Should any additional fees be due, the Commissioner is authorized to charge any additional fees, such as fees for extensions of time or additional claims, to Deposit Account No. 08-2461. Should the Examiner have any questions regarding this response, the undersigned would be pleased to address them.

Respectfully submitted,

/Daniel A. Scola, Jr./
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CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111** has been served, by first class mail, on January 29, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

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/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
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Attorney for the Patentee

EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	January 29, 2013	M&E Docket:	117744-00023

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U.S. Patent and Trademark Office
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Alexandria, VA 22313-1450

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I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on January 29, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D.
UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University. A Ph.D. in Chemical and Bio Engineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia.

3. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation, processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the content uniformity of active and methods for testing same.

4. I have read the '080 Patent and the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Office Action") and the references cited therein.

II. Producing resulting films in accordance with the '080 Patent

5. The resulting films discussed herein were manufactured for commercial use and regulatory approval in accordance with the invention disclosed in the '080 Patent by:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and an active, said matrix having a uniform distribution of said active by mixing the components in a high shear mixer;

(b) casting said flowable polymer matrix having a viscosity within the range from about 400 to about 100,000 cps onto a substrate on a commercial coating line;

(c) conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix in a custom drying oven for a commercial coating line, thereby rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 minutes to maintain said uniform distribution of said pharmaceutical active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming a resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and the resulting film as tested by analytical chemical means, see below, varies by no more than 10% with respect to the desired amount of the active present in substantially equally sized individual dosage units sampled from different location of the resulting film, by said locking-in or substantially preventing migration of said pharmaceutical active is maintained, wherein said resulting film is suitable for commercialization and regulatory approval.

III. Analytical Chemical Testing for Content Uniformity of Patentee's Resulting Films

6. Individual dosage unit film samples all having the same dimensions were cut out from the resulting films using a commercial packaging machine. The samples were analyzed by a validated method, in compliance with Food and Drug Administration ("FDA") standards and regulations regarding same, in which the individual dosage units were at least partially dissolved, the active was entirely extracted from the film, and the extract was analyzed by High Performance Liquid Chromatography (HPLC) against an external standard to quantify the amount of active present in each individual dosage unit.

7. According to the inventive process set forth and claimed in the '080 Patent, each individual dosage unit film has a "target" or "desired" amount of active contained therein. The target amount of active, when it is a pharmaceutical, is referred to as the "Label Claim", thus identifying the amount of pharmaceutical active in the film to a user. Each unit dose film cut from the same batch of bulk film must have the desired content of pharmaceutical active, varying no more that 10% from the target or desired amount. That is, for each unit dose, the amount of active should be between 90% and 110% of the target or desired amount.

8. Patentee manufactures batches of film containing actives. Each batch is a separate manufacturing lot, ranging from 500,000 to 2,000,000 films per lot.

9. To demonstrate the uniformity of individual dosage unit films, I compiled Individual Film Dosage Unit Assay Data from seventy-three (73) different commercial lots of Patentee's resulting film products manufactured in accordance with the '080 Patent invention.

10. Ten (10) individual dosage units were removed from different locations of each lot, at least partially dissolved, and tested for the amount of active present in each sampled individual dosage unit.

11. Individual Film Dosage Unit Assay Data shows the content uniformity test results for the 730 sampled individual dosage units, ten each from the seventy-three (73) separate lots.

12. It can be seen from Appendix A that the active content of each individual dosage unit remains well within the control limits of 90% to 110%. The target or desired amount is 8.00 mg of active per individual dosage unit. The range of analytical chemical testing results among those 730 individual dosage units was 93.50% (7.48 mg) to 105.80% (8.47 mg) of the target or desired amount of active. This uniformity of content level is consistent with that described in the '080 Patent.

IV. '080 Patent Process Produces Films With Required Content Uniformity of Active

13. The results, shown in Appendix A, establish that the resulting films produced by the inventive method of the '080 Patent have a distribution of active within the limits required by the '080 Patent, in this case, performing analytical chemical tests for content uniformity of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating said substantially uniform distribution of the pharmaceutical active, in that the pharmaceutical active varies by no more than 10%.

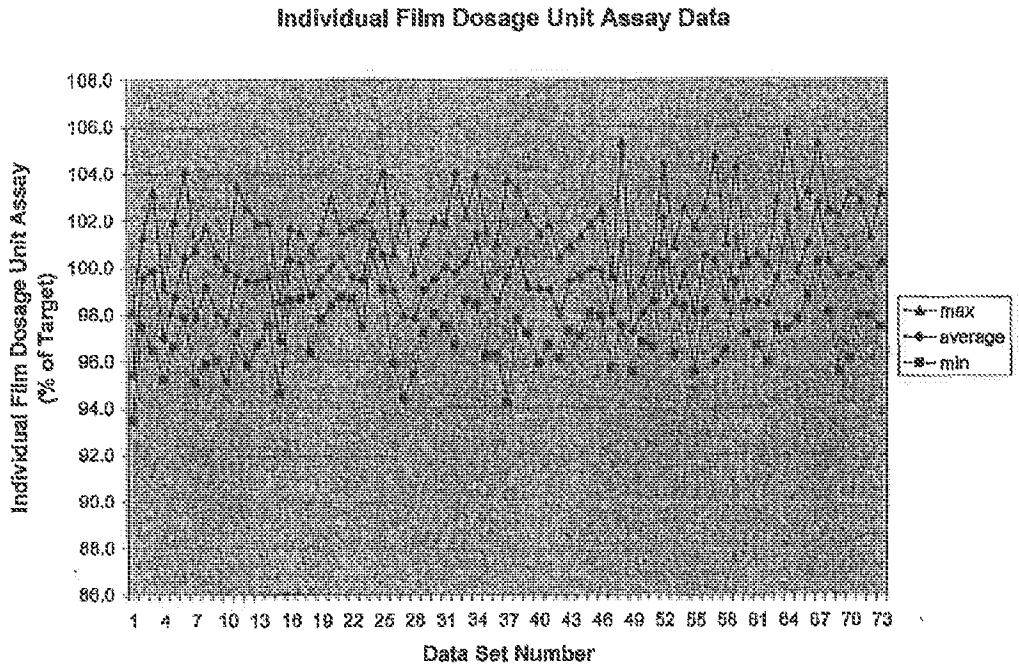
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 29th, day of January, 2013

B. Arlie Bogue

APPENDIX A

APPENDIX A



CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R.§1.132** has been served, by first class mail, on January 29, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
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265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

EXHIBIT B

PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080 B2	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	January 29, 2013	M&E Docket:	117744-00023

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Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION BY GERALD FULLER, PH.D. UNDER 37 C.F.R.§1.132

Sir/Madam:

I, Gerald Fuller, Ph.D., do hereby make the following declaration:

I. **Technical Background**

1. I have worked in the field of fluid dynamics and rheology for 38 years, including research in the processing of complex polymeric liquids. I have extensive knowledge of the use of flowable polymer compositions in various coating and film-making. I have a B.Sc. in Chemical Engineering from the University of Calgary (1975), a M.S. in Chemical Engineering from Caltech (1977) and a Ph.D. in Chemical Engineering from Caltech (1980).

2. My work experience includes measurement of the viscoelasticity of various polymeric materials, including hydrocolloids. I have technical experience in industry working as a consultant for film-making companies, such as 3M and DuPont.

3. I am currently a professor at Stanford University where I hold the title: Professor Fletcher Jones Chair in the School of Engineering. I have taught fluid mechanics and rheology. Appendix I is a copy of my Curriculum Vitae.

4. I have published extensively on the subject of rheology and complex fluids and Appendix I provides a list of my publications and journal articles.

5. I have read the Office Action, U.S. Patent 7,897,080 B2, the references cited in the Office Action and Dr. Cohen's Declaration submitted by the Requestor.

II. The Declaration of Dr. Cohen

6. It is my opinion that the film process as described by Chen at commercial scale would not inherently result in a film having a uniform distribution of active in the film. In particular, it is also my opinion that the film process of Chen would not inherently result in a film having a uniformity of content of active in substantially equal sized individual dosage units sampled from Chen's resultant film, where the active in the dosage units varies no more than 10%.

7. The process described by Chen does not describe how to dry in a manner that would avoid redistribution and inhomogeneity of a dissolved solute or suspended actives due to well-known thermodiffusive effects. The effects, also referred to as the Soret effect, can drive inhomogeneities during the drying of a previously homogeneous mixture. In other words, even if a solution containing a solute or suspended actives is spatially homogeneous in that constituent, the act of drying the solution to create a solid film can cause redistribution of the solute or suspended actives through the creation of temperature variations. This is the result of temperature gradients within the polymer film matrix causing the solute or suspended actives in the film to migrate and accumulate in different locations even if the solute or suspended actives were initially uniformly distributed. The Soret effect, which was described in 1800's, is a classical phenomenon, and is well-known to the chemical process industry. (see Appendix II)

8. Dr. Cohen's assumption that Chen's process will lead to films that are spatially homogeneous in composition is flawed because it does not recognize that thermodiffusive effects can result in spatial redistribution of constituents even if they were initially homogeneous prior to the application of heating during the process of film formation. Because Chen does not describe the film drying process, it cannot be assumed that any resulting temperature gradients within the polymer film matrix during the drying process will not lead to thermodiffusion and spatial inhomogeneity.

9. Chen does not discuss the development of viscoelasticity in the film during the drying process. Chen discloses the use of hydrocolloids and it is well-established that these materials can increase viscosity but will not necessarily enhance viscoelasticity. It is well known that viscosity is only one property within the general description of viscoelasticity. Even though these materials, such as Carbopol®, can lead to shear thinning materials, they are often inelastic and purely viscous. Chen does not recognize the mechanism of viscoelasticity of a film undergoing drying needs to be effectuated to retain the spatial uniformity of the constituents of that film. The development of viscoelasticity has the ability of arresting processes such as the Soret effect that can induce inhomogeneities. The Monosol process that creates a viscoelastic film within the first four (4) minutes of drying has the important benefit of locking in a spatially homogeneous distribution of components by inhibiting the effects of thermodiffusion to obtain active uniformity that does not vary more than 10% in the amount of active present in substantially equal sized individual dosage units.

10. Dr. Cohen is incorrect in his assumption that simply increasing the viscosity of a hydrocolloid material through film drying will retain spatial uniformity of the constituents of a film. In the absence of conditions which rapidly build viscoelasticity, components can diffuse spatially in a viscous media in response to thermodiffusive effects. The development of a rapid viscoelastic network formation is able to spatially constrain the diffusion of components and inhibit thermodiffusivity and retain spatial uniformity to the desired degree.

III. Glossy and Transparent Do Not Indicate or Suggest Uniformity of Content

11. The Examiner has stated:

> "Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection. In particular, Chen's dried film product of Example 1 is cut into dosage units ready for packing (p. 17, lines 31-32) and has a weight of 0.028 ± 0.001 g/dosage film, a density of 1.0485 ± 0.009 g/cm^2, a water content of 1.7 ± 0.24%, and as noted above, a thickness of 2.1 ± 0.12 mil (see Table 4); and the dried films are glossy and substantially transparent (p. 17, line 15), i.e., they are visually free of aggregation…. (Action at p.13)
>
> In particular, in order to arrive at a dried film product as in Chen, which is made using the same materials as disclosed in the '080 patent and the same basic process steps here claimed, wherein the dried film is glossy and substantially transparent and has the gram per dosage, thickness, density and water content noted above for Example 1, then a viscoelastic film is inherently formed during Chen's 9-minute drying." (Action at p.15)

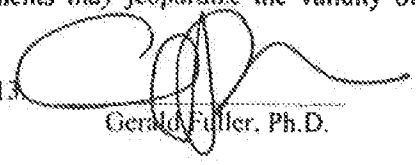
12. The term "glossy' is not interchangeable with, nor equivalent to the uniformity of content of components of a film, nor the content uniformity of an active in the film. It is also not interchangeable with a specific variation of active content in unit dosage samples taken from a film. "Glossy" is a general term for a uniform reflectiveness of light off of a surface. It is a type of visual surface uniformity, but it is not indicative, nor suggestive of the content uniformity of a film, nor the uniformity of distribution of active, *e.g.* solute, particles or particulates of pharmaceutical active, which are present in the film.

13. The term "transparent" is defined by the Examiner as "visually free of aggregation." The term "transparent" is conventionally defined as "having the property of transmitting light without appreciable scattering so that bodies lying beyond are seen clearly." (See http://www.merriam-webster.com/dictionary/transparent) This term, however, regardless of which definition is applied, is also a visual appearance characteristic that is neither indicative of nor suggestive of the uniformity of content of the film. In particular, this term does not necessarily provide any indication or suggestion of a specific variance of active per unit dose of film sampled therefrom.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that

these statements were made with the knowledge that willful false statements and the like are punishable by fine, or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 29 day of January, 2013



Gerald Fuller, Ph.D.

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION BY GERALD FULLER, PH.D. UNDER 37 C.F.R.§1.132** has been served, by first class mail, on January 29, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

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BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

APPENDIX I

GERALD G. FULLER
PERSONAL AND PROFESSIONAL VITAE

BIOGRAPHICAL INFORMATION
Date of Birth: April 7, 1953.
Place of Birth: Washington, D.C.

EDUCATION
Ph.D., Chemical Engineering, California Institute of Technology, February 1980.
M.S., Chemical Engineering, California Institute of Technology, June 1977.
B.Sc., Chemical Engineering, University of Calgary, June 1975.

SCHOLARSHIPS AND HONORS

2011 Corresponding Member of the Russian and International Engineering Academy
2009 Distinguished Service Award, Society of Rheology.
2009 Associate Member, University of Wales Institute of Non-Newtonian Fluid Mechanics.
2009 Honorary Degree of Doctor of Philosophy of the University of Crete
2009 Journal of Rheology Publication Award for "Analysis of the magnetic rod interfacial stress rheometer" by Sven Reynaert, Carlton F. Brooks, Paula Moldenaers, Jan Vermant, and Gerald G. Fuller, Volume 52(1) pp. 261-285 (2008).
2008 Named one of the "One Hundred Engineers of the Modern Era" by the American Institute of Chemical Engineers (AIChE) marking the 100th Anniversary of the AIChE
2008-12, President of the International Committee on Rheology.
2008 to present, Advisory Committee for *Physics Today*, 2008.
2006, Cox Medal for Excellence in Fostering Undergraduate Research.
2006, Named the Fletcher Jones II Professor of Engineering at Stanford University.
2006, Foreign Associate of the Moroccan Academy of Science and Technology.
2005, National Academy of Engineering.
2004, Julian C. Smith Lectureship in Chemical and Biomolecular Engineering, Cornell University.
2004, Pearson Lecturer in Chemical Engineering, UCSB.
2004-08, Chairman of the XVth International Congress on Rheology.
2003, Holtz Lecturer, Dept of Chemical Engineering, Johns Hopkins University.
1999-04, Visiting Professor, Dept. Mechanical Engineering, Kings College, London.
1999-01President of the Society of Rheology.
1997, Bingham Medal Award, The Society of Rheology.
1993, Fellow of the American Physical Society.
1990, Theile Lecturer, Department of Chemical Engineering, Notre Dame University, October.
NSF Presidential Young Investigator Award 1985.
1975-79, National Research Council of Canada Postgraduate Scholarship.
Society of Chemical Industry Gold Key Award 1975.
1975, Association of Professional Engineers, Geologists and Geophysicists, Gold Medal in Chemical Engineering.

1974, Hudson's Bay Oil and Gas Gold Medal in Chemical Engineering.
1972, Dome Petroleum Scholarship in Chemical Engineering.
1971, Queen Elizabeth Scholarship.

WORK EXPERIENCE

August 1, 2008 to July 31, 2009 and September 1, 1996 - February 1, 2001
Chairman, Department of Chemical Engineering, Stanford University
October 1990 - present
Professor, Department of Chemical Engineering, Stanford University
June 1996 - August 1996
Visiting Professor, University of Strasbourg, France
January 1994 - July 1994
Visiting Associate Professor, Ecole des Mines de Paris, Nice, France
July 1992 - August 1992
Visiting Scientist, Materials Science, E.P.F.L., Lausanne, Switzerland
June 1989 - September 1989
Visiting Scientist, Chemical Engineering, Katholieke Universiteit, Leuven, Belgium
October 1985 - September 1990
Associate Professor, Chemical Engineering, Stanford University
January 1987 - August 1987
Visiting Scientist, AT&T Bell Laboratories Murray Hill, New Jersey
October 1980 - September 1985
Assistant Professor, Chemical Engineering, Stanford University
February 1980 - September 1980
Visiting Scientist, Centre de Recherches sur les Macromolecules Strasbourg, France
October 1975 - February 1980
Teaching and Research Assistant, California Institute of Technology, Pasadena, California
May 1975 - September 1975
Research Assistant in Theoretical Chemistry, University of Calgary, Calgary, Alberta
May 1974 - September 1974
Assistant Engineer, Shell Canada Ltd., Calgary, Alberta
May 1973 - September 1973
Gas Plant Operator, Imperial Oil Ltd., Edmonton, Alberta
May 1972 - September 1972
Laboratory Assistant, ATCO Research and Development Calgary, Alberta

PROFESSIONAL ACTIVITIES

Editorial Board Member for the J. Polymer Science: Polymer Physics, 2003 – present.
Past President, Society of Rheology, 2001-2003.
President, Society of Rheology, 1999-2001.
Vice President, Society of Rheology, 1997-1999.

Chair, Local Arrangements Committee, Society of Rheology, 1998.
Panelist, NSF Career Grant Committee, 1997.
Member at Large, Executive Committee of the Society of Rheology, 1995 - 1997.
Member Twenty-eighth Senate of the Academic Council, Stanford University, 1995-1996.
Chair of the Technical Committee, Society of Rheology, 1995.
Panelist, NSF Workshop on Particle Science and Technology, 1993.
Member, Nominating Committee, Society of Rheology, 1989.
Member, Bingham Medal Award Committee, Society of Rheology, 1987 - 1989.
Editorial Board Member for the Journal Rheologica Acta.
Member of the A.I.Ch.E., Society of Rheology, APS, ACS.

PUBLICATIONS

Books

1. G.G. Fuller, "Optical Rheometry of Complex Fluids", Oxford University Press, New York, 1995.
2. Lydie Navard, Patrick Navard and Gerald Fuller, "Scientifically Yours", Corlet Imprimeur, S.A., France, 1995.

Contributions to Books

1. G. G. Fuller and C. M. Ylitalo, "Optical Rheometry of Polymeric Liquids", chapter 6 in Polymer Rheology and Processing, A. Collyer and L. Utracki, Editors, Elsevier Applied Science, London, 1990.
2. G.G. Fuller, J.A. Zawada and R.H. Colby, "Investigating Miscible Polymer Blend Dynamics with Optical and Mechanical Rheometry", Keynote Lectures in Selected Topics of Polymer Science, proceedings of Alicante Seminars. (1994).
3. G.G. Fuller, J. van Egmond D. Wirtz, E. Peuvrel-Disdier, E. Wheeler and H. Takahashi, "Enhancement of Concentration Fluctuations in Solutions Subject to External Fields", ACS Symposium Series in "Flow Induced Structure in Polymers", A.I. Nakatiani and M.D. Dadmun, editors, 597 (1995) 22-34.
4. Gerald G. Fuller, "Fundamentals of Optical Rheometry", contribution to "Rheo-Physics of Multiphase Polymeric Systems, Application of Rheo-Optical Techniques in Characterization", (1995), pg. 15, Sondergaard, editor, Technomic Publishing Co., Inc., Lancaster, PA.

Particle-laden interfaces: rheology, coalescence, adhesion and buckling G. G. Fuller, E. J. Stancik and S. Melle. in *Colloidal Particles at Liquid Interfaces,* edited by B. Binks and T. Horozov, Cambridge University Press, 2006.

Refereed Publications

1. R. Paul and G.G. Fuller, "Applications of Field Theoretical Methods to the Calculation if Infrared Band Shapes of Molecules in Strongly Interacting Solvents", J. Chem. Phys. 64 (1976) 3809-3825.
2. G.G. Fuller, "A Modified Redlich-Kwong-Soave Equation of State Capable of Representing the Liquid State", I&EC Fundamentals 15 (1976) 254-257.
3. G.G. Fuller, J.M. Rallison, R. Schmidt, and L.G. Leal, "Measurements of Velocity Gradients in Laminar Flow by Homodyne Light Scattering Spectroscopy", J. Fluid Mech. 100 (1980) 555-575.
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5. G.G. Fuller and L.G. Leal, "Flow Birefringence of Dilute Polymer Solutions in Two-Dimensional Flows", Rheol. Acta 19 (1980) 580-600.
6. G.G. Fuller and L.G. Leal, "Effect of Molecular Weight and Flow Type on Flow Birefringence of Dilute Polymer Solutions", Rheology, (G. Astarita, G. Marrucci, L. Nicolais, Eds.) vol. 2, pp. 393-398, Plenum Press, New York, 1980.
7. G.G. Fuller and L.G. Leal, "The Effects of Conformation-Dependent Friction and Internal Viscosity on the Dynamics of the Nonlinear Dumbbell Model for a Dilute Polymer Solution", J. Non-Newt. Fluid Mech. 8 (1981) 271- 310.

8. G.G. Fuller and L.G. Leal, "Network Models of Concentrated Polymer Solutions Derived from the Yamamoto Network Theory", J. Polym. Sci.: Phys. Ed. 19 (1981) 531-555.
9. G.G. Fuller and L.G. Leal, "Flow Birefringence of Concentrated Polymer Solutions in Two-Dimensional Flows", J. Polym. Sci.: Phys.: Ed. 19 (1981) 557-587.
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11. G.G. Fuller, "Dynamics of Adsorbed Polymer Chains Subjected to Flow: The Dumbbell Model", J. Polym. Sci.: Polym. Phys. Ed. 21 (1983) 151-157.
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13. P.L. Frattini and G.G. Fuller, "A Note on Phase Modulated Flow Birefringence: A Promising Rheo-Optical Method", J. Rheol. 28 (1984) 61-70.
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19. B.E. Zebrowski and G.G. Fuller, "Rheo-Optical Studies of Concentrated Polystyrene Solutions Subjected to Transient Simple Shear Flow", J. Polym. Sci.: Polym. Phys. Ed. 23 (1985) 575-590.
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21. A.W. Chow, G.G. Fuller, D.G. Wallace and J.A. Madri, "The Rheo-Optical Response of Rod-Like Chains Subject to Transient Shear Flow, Part II. Two- Color Flow Birefringence Measurements", Macromolecules 18 (1985) 793- 804.
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Geometries: II. Time Dependent Shear Flow", J. Non-Newt. Fluid Mech. 18 (1985) 111-122.
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27. B.E. Zebrowski and G.G. Fuller, "Rheo-Optical Studies of Poly-Electrolyte Solutions in Simple Shear Flow", J. of Rheology 29 (1985) 943-954.
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Patents

Gerald G. Fuller, Ronald Garritano, Paul Mode, Measuring shear viscosity of fluids, US5115669, May. 26, 1992.
A. Freeman, G. Fuller, D. Sierra, S. Conston, A. Michaels, Cell separation device and in-line orifice mixer system, US5,968,018, Oct. 19, 1999.
A. Franck, J. Vermant, G. Fuller, System and Method for Interfacial Rheometry, US 7,926,326, 2011.
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Keynote and Plenary Lectures

1. G.G. Fuller and J.-J. Lee, The Dynamics of Adsorbed Macromolecules Subjected to Flow (invited lecture), presented at the I.U.P.A.C. 28th Macromolecular Symposium, University of Massachusetts, Amherst, Massachusetts, July 1982.
2. G.G. Fuller, Adsorbed Polymer Layers Subjected to Flow (invited lecture). Workshop on Polymer-Flow Interaction. The La Jolla Institute, La Jolla, California, July 1985
3. G.G. Fuller, Invited Panelist on Coating Fundamentals, TAPPI Coating Conference, Washington, D.C., May 1986.
4. G.G. Fuller, Optical Rheometry of Polymeric Liquids (invited participant), U.S.-West Germany Polymer Science Symposium, Napa, California, September, 1987.
5. G.G. Fuller, Optical Rheometry (Keynote Lecture), Xth International Congress on Rheology, Sydney, Australia, August, 1988.
6. G. G. Fuller, Optical Rheometry of Polymeric Liquids (Keynote Lecture), National ACS Meeting, Los Angeles, CA, September 25-30, 1987.
7. G. G. Fuller, Optical Rheometry of Polymeric and Colloidal Liquids (invited lecture), Japan Society of Rheology, Nagaoka, Japan, October 2-7, 1988.
8. G. G. Fuller, Optical Rheometry of Polymeric Liquids (invited lecture). International Symposium on Polymer Analysis and Characterization, ACS Meeting, Dallas, TX, April 9-14, 1989.

9. G. G. Fuller, Optical Rheometry of Polymeric and Colloidal Liquids (invited participant), Workshop on the Dynamics of Concentrated Systems, Los Alamos Laboratory, New Mexico, June 13-15, 1989.
10. G. G. Fuller, Extensional Viscometry of Polymer Solutions (plenary lecture). Symposium on Rheology Modifiers, National ACS Meeting, Miami Beach, Florida, September 10-14, 1989.
11. G. G. Fuller, Optical Rheometry (invited lecture). Symposium on Polymer Rheology and Processing, Pacifichem 89, Honolulu, Hawaii, Dec. 17-22, 1989.
12. G. G. Fuller, Infrared Polarimetry Studies for Multi-Component Polymer Melts (invited lecture), International Discussion Meeting on Relaxation in Complex Systems, Heraklion, Crete, June 18-19, 1990.
13. G. G. Fuller, Infrared Optical Rheometry of Multicomponent Polymer Melts (keynote lecture), British Society of Rheology, Golden Jubilee Meeting, Edinburgh, Scotland, September 3-9, 1990.
14. G. G. Fuller, Optical Rheometry, Thiele Lectureship Award, Notre Dame University, Notre Dame, IN, October 10, 1990.
15. G. G. Fuller, Dynamics of Polymer Liquids using Optical Rheometry (keynote lecture), 23rd Annual Mardi Gras Symposium in Theoretical Chemistry, New Orleans, LA, February 5, 1991.
16. G. G. Fuller, Dynamics of Multcomponent and Heterogeneous Polymer Liquids (keynote lecture), APS 1991 March Meeting, Cincinnati, OH.
17. G.G. Fuller, Rheo-Optics of Multicomponent Polymeric Liquids (invited lecture), Materials Research Society Fall Meeting, Boston, MA, December 2-6, 1991.
18. Gerald G. Fuller, Optical Rheometry of Polymer Liquids (keynote lecture), XIth International Congress on Rheology, Brussels, August, 1992.
19. Gerald G. Fuller, Optical Rheometry of Multicomponent Complex Liquids (keynote lecture), 16th All Union Symposium on Rheology, Dnepropetrovsk, Ukraine, September 1992.
20. Gerald G. Fuller, Dynamics of Compatible Blends (invited lecture), Spanish National Council of Scientific Research, Alicante, Spain, July 1993.
21. J.A. Zawada, G.G. Fuller and R.H. Colby, Isolating Component Contributions to the Overall Rheology in 1,4-Polyisoprene/1,2-Polybutadiene Miscible Blends (invited lecture), presented at the International Conference on Rheometry of Polymers from the "Solution to the Melt", Abbaye Royale de Fontevraud, France, May 1993.
22. Gerald G. Fuller, Isolating Component Contributions to the Overall Rheology in 1,4-Polyisoprene/1,2-Polybutadiene Miscible Blends (invited lecture), presented at the Theoretical and General Rheology, British Society of Rheology Meeting, Cambridge, England, September 22-24, 1993.
23. Gerald G. Fuller, Orientational Coupling in Bidisperse Polymer Blends (invited lecture), presented at the 2nd International Meeting on Extensional and Shear Flow from the Solution to the Melt, St. Andrews, Scotland, June 19-22, 1994.
24. Gerald G. Fuller, Optical Rheometry of Multicomponent Polymer Liquids (invited lecture), presented at the IUPAC International Symposium on Macromolecules, Akron, OH, July 11-15, 1994.
25. Gerald G. Fuller, Flow-Induced Structure in Multi-Component Polymers (invited

lecture), presented at the ACS National Meeting, Washington, DC, August 21-26, 1994.
26. Gerald G. Fuller, Structure and Dynamics of Multi-Component Polymer Liquids (keynote lecture), presented at the 4th European Rheology Conference, Seville, Spain, September 4-9, 1994.
27. Gerald G. Fuller, Recent Advances in Optical Rheometry (keynote lecture), presented at the Pacific Conference on Rheology and Polymer Processing, Kyoto, Japan, September 26-30, 1994.
28. Gerald G. Fuller, Structure and Dynamics of Complex Liquids by Optical Rheometry (keynote lecture), Conference on Complex Fluids, International Centre of Condensed Matter Physics, University of Brasilia, Brazil, December 13-16, 1994.
29. Gerald G. Fuller, Flow-Induced Concentration Fluctuations in Complex Liquids (keynote lecture), Polymer Processing Society-11, Seoul, Korea, March 27-30, 1995.
30. Gerald G. Fuller, optical Studies of Flow-Orientation and Relaxation in Monolayer Films (invited lecture), Symposium on Interfaces and Surfaces in the Rheology of Polymers, ACS National Meeting, Anaheim, April 2-6, 1995.
31. Gerald G. Fuller, Flow-Induced Orientation in Langmuir Monolayers (invited lecture), London Mathematical Society Symposium on Mathematical Models of Liquid Crystals and Related Polymeric Systems, University of Durham, England, July 10-20, 1995.
32. Interfacial Dynamics of Polymer Monolayers (keynote lecture), 36th IUPAC International Symposium on Macromolecules, Seoul, Korea, August 4-9, 1996.
33. Flow-Induced Orientation of Monolayers (invited lecture), Gordon Research Conference on Organic Thin Films, Ventura, CA, January 28 - February 2, 1996.
34. Dynamics of Polymeric Fluids: Influence of Flow on Microstructure (invited lecture), Nineteenth Asilomar Conference on Polymeric Materials, Pacific Grove, CA, February 11-14, 1996.
35. Concentration Fluctuations of Sheared Polymer-Polymer Solutions (invited lecture), The American Physical Society, Division of High Polymer Physics Meeting, St. Louis, MO, March 18-21, 1996.
36. Orientational Dynamics of Polymer Liquids and Monolayers (invited lecture), CERSIM Colloque '96, Laval University, Quebec, Que., Nov. 29, 1996.
37. Flow-Induced Dynamics of Polymer Liquids and Interfaces (invited lecture), Polymers West Gordon Research Conf., Ventura, CA, January 5 - 10, 1997.
38. Elongational Flow of a Two-dimensional Polymer Nematic (invited lecture), MRS Spring 1997 Meeting, San Francisco, CA, March 31- April 4, 1997.
39. Flow orientation of a two-dimensional polymer liquid crystal (invited lecture), The Second International Conference on Dynamics of Polymeric Liquids, Capri, Italy, May 7 - 10, 1997.
40. Dynamics and Structure of Langmuir Monolayers Subject to Flow (invited lecture), 3rd International Discussion Meeting on Relaxations in Complex Systems, Vigo, Spain, June 30 - July 11, 1997.
41. Optical Rheometry of Complex Liquids and Interfaces (Bingham Plenary Lecture), 69th Annual Meeting of the Society of Rheology, Columbus, OH

October 19-23, 1997.
42. Interfacial Rheometry of Complex Interfaces (Invited Paper), Symposium on Nonequilibrium Dyna;m;ic Processes at Colloidal Interfaces, ACS Spring Meeting, Dallas, TX, March 29 - April 2, 1998.
43. Recent Advances in Optical Rheometry (Keynote Lecture), The Polymer Processing Society, 14th Annual Meeting, Yokohama, Japan, June 8-12, 1998.
44. Dynamics and Crystalline Connectivity of Stereoblock Polypropylene (Invited Lecture), Mitsubishi Chemical Workshop on Polymer Manufacturing, Mizushima, Japan, June 4-5, 1998.
45. Rheology and Dynamics of Complex Langmuir Films (Invited Lecture), 72nd ACS Colloid and Surface Science Symposium, Pennsylvania State University, June 21-24, 1998.
46. Interfacial Rheology of Complex Interfaces (Keynote Lecture), 2nd Meeting of the Hellenic Society of Rheology and International Symposium, Heraklion, Crete, Greece, Aug. 21-Sept. 2, 1998.
47. Recent Advances in Optical Rheometry (Keynote Lecture), 5th European Rheology Conference, Portoroz, Slovenia, September, 6-11, 1998.
48. Flow-induced Morphology in Polymer-Polymer Emulsions (Invited Paper), AIChE Annual Meeting, Miami Beach, FL, Nov. 15-20, 1998.
49. Crystallization and Dynamics of Stereoblock Polyporopylenes (Invited Paper), Gordon Research Conference on Elastomers, Networks and Gels, New London, NH, July 18-23, 1999.
50. Optical and Extensional Rheology (Invited Lectures), Sixth European School of Rheology, 6th-10th September 1999, Leuven, Belgium.
51. Structure and Dynamics of Elastomeric Polypropylene (Invited Paper), First Southern Europe Conference on Rheology, Calabria, Italy, 7th-11th September 1999.
52. The Rheology of Two-Dimensional Systems (Plenary Lecture), Perspectives on Rheology for the 21C, 10th Anniversary Meeting of the Korean Society of Rheology, Seoul, Korea, Nov. 9-10, 1999.
53. Rheology in Two Dimensions (Invited Lecture), David V. Boger Symposium, Melbourne, Australia, Nov. 15-16, 1999.
54. The Rheology of Complex Interfaces (Plenary Lecture), Tiger-Hen Day - Joint Polymer Science Symposium between the University of Delaware and Princeton University, Newark, DE, Jan. 15, 2000.
55. Rheology in Two Dimensions (Plenary Lecture), Workshop on Surfactant Flows at Interfaces, The Institute for Surface and Interface Science, UCI, Laguna Beach, CA, April 28 & 29, 2000.
56. Dynamics of Polymers in 2D (Invited Lecture), Dillon Symposium of the APS March Meeting, Minneapolis, MN, Mar. 19-24, 2000.
57. Order and Disorder of Polymer Monolayers (Invited Lecture), Multi-Level Ordering by Competing Short and Long Range Interactions in Macromolecular Systems Discussion Meeting, Weingarten, Germany, June 3-8, 2000.
58. Interfacial Rheology in Polymer Processing (Invited Lecture), The Polymer Processing Society, Zlin, Czech Republic, Aug. 16-18, 2000.
59. Rheology Of Complex Fluid Interfaces (Invited Lecture), LB 9-Potsdam 2000,

The Ninth International Conference on Organised Molecular Films, Potsdam, Germany, 8/28-9/1, 2000.
60. Rheology in Two Dimensions (Invited Lecture), Rhelogical aspects of surfactant based systems, Collingwood College, University of Durham, England, 18-19 Sept. 2000.
61. The dynamics of polymer chains trapped in two dimensions (Invited Lecture), POLYMERS (WEST) Gordon Conference, January 7-11, 2001, Ventura, California.
62. DNA Chains Slithering on Interfaces: Chain Dynamics in 2D (Invited Lecture), Chains@Interfaces 2001" Euroconference, Evora, Portugal, January 14 - 19, 2001.
63. Rheology in Two Dimensions (Invited Lecture), London Rheology Group, Mechanical Engineering Department, Kings College, London, England, February, 22, 2001.
64. Perspectives on Chemical Engineering (Invited Lecture), Korean Academy of Engineering, Seoul, Korea, May 29, 2001.
65. Interfacial Rheology: Stresses and Strains in Flatland (Invited Lecture), Korean Society of Rheology, Postech, Korea, May 31, 2001.
66. Crystallization and dynamics of stereoblock polypropylene (Invited Lecture), Gordon Conference, Polymers East, New Hampshire, July 9 - 12, 2001.
67. Rheology in Two Dimensions (Invited Lecture), Swiss Rheology Society, Lausanne, Switzerland, September 4, 2001.
68. Complex Fluid Interfaces, Conference On Process Modelling, Lake Vyrnwy Hotel, Powys, Mid-Wales, UK, March 25-27, 2002.
69. Orientation Dynamics of Stereoblock Polypropylene (Invited Lecture), Symposium on Complex Liquids, Capri May 26-29, 2002.
70. Orientation and Crystallization of Polypropylene, (Keynote Address), Polymer Processing Society, Guimares, Portugal, June 16-20, 2002.
71. Structure and Dynamics of Particle Monlayers at a Liquid-Liquid Inteface Subjected to Shear Flow (Invited Lecture), Faraday Discussion 123 on Non-Equilibrium Behavior of Colloidal Dispersions, Edinburgh, UK, Sept. 9-11, 2002.
72. Rheology of Complex Fluid Interfaces (Invited Lecture), Polymer Processing Society, Tapei, Taiwan, Nov. 3-7, 2002.
73. Interfacial Rheology and Emulsion Stability (Invited Lecture), Third International Symposium on Food Rheology and Structure, Zürich/Switzerland, Feb. 9 - 13, 2003.
74. 2D Suspensions (Invited Lecture), Rheometry II, Miskin Manor, Cardiff, Wales UK, April 14-16, 2003.
75. Holtz Lecturer, Department of Chemical Engineering, Johns Hopkins University, April 24 - 25, 2003.
76. Dynamics of 2-Dimensional Colloidal Crystals (Invited Lecture), 3rd Chemical Engineering Conference for Collaborative Research in Eastern Mediterranean (EMCC-3), May 14-16, 2003, Thessaloniki, Greece
77. Flow-induced Crystallization of Elastomeric Polypropylene (Invited Lecture), Polymer Processing Society, Melbourne, Australia, July 6 - 10, 2003.
78. Coalescence of Particle-Laden Interfaces (Invited Lecture), Unilever Rheology

Workshop, Clinton Inn, Tenafly, NJ, August 19-20, 2003.
79. Interfacial Rheology of Polymer Monolayers (Invited Lecture), Symposium Honoring Paul Flory, ACS Annual Meeting, New York, NY, September 7 - 11, 2003
80. Lecturer, European School on Rheology (Invited Lecture), University of Leuven, Belgium, September 15 - 19.
81. Stabilization of Pickering Emulsions (Invited Lecture), Nestle Rheology Workshop, Lausanne, Switzerland, September 23 - 25, 2003.
82. Emulsion Stability and Interfacial Rheology (Invited Lecture), Special Panel Discussion on Rheology, American Association of Cereal Chemists, Portland, Oregon, September 28 - October 2, 2003.
83. Stabilization of Emulsions by Protein Interfaces (Keynote Lecture), Food Processing Division, AIChE Annual Meeting, San Francisco, CA, November, 2003.
84. Interfacial Rheology (Invited Lecture), TA Instruments Workshop, San Antonio, TX, February 2 – 4, 2004.
85. Particle-laden Interfaces (Invited Lecture), Neue Ansätze für innovative Polymerwerkstoffe (Professor Eisenbach Birthday Celebration), University of Stuttgart, Stuttgart, Germany, February 16 – 17, 2004.
86. Particle Stabilized Emulsions (Invited Lectures), Particles 2004, Orlando, FL, March 7 – 9, 2004.
87. Complex Fluid Interfaces (Visiting Professor), Hong Kong University of Science and Technology, Hong Kong, April 5 – 8, 2004.
88. "Complex Fluid Interfaces" and "Connect the Drops – Particle Stabilized Emulsions", Smith Lectureship, Cornell University, Ithaca, NY, April 19 – 20, 2004.
89. "Complex Fluid Interfaces" and "Connect the Drops – Particle Stabilized Emulsions", Pearson Lectureship, UCSB, Santa Barbara, CA, May 9 – 13, 2004.
90. Particle Stabilized Emulsions (Plenary Lecture), Rheology Symposium of the Rheology Group of Brazil, Rio de Janeiro, Brazil, July 7 – 9, 2004.
91. Foam Stability (Invited Lecture), Unilever Workshop, Edgewater, NJ, July 22 – 23, 2004.
92. Two-Dimensional Melts and Suspensions (Invited Lecture), SoftComp Symposium, University of Leuven, Leuven, Belgium, 20-21, 2005.
93. Rheology and Stability of Complex Fluid Interfaces (Plenary Lecture), Unilever Corporate Review, Sharnbrook, England, May 9-12, 2005.
94. Rheology of Complex Fluid Interfaces (Keynote Lecture), 6th Liquid Matter Conference, Utrecht, The Netherlands, July 2-6, 2005.
95. Complex Fluid Interfaces and Emulsion Stability (Plenary Lecture), BASF Symposium, Ludwigshafen, Germany, Sept. 5-6, 2005.
96. Short Course on Rheology (Invited Lecturer), University of Leuven, Leuven, Belgium, Sept. 12-15, 2005.
97. Particle-stabilized emulsions with controllable stability (Keynote Lecture), Nanotechnology Talks IV, Frankfurt, Germany, Sept. 29-30, 2005.
98. Two Dimensional Polymer Glasses (Invited Lecture), Dealy Symposium: Molecular Structure and Rheology, Annual Meeting of the Society of Rheology, Vancouver,

Canada, October 16-20, 2005.
99. Two Dimensional Polymer Melts, Gordon Research Conference on Colloidal, Macromolecular & Polyelectrolyte Solutions (Invited Lecture), Ventura, CA, February 5 – 10, 2006.
100. Complex Fluid Interfaces: Applications in Consumer Products and the Life Sciences, The Lodge Commemorative Meeting on Rheology (Keynote Lecture), Cardiff, Wales, April 10-12, 2006.
101. Collagen Monolayers (Invited Lecture), Materials Research Society, San Francisco, CA, April 17-20, 2006.
102. Interfacial Rheology: Applications from Industry and Nature (Invited Lecture), 2006 Users Meeting and Symposium, TA Instruments, Newport, Rhode Island, May 8-11, 2006.
103. Two Dimensional Suspensions and Polymer Melts (Invited Lecture), IV Workshop on Non Equilibrium Phenomena in Supercooled Fluids, Glasses and Amorphous Materials, Pisa, Italy, September 17-22, 2006.
104. Solid Stabilized Emulsions (Keynote Lecture), World Congress on Emulsions, Lyon, France, October 3-6, 2006.
105. Solid Stabilized Emulsions (Invited Lecture), Special Symposium Honoring William Russel of Princeton, ACS National Meeting, Washington, DC, March 26, 27, 2007.
106. Complex Fluid Interfaces (Plenary Lecture), Annual European Rheology Conference, Naples, Italy, April 12-14, 2007.
107. Interfacial Rheology (Plenary Lecture), Korean Society of Rheology Annual Meeting, Seoul, S. Korea, May 17, 2007.
108. Structure and Dynamics of Complex Fluid Interfaces (Keynote Lecture), ACS Colloids Meeting, University of Delaware, Newark, DE, June 24-27, 2007.
109. European Short Course on Rheology (Invited Lecturer), Leuven University, Leuven, Belgium, September 2-7, 2007.
110. Flow processing and rheology of complex fluid interfaces (Plenary Lecture in Interfacial Phenomena), AIChE Annual Meeting, Salt Lake City, UT, Nov. 4-9, 2008.
111. Two Problems in Biomedicine: Rheology to the Rescue (Plenary Lecture). Korean Society of Rheology, Hanna Square at Korea University, Monday, Nov. 19, 2007, Plenary Lecture.
112. Interfacial Flow Processing of Biological Materials (Keynote Lecture), Frontiers in Microrheology Workshop, California NanoSystems Institute, UCLA, Los Angeles, Feb. 6-10, 2008.
113. Rheology and Materials Processing (Invited Lecturer), Science and Technology Panel of the Moroccan Academy of Science and Technology, University of Mohamedia, Feb. 18, 2008.
114. Interfacial Flow Processing of Biological Materials (Plenary Lecture), Workshop on Complex Flows of Complex Fluids, Institute of Non-Newtonian Fluid Mechanics and the British Society of Rheology, University of Liverpool, UK, March 17-19, 2008.
115. Interfacial Rheology (Keynote Lecture), TA 3rd User Meeting on Rheology and Thermal Analysis, Scottsdale, AZ, May 4-7th, 2008.
116. Interfacial processing of collagen monolayers for contact guidance of mammalian cells (Keynote Lecture), Surfactants in Solutions (SIS) meeting in Berlin, Germany, Aug. 17-21, 2008.
117. Interfacial Flow Processing of Collagen, Invited Lecture at the Symposium Honor

Bud Homsy, AIChE Annual Meeting, Philadelphia, November 15-21, 2008.
118. Interfacial Flow Processing of Collagen Substrates, De Gennes Discussion Conference, Chamonix, France, Feb. 2-5, 2009.
119. Rinsing flows: using polymeric liquids as soft adhesives, Presentation to the Moroccan National Society of Science and Technology, February 24, 2009.
120. Rheology of High Interface Systems, Two Day Short Course to the Multiphase Flow Assurance Innovation Center, Oslo, Norway, March 23, 24, 2009 (with J. Vermant and S. Cox).
121. Interfacial Rheology (Invited Lecture), Rheology Research Center, University of Wisconsin, Madison, WI, April 3, 2008.
123. Oriented Collagen Substrates for Directed Cell Growth (Keynote Lecture), Inaugural Meeting of the Romanian Society of Rheology, Bran, Transylvania, Romania, June 15-19, 2009.
124. Interfacial rheology of Meibomian fluids (Invited Lecture), "Solving Dye Eye" Symposium, Sydney Australia, August 3-7, 2009.
125. Rinsing flows: Transforming polymeric liquids into soft adhesives (Plenary Lecture), 20th Anniversary of the Korean Society of Rheology, Seoul, Korea, August 19-21, 2009.
126. Lectures on "Extensional Viscosity" and "Interfacial Viscosity", European Rheology School, University of Leuven, Belgium, September 21-25, 2009.
127. Rheology to the Rescue: Two Problems in Biomedicine, Presentation of an Honorary Degree from the University of Crete, Heraklion, Greece, November 25, 2009.
128. Particle Removal by Rinsing Non-Newtonian Fluids (Keynote Lecture), Symposium on Complex Fluids, IIT Madras, Chennai, India, 4 – 9 January, 2010.
129. Rinsing Flows, A New Class of Non-Newtonian Flow (Invited Lecture), Welsh Conference on Rheometry, March 29-31, 2010, at Lake Vyrnwy, Wales UK.
130. Rinsing Flows: Turning Polymeric Liquids into Soft Adhesives (Plenary Lecture), Inaugural Meeting of the Brazilian Society of Rheology, Rio de Janeiro, Brazil, July 14-16, 2010.
131. Interfacial Rheology (Series of Invited Lectures), DynaSoft2010: Dynamics in Soft Condensed Matter, Corsica, France, August 2-13, 2010.
132. Rinsing Flows of Non-Newtonian Fluids, Invited Lectures, International workshop on colloids and interface: Microstructure Fluids and Materials KAIST, Korea, 18th-20th August, 2010.
133. Particle Removal by Rinsing Polymeric Liquids (Plenary Lecture), South African Society of Rheology, 3rd Conference on Rheology, Cape Town, SA, September 8-10, 2010.
134. Bulk and Interfacial Rheology of Meibum and Its Effect on Dewetting (Invited Lecture), G. Fuller, D. Leiske, and L. Rosenfeld, International Congress on Industrial and Applied Mathematics, Vancouver, July 20-24, 2010.
135. Lifting physisorbed colloidal particles from solid surfaces (Keynote Lecture), ACS Meeting, March 27-31, 2011 in Anaheim, California
136. Rheology of Biological Interfaces (Plenary Lecture), University of Wales Institute of non-Newtonian Fluid Mechanics 20th, Apr. 18-20, 2011, Portmeirion Village, Wales.
137. Interfacial Rheology of Biological Fluids (Keynote Lecture), 7th Annual European Rheology Conference AERC, May 10-14, 2011 Suzdal, Russia.

138. Rinsing Flows: Ablation of non-Newtonian Liquids from Solid Surfaces (Plenary Lecture), Nordic Society of Rheology, Helsinki, Finland, June 8-10, 2011.
239. Rheology of Biological Interfaces (Plenary Lecture), Lorentz Workshop on the topic "Dynamics of complex fluid-fluid interfaces", University of Leiden, The Netherlands, September 26-29, 2011.

Contributed Conference Presentations

1. G.G. Fuller and L.G. Leal, Flow Birefringence of Concentrated Polymer Solutions Subjected to Two Dimensional Flows, presented at the Golden Jubilee Meeting of the Society of Rheology, Boston, Massachusetts, October 1979.
2. L.G. Leal, G.G. Fuller and W.L. Olbricht, Studies of the Flow Induced Stretching of a Macromolecule in Dilute Solution, presented at the Viscous Drag Reduction Symposium, Dallas, Texas, November 1979.
3. G.G. Fuller and L.G. Leal, Effect of Molecular Weight and Flow Type on Flow Birefringence of Dilute Polymer Solutions, presented at the VIIIth International Congress on Rheology, Naples, Italy, September 1980.
4. L.G. Leal and G.G. Fuller, Experimental and Theoretical Studies of Entanglement Network Models for Macromolecular Solutions, presented at the AIChE National Meeting Chicago, Illinois, November 1980.
5. G.G. Fuller, Dynamics of an Adsorbed Polymer Molecule Subjected to Flow, presented at the 159th meeting of the Electrochemical Society, Minneapolis, Minnesota, May 1981.
6. G.G. Fuller, Response of Adsorbed Polymer Molecules to an Imposed Flow, presented at the 28th Congress I.U.P.A.C., Vancouver, B.C., Canada, August 1981.
7. G.G. Fuller, The Response of Adsorbed Polymer Chains Subjected to Flow, presented at the AIChE National Meeting, New Orleans, Louisiana, November 1981.
8. G.G. Fuller, A.W. Chow and P.L. Frattini, Flow Birefringence in Time Dependent Flows, presented at the 54th Annual Meeting of the Society of Rheology, Evanston, Illinois, October 1982.
9. G.G. Fuller and A.W. Chow, Flow Birefringence of Rod Like Polymers in Transient Shear Flow, 185th ACS National Meeting, Seattle, Washington, March 1983.
10. G.G. Fuller, A.W. Chow and D. Wallace, Response of Collagen Solutions to Transient Shear by Two-Color Flow Birefringence, presented at the Fifth International Congress on Biorheology, Baden-Baden, FRG, August 1983.
11. G.G. Fuller and P.L. Frattini, The Response of Red Blood Cells to Transient Shear Flows by Phase Modulated Dichroism, presented at the Fifth International Congress on Biorheology, Baden-Baden, FRG, August 1983.
12. G.G. Fuller and J.-J. Lee, Flow-Enhanced Desorption of Adsorbed Polymer Chains, presented at the 186th ACS National Meeting, Washington, D.C., August 1983.
13. G.G. Fuller and P.L. Frattini, Flow-Induced Dichroism and Average Angle of Orientation of Colloidal Suspensions in Transient Shear Flow, presented at the

186th ACS National Meeting, Washington, D.C., August 1983.
14. G.G. Fuller and A.W. Chow, Response of Collagen Solutions to Transient Shear Flow by Two-Color Flow Birefringence, presented at the 55th Annual Meeting of the Society of Rheology, Knoxville, Tennessee, October 1983.
15. G.G. Fuller and P.L. Frattini, Flow-Induced Dichroism and Average Angle of Orientation of Colloidal Suspensions in Transient Shear Flow, presented at the 55th Annual Meeting of the Society of Rheology, Knoxville, Tennessee, October 1983.
16. G.G. Fuller and J.-J. Lee, Flow-Enhanced Desorption of Adsorbed Polymer Chains, presented at the 55th Annual Meeting of the Society of Rheology, Knoxville, Tennessee, October 1983.
17. G.G. Fuller and P.L. Frattini, Dynamics of Suspended Particles in Transient Shear Flow by Phase Modulated Flow Dichroism, 36th Annual Meeting of the Division of Fluid Mechanics, APS, Houston, Texas, November 1983.
18. G.G. Fuller and J.-J. Lee, Polymer Adsorption under Flowing Conditions by Ellipsometry, 58th ACS Colloid and Surface Sciences Symposium, Carnegie-Mellon University, Pittsburgh, Pennsylvania, June 10-13, 1984.
19. G.G. Fuller and P.L. Frattini, Colloidal Solutions in Transient Shear Flow by Phase-Modulated Conservative Dichroism, 58th ACS Colloid and Surface Sciences Symposium, Carnegie-Mellon University Pittsburgh, Pennsylvania, June 10-13, 1984.
20. G.G. Fuller and A.W. Chow, Response of Rigid Collagen Protein Chains in Semi-Dilute Solution to Transient Simple Shear Flow by Two-Color Flow Birefringence, 58th ACS Colloid and Surface Sciences Symposium, Carnegie Mellon University, Pittsburgh, Pennsylvania, June 10- 13, 1984.
21. G.G. Fuller and B.E. Zebrowski, The Effect of Molecular Weight on Transient Birefringence of Concentrated Polymer Solutions, Proceedings of the IXth International Congress on Rheology, Acapulco, Mexico, October 1984.
22. G.G. Fuller and A.W. Chow, Two-Color Flow Birefringence of Collagen Subjected to Transient Shear Flow, Proceedings of the IXth International Congress on Rheology, Acapulco, Mexico, October 1984.
23. G.G. Fuller and J.-J. Lee, Adsorption and Desorption of Flexible Polymer Chains in Flowing Systems, Proceedings of the IXth International Congress on Rheology, Acapulco, Mexico, October 1984.
24. G.G. Fuller and P.L. Frattini, Microscale Dynamics of a Sheared Suspension by Linear Dichroism, Proceedings of the IXth International Congress on Rheology, Acapulco, Mexico, October 1984.
25. G.G. Fuller and A.W. Chow, Dynamics of Rod-Like Polymers Subject to Transient Flows, AIChE Annual Meeting San Francisco, California, November 1984.
26. G.G. Fuller and B.E. Zebrowski, Flow Birefringence Measurements of Concentrated Monodisperse and Bimodal Flexible Chain Solutions in Transient Flow, AIChE Annual Meeting, San Francisco, California, November 1984.
27. G.G. Fuller and P.L. Frattini, Dynamics of Dilute Colloidal Suspensions by Linear Dichroism, AIChE Annual Meeting, San Francisco, California, November 1984.

28. G.G. Fuller and O Ok Park, Transport of Rod-Like Polymers Through Small Channels, AIChE Annual Meeting, San Francisco, California, November 1984.
29. G.G. Fuller and P.L. Frattini, Dynamics of Colloidal Suspensions Subject to Transient Shear Flow, 5th International Physico-Chemical Hydrodynamics Conference, Tel Aviv, Israel, December 1984.
30. G.G. Fuller, B.E. Zebrowski and A.W. Chow, Response of Rod-Like and Flexible Polymer Chains to Transient Flows, 5th International Physico-Chemical Hydrodynamics Conference, Tel Aviv, Israel, December 1984.
31. G.G. Fuller, Optical Methods for Transient Flows, 56th Annual Meeting of the Society of Rheology, Blacksburg, Virginia, February 1985.
32. G.G. Fuller, Optical Methods for Suspension Rheology, European Mechanics Colloquium, No. 191, England, April 1985.
33. G.G. Fuller, Optical Techniques in Suspension Rheology, 5th International Conference on Surface and Colloid Science, Clarkson University, Potsdam, New York, June 1985.
34. G.G. Fuller, Optical Techniques in Suspension Rheology, AIChE National Meeting, Seattle, Washington, August 1985.
35. G.G. Fuller, Optical Techniques in Suspension Rheology, ACS Annual Meeting, Chicago, Illinois, September 1985.
36. G.G. Fuller and A.J. Salem, Small Angle Light Scattering as a Probe of Particle Orientation in Sheared Suspensions, AIChE Annual Meeting, Chicago, Illinois November 1985.
37. G.G. Fuller, Optical Techniques in Suspension Rheology, AIChE Annual Meeting, Chicago, Illinois, November 1985.
38. G.G. Fuller and S.J. Johnson, Optical Rheometry of Particles Suspended in NonNewtonian Fluids, International Conference on Viscoelasticity of Polymeric Liquids Grenoble, France, January, 1986.
39. G.G. Fuller, Optical Rheometry, 2nd Conference of European Rheologists, Prague, Czechoslovakia, June, 1986.
40. G.G. Fuller, S.J. Johnson and A.J. Salem, Optical Rheometry of Dispersions, 10th U.S. National Congress of Applied Mechanics, Austin, Texas, June, 1986.
41. S.J. Johnson and G.G. Fuller, The Motion of Colloid Particles Suspended in Polymeric Liquids, 60th Colloid and Surface Science Symposium, Atlanta, Georgia, June 1986.
42. G.G. Fuller, B. Zebrowski, C. Cathey, and J. Kornfield Electro-hydrodynamics of Colloidal Particles, Annual Meeting of the A.I.Ch.E., Miami Beach, Florida, November. 1986.
43. J.A. Kornfield and G.G. Fuller, Infra-red Dichroism as a Probe of Molecular Dynamics in Polydisperse Polymer Melts, Society of Rheology Winter Meeting, Santa Monica, CA, January, 1987.
44. G.G. Fuller and C.A. Cathey, An Extensional Viscometer for Low Viscosity Liquids at High Strain Rates, Society of Rheology Winter Meeting, Santa Monica, CA, January 1987.
45. S.J. Johnson and G.G. Fuller, The Fluid Dynamics of Colloidal Particles Suspended in Polymeric Liquids, Faraday Discussion No. 83: Brownian Motion, Cambridge, England, April, 1987.

46. G.G. Fuller, Optical Rheometry of Suspensions and Dispersions, Engineering Foundation Conference on Fluid-Particle Interactions, Davos, Switzerland, May 1987.
47. G.G. Fuller and K.S. Wagner, The Kinetics of Electric Field Induced Structure in Concentrated Suspensions, 18th Annual Meeting of the Fine Particle Society, Boston, Massachusetts, August, 1987.
48. J.S. Lee and G.G. Fuller, Development of Couette Flow and Shear Wave Propagation by Flow Birefringence, 59th Annual Meeting of the Society of Rheology, Atlanta, Georgia, October, 1987.
49. G.G. Fuller, Optical Rheometry of Lyotropic Liquid Crystals, 59th Annual Meeting of the Society of Rheology, Atlanta, Georgia, October, 1987.
50. G.G. Fuller, S.J. Johnson, and A.J. Salem, Dynamics of Particles Suspended within a Second Order Fluid, A.I.Ch.E. Annual Meeting, New York, NY, November, 1987.
51. G.G. Fuller and J.S. Lee, The Rayleigh Problem for Viscoelastic Fluids by Spatially Scanned Flow Birefringence, A.I.Ch.E. Annual Meeting, New York New York, November, 1987.
52. G.G. Fuller, The Development of an Instrument for Studying Low Viscosity Materials in Extensional Flow International Conference on Extensional Flow, Chamonix, France, January, 1988.
53. J.A. Kornfield, G.G. Fuller, and D.S. Pearson, Component Dynamics in Binary-Blend Rheology, APS Division of High-Polymer Physics Meeting, New Orleans, Louisiana, March, 1988.
54. G.G. Fuller, P. Moldenaers, and J. Mewis, Conservative Dichroism Measurements of Polymer Liquid Crystal Domain Structure in Flow, APS Division of High-Polymer Physics Meeting, New Orleans, Louisiana, March, 1988.
55. K.J. Mikkelsen, C.W. Macosko, and G.G. Fuller, Opposed Jets: An Extensional Rheometer for Low Viscosity Liquids, Xth International Congress on Rheology, Sydney, Australia, August, 1988.
56. C. A. Cathey and G.G. Fuller, The Mechanical and Optical Response of Low Viscosity Polymeric Liquids in Extensional Flow, Xth International Congress on Rheology, Sydney, Australia, August, 1988.
57. J. A. Kornfield and G.G. Fuller, Infrared Dichroism as a Probe of the Linear Viscoelasticity of Polydisperse Melts, Xth International Congress on Rheology, Sydney, Australia, August, 1988.
58. G. G. Fuller, Particle Orientation Measurements in Magnetic Media by High Speed Polarimetry, Symposium on Particulate Recording Media, Carnegie-Mellon University, Pittsburgh, PA, October 26-27, 1988.
59. G. G. Fuller, P. Moldenaers, and J. Mewis, Domain Structure in Polymer Liquid Crystals Subjected to Flow, A.I.Ch.E. Annual Meeting, Washington, D. C., Nov. 27 - Dec. 2, 1988.
60. C. A. Cathey and G. G. Fuller, Extensional Flow Properties of Flexible Chains, A.I.Ch.E. Annual Meeting, Washington, D. C., Nov. 27 - Dec.2, 1988.
61. W. R. Burghardt and G. G. Fuller, Rheo-optical Studies of Domain Dynamics in Polymer Liquid Crystal Rheology, 60th Annual Meeting of the Society of

Rheology, Gainesville, FL., February 12-16, 1989.
62. C. M. Ylitalo, K. A. Kornfield, and G. G. Fuller, Molecular Weight Dependence of Molecular Relaxation in Bidisperse Melt Rheology, 60th Annual Meeting of the Society of Rheology, Gainesville, FL., February 12-16, 1989.
63. K. Smith and G. G. Fuller, Electric Field-Induced Structure in Dense Colloidal Dispersions, 60th Annual Meeting of the Society of Rheology, Gainesville, FL., February 12-16, 1989.
64. V. Abetz and G. G. Fuller, Two-Color Rotary Polarization Modulation Flow Birefringence, 60th Annual Meeting of the Society of Rheology, Gainesville, FL., February 12-16, 1989.
65. K. Mikkelsen, T. Schweizer, and G. G. Fuller, Opposed Jets Extensional Rheometry on the M1 Standard Fluid, International Conference on Extensional Flow, Combloux, France, March 20-21, 1989.
66. K. Smith, P. Adriani, G. Fuller and A. Gast, "Structural Anistropy of Dense Colloidal Dispersions Subject to Electric Fields", 61st Annual Meeting of the Society of Rheology, Montreal, Quebec, October 21-26, 1989.
67. G. G. Fuller and J.-S. Lee, "Shear Wave Propagation in Polymeric Liquids", AIChE 1989 Annual Meeting, San Francisco, CA, Nov. 5-10, 1989.
68. G. G. Fuller and C. L. Valencia, "Measurements of Orientation Processes in Poling NLO Polymer Films", AIChE 1989 Annual Meeting, San Francisco, CA, Nov. 5-10, 1989.
69. G. G. Fuller and J.-S. Lee, "Shear Wave Propagation in Polymeric Liquids", APS 42nd Annual Meeting of the Division of Fluid Mechanics, NASA Ames Research Center, Palo Alto, CA, Nov. 19-21, 1989.
70. G. G. Fuller, "Optical Rheometry of Polymeric Liquids", Golden Gate Polymer Forum, 1990 Asilomar Conference, Asilomar, CA, March 18-20, 1990.
71. G. G. Fuller and K. Smith, "Electro-hydrodynamics of Colloidal Dispersions", Second World Congress on Particle Technology, Kyoto, Japan, September 19-22, 1990
72. G. G. Fuller, "Optical Rheometry of Dense Suspensions", NSF-DOE Workshop on Flow of Particulates and Fluids, Gaithersburg, MD, October 1-3, 1990.
73. W. R. Burghardt and G. G. Fuller, "The Microstructure of Polymer Liquid Crystals Subject to Transient Flows", 62nd Annual Meeting of the Society of Rheology, Santa Fe, NM, October 21-25, 1990
74. G. G. Fuller and C. M. Ylitalo, "Infrared Polarimetry Studies for Multicomponent Polymer Melts", 62nd Annual Meeting of the Society of Rheology, Santa Fe, NM, October 21-25, 1990.
75. W. R. Burghardt and G. G. Fuller, "The Role of Director Tumbling in Polymer Liquid Crystals", A.I.Ch.E. 1990 Annual Meeting, Chicago, IL, November 11-16, 1990.
76. G. G. Fuller and J. van Egmond, "Flow-induced Phase Separation in Polymer Solutions", A.I.Ch.E. 1990 Annual Meeting, Chicago, IL, November 11-16, 1990.
77. G.G. Fuller, C. Ylitalo and J. Zawada, "Dynamics of Polymer Blends", 201st ACS National Meeting, Atlanta, GA, April 14-19, 1991.
78. G.G. Fuller and C.M. Ylitalo, "Infrared Polarimetry Studies for Multicomponent

Polymer Melts", Prague Meeting on Macromolecules, Prague, Czechoslovakia, July 15-18, 1991.
79. J. van Egmond and G.G. Fuller, "Rheo-Optics of Flow Induced Phase Separation", ACS Annual Meeting, New York, N.Y., August 25-30, 1991.
80. G.G. Fuller, "Extensional Mechanical and Optical Properties of Dilute Polymer Solutions", VIth IFP Research Conference on Exploration-Production, St. Rapha'l, France, September 4-9, 1991.
81. G.G. Fuller and J. van Egmond, "Flow-Induced Phase Separation of Polymer Solutions", International Conference on Dynamics of Polymeric Liquids, Capri, Italy, September 11-14, 1991.
82. J. Zawada, C. Ylitalo and G.G. Fuller, "Component Relaxation Dynamics in Poly(ethylene oxide)-Poly(methyl methacrylate) Blends", AIChE Meeting, Los Angeles, CA, November 17-22, 1991.
83. D. Werner, G.G. Fuller and C.W. Frank, "Interrogation of Polymer Blends under Shear Flow by Small Angle Light Scattering and Excimer Fluorescence", AIChE Meeting, Los Angeles, CA, November 17-22/91.
84. C. Valencia and G.G. Fuller, "Poling of Polymer Films for Integrated Optics Applications", AIChE Meeting, Los Angeles, CA, November 17-22/91.
85. J.A. Zawada and G.G. Fuller, "Component Relaxation Dynamics in Miscible Blends of Poly(ethylene oxide) and Poly(methyl methacrylate), 63rd meeting of the Society of Rheology, Rochester, N.Y., October 20-24, 1991.
86. L.A. Archer, G.G. Fuller and L. Nunnelley, "Dynamics of Polymeric Liquids using Polarization Modulated Laser Raman Scattering", poster presented at the Gordon Research Conference Polymers-West in Ventura, CA, January 6-10, 1992.
87. L.A. Archer and G.G. Fuller, "Polarization Modulated Laser Raman Scattering", presented at the XIth International Congress on Rheology, Brussels, August 1992.
88. D. Wirtz, K. Berend and G.G. Fuller, "Electric Field-induced Structure in Critical Polymer Solutions", poster presented at the XIth International Congress on Rheology, Brussels, August 1992.
89. P. D'Haeme, G.G. Fuller and J. Mewis, "Shear Thickening Effect in Highly Concentrated Colloidal Dispersions", presented at the XIth International Congress on Rheology, Brussels, August 1992.
90. E.L. Meyer and G.G. Fuller, "Aggregate Structures in Water-soluble Polymer Systems", presented at the XIth International Congress on Rheology, Brussels, August 1992.
91. J.W. van Egmond and G.G. Fuller, "Flow-induced Structure and Dynamics of Concentration Fluctuations of Polymer Solutions", presented at the XIth International Congress on Rheology, Brussels, August 1992.
92. D.E. Werner, G.G. Fuller and C.W. Frank, "Flow Induced Phase Transitions for Incompatible Blends", presented at the XIth International Congress on Rheology, Brussels, August 1992.
93. D. Wirtz, K. Berend and G.G. Fuller, "Small Angle Light Scattering, Dichroism and Birefringence Induced by an Electric Field in a Polymer Solution near the Critical Point", AIChE 1992 Annual Meeting, Miami Beach, FL, November 2,

1992.
94. J. van Egmond and G.G. Fuller, "Flow Induced Concentration Fluctuations in a Polymer Solution subject to Extensionsl Flow", AIChE 1992 Annual Meeting, Miami Beach, FL, November 4, 1992.
95. L.A. Archer and G.G. Fuller, "Orientation Dynamics of a Polymer Melt using Polarization Modulated Laser Raman Scattering", AIChE 1992 Annual Meeting, Miami Beach, FL, November 5, 1992.
96. P. D'Haene, J. Mewis and G.G. Fuller, "Scattering Dichroism Measurements of Flow-Induced Structure of a Shear Thickening Suspension", AIChE 1992 Annual Meeting, Miami Beach, FL, November 6, 1992.
97. J. van Egmond and G.G. Fuller, "Simultaneous Small Angle Light Scattering and Polairmetry Measurements on Flow-Induced Phase Separation", The Society of Rheology, 64th Annual Meeting, Santa Barbara, CA, February 1993.
98. J. van Egmond and G.G. Fuller, "An Hydrodynamic Instability in Polymer Solutions due to Coupling of Nonhomogeneity in Concentration and Stress", The Society of Rheology, 64th Annual Meeting, Santa Barbara, CA, February 1993.
99. D. Wirtz, K. Berend and G.G. Fuller, "Structural Dynamics of Concentrated Polymer Solutions in Electric Fields", The Society of Rheology, 64th Annual Meeting, Santa Barbara, CA, February 1993.
100. E.L. Meyer, J. van Egmond and G.G. Fuller, "Extensional Flow-Induced Aggregation in Polymer Systems", The Society of Rheology, 64th Annual Meeting, Santa Barbara, CA, February 1993.
101. Wirtz, K. Berend and G.G. Fuller, "Electric Field Induced Structure and Dynamics in Polymer Solutions and Gels", APS Meeting, Seattle, WA, March 22-26, 1993.
102. J. Lai, E. Meyer and G.G. Fuller, "Structure and Dynamics of Polymer-Polymer Solutions and Liquid Crystalline Polymer Emulsions", 2nd International Discussion Meeting on Relaxations in Complex Systems, Alicante, Spain, July 1993.
103. J.A. Zawada, G.G. Fuller and R.H. Colby, "Component Contributions to the Overall Rheology in 1,4-Polyisoprene/1,2-Polybutadiene Miscible Blends", Society of Rheology, Boston, MA, October 1993.
104. L.A. Archer and G.G. Fuller, "Orientation and Dynamics of Block-copolymer Melts using Laser Raman Scattering", Society of Rheology, Boston, MA, October 1993.
105. J. Lai and G.G. Fuller, "Structure and Dynamics of Polymer-Polymer Solutions under Shear Flow", Society of Rheology, Boston, MA, October 1993.
106. M. Friedenberg, G.G. Fuller, C.W. Frank and C.R. Robertson, "Rheo Optical Studies of Orientational Dynamics in a Polymer Liquid Crystal Monolayer", Gordon Research Conference for Organic Thin Films, Ventura, CA, February 1994.
107. M. Friedenberg, G.G. Fuller, C.W. Frank and C.R. Robertson, "Optical Studies of Monolayer Rheology", 1994 ACS Meeting, Stanford, CA, June 1994.
108. T. Takahashi, J. Vermant, G. G. Fuller, J. Mewis, Simultaneous Mechanical and Optical Measurements of a Polymer Liquid Crystal in Transient Shear, Pacific

Conference on Rheology and Polymer Processing, Kyoto, Japan, September 26-30, 1994.
109. J. Lai and G.G. Fuller, "A Rheo-Optical Study of the Shear Effects on Polymer Blend Solutions", The Society of Rheology 66th Annual Meeting, Philadelphia, PA, October 1994.
110. D.E. Werner, G.G. Fuller and C.W. Frank, "Aparent Phase Transitions in Polymer Blends Induced by Oscillatory Shear Flow", The Society of Rheology 66th Annual Meeting, Philadelphia, PA, October 1994.
111. K. Huang and G.G. Fuller, "Two-Dimensional Raman Scattering: a new Technique for Investigating the Dynamics of Multicomponent Polymer Systems", The Society of Rheology 66th Annual Meeting, Philadelphia, PA, October 1994.
112. M. Friedenberg, G.G. Fuller, C.W. Frank and C.R. Robertson, "Rheo Optical Studies of Orientation Dynamics in Two-Dimensions: Monolayers at the Air-Water Interface", The Society of Rheology 66th Annual Meeting, Philadelphia, PA, October 1994.
113. L. Archer and G.G. Fuller, "Optical and Mechanical Properties of a Star Diblock Copolymer in Oscillatory Shear Flows", 1994 AIChE Meeting, San Francisco, CA, November 13-18, 1994.
114. J. Lai and G.G. Fuller, " Structural Dynamics of a Polymer Blend Solution under Oscillatory Flow", 1994 AIChE Meeting, San Francisco, CA, November 13-18, 1994.
115. M. Friedenberg, G.G. Fuller, C.W. Frank and C.R. Robertson, "Optical Studies of Flow-Orientation and Relaxation in Monolayer Films", 1994 AIChE Meeting, San Francisco, CA, November 13-18, 1994.
116. E.L. Meyer, G.G. Fuller and R.H. Reamey, "Liquid Crystal Droplet Emulsions: Observation of Biconcave Disc Shape", 1994 AIChE Meeting, San Francisco, CA, November 13-18, 1994.
117. K. Huang and G.G. Fuller, "Investigation of Polymer Blend Rheology using Two-Dimensional Raman Scattering", 1994 AIChE Meeting, San Francisco, CA, November 13-18, 1994.
118. M. C. Friedenberg, T. Maruyama, G. G. Fuller, C. W. Frank, C. R. Robertson, "Flow-Induced Orientation and Relaxation in Polymer Monolayers", APS 1995 March Meeting, San Jose, CA, March 20-23, 1995.
119. J. Lai, G. G. Fuller, "Coupling of Viscoelasticity and Structure in Polymer Blend Solutions under Oscillatory Shear Flow", APS 1995 March Meeting, San Jose, CA, March 20-23, 1995.
120. U. Seidel, R. Stadler, G. G. Fuller, "Relaxation Dynamics of Bidisperse Temporary Networks", APS 1995 March Meeting, San Jose, CA, March 20-23, 1995.
121. K. Huang, E. D. Carlson, G. G. Fuller, "Microstructural Dynamics of a Homopolymer Melts Approaching the Mechanical Glass Transition", APS 1995 March Meeting, San Jose, CA, March 20-23, 1995.
122. P.L. Maffetone, M. Grosso, S. Crescitelli, M.C. Friedenberg, G.G. Fuller, C.W. Frank and C.R. Robertson, "Orientation Dynamics of a Polymer Liquid Crystal Monolayer", presented by P.L. Maffetone at the 12th Annual Meeting of the

Polymer Processing Society, Sorrento, Italy, May 27-31, 1996.
123. M.C. Friedenberg, P.L. Maffetone, G.G. Fuller, C.W. Frank and C.R. Robertson, "Interfacial Dynamics of Polymer Monolayers", presented at the IUPAC Macro Seoul '96 Conference, Seoul, Korea, August 4-9, 1996.
124. T. Maruyama. J. Lauger, P.L. Maffetone, G.G. Fuller, C.W. Frank and C.R. Robertson, "Interfacial Rheology of Monolayers" presented at the XIIth International Congress on Rheology, Quebec, Canada, August 18-23, 1996.
125. E. Wheeler, P. Izu, G. Fuller, "Rheo-optical Investigation of the Dynamics of Wormlike Micelles", XIIth International Congress on Rheology, Quebec City, Quebec, Canada, August 18- 23, 1996.
126. T. Maruyama, G. Fuller, C. Frank, C. Robertson, "Interfacial Rheology of Monolayers", XIIth International Congress on Rheology, Quebec City, Quebec, Canada, August 18-23, 1996.
127. T. Maruyama, G. Fuller, C. Frank, C. Robertson, "Fluid Dynamics of Langmuir Monolayers", First International Workshop on "Thin Organic Films: properties and applications",Gallipoli, Italy, September 23-26, 1996.
128. E. K. Wheeler, P. Izu, G. G. Fuller, "A Rheo-optical Investigation of Wormlike Micelles", The Society of Rheology 67th Annual Meeting, Sacramento, CA, October 8-12, 1995.
129. T. Maruyama, G. Fuller, C. Frank, C. Robertson, "Dynamics of Liquid Crystalline Monolayers", The Society of Rheology 67th Annual Meeting, Sacramento, CA, October 8-12, 1995.
130. G. Fuller, T. Maruyama, C. Frank, C. Robertson, "Fluid Dynamics of Langmuir Films", The American Physical Society, Division of High Polymer Physics Meeting, St. Louis, MO, March 18-21, 1996.
131. G.G. Fuller, M. Friedenberg, P. Maffetone, M. Grosso, "Dynamics of Two Dimensional Polymer Liquid Crystals", 1996 AIChE Meeting, Chicago, IL, November 10-15, 1996.
132. T. Maruyama, J. Lauger, G. Fuller, C. Frank, C. Robertson, "Interfacial Dynamics of Monolayers", 1996 AIChE Meeting, Chicago, IL, November 10-15, 1996.
133. G.G. Fuller, C.R. Robertson, C.W. Frank, J. Laeuger, T. Maruyama, "Fluid Dynamics of Langmuir Monolayers", 1996 Materials Research Society Fall Meeting, Boston, MA, December 2-6, 1996.
134. Eric D. Carlson, Toshitsugu Terakawa, Gerald G. Fuller, Mark T. Krejchi, Chirag Shah and Robert M. Waymouth, "Rheological Investigation of Stereoblock Polypropylene", The Society of Rheology 68th Annual Meeting, Galveston, TX, February 17-20, 1997.
135. Toshitsugu Terakawa and Gerald G. Fuller, "Shear-Induced Structure of Rubber Toughened Styrenic Polymer using Sals", The Society of Rheology 68th Annual Meeting, Galveston, TX, February 17-20, 1997.
136. Elizabeth K. Wheeler, Peter Fischer and Gerald G. Fuller, "Time-Periodic Flow Induced Structures in Visco-Elastic Surfactant Solutions", The Society of Rheology 68th Annual Meeting, Galveston, TX, February 17-20, 1997.
137. Carlton F. Brooks, Channing R. Robertson, Curtis W. Frank and Gerald G. Fuller, "Magnetic Rod Surface Stress Rheometer", The Society of Rheology

68th Annual Meeting, Galveston, TX, February 17-20, 1997.
138. T. Maruyama, J. Lauger, G. G. Fuller, C. W. Frank and C. R. Robertson, "Flow-Induced Orientation of a Fatty Acid Monolayer", The Society of Rheology 68th Annual Meeting, Galveston, TX, February 17-20, 1997.
139. T. Maruyama, G. G. Fuller and P.-L. Maffettone, "Extensional Flow of a Two-Dimensional Nematic", The Society of Rheology 68th Annual Meeting, Galveston, TX, February 17-20, 1997.
140. G. Fuller, Dynamics of Complex Monolayers, ACS Spring Meeting, San Francisco, CA , April 13 - 18, 1997.
141. G. Fuller, Optical Rheometry of Dense Suspensions, International Fine Particle Research Institute, Osaka, Japan, June 8 - 13, 1997.
142. G. Fuller, Interfacial Rheometry of Complex Interfaces, International Union of Theoretical and Applied Mechanics, The University of Sydney, Sydnew, Australia, July 20 - 25, 1997.
143. T. Maruyama, P. Fishcer, G. Fuller, Dynamics of Polymer Monolayers, Second Pacific Rim Conference on Rheology, Melbourne, Australia, July 27 - 31, 1997.
144. C. Brooks, G. Fuller, C. Frank, C. Robertson, Interfacial Stress Rheometer, 8th International Conference on Organized Molecular Films, Asilomar, CA, August 24 - 29, 1997.
145. E.K. Wheeler, P. Fischer, G. Fuller,Rheo-optical investigations of viscoelastic micellar solutions, 69th Annual Meeting of the Society of Rheology, Columbus, OH October 19-23, 1997.
146. P. Fischer, A. Ritcey, G. Fuller, Flow Properties of "Hairy Rod" Monolayers formed by Cellulose Derivatives with and with out attached Chromophores, 69th Annual Meeting of the Society of Rheology, Columbus, OH October 19-23, 1997.
147. C. Brooks, J. Hur, G. Fuller, C. Frank, C.Robertson, Mechanical Rheometry Study of a Polymer Liquid Crystal Monolayer, 69th Annual Meeting of the Society of Rheology, Columbus, OH October 19-23, 1997.
148. E. Carlson, G. Fuller, R. Waymouth, Rheo-optical Study of Elastomeric Polypropylene, 69th Annual Meeting of the Society of Rheology, Columbus, OH October 19-23, 1997.
149. K. Yim, G. fuller, Flow-Induced Orientation in a Two Dimensional POlymer Solution, AIChE 1997 Annual Meeting, Los Angeles, November 16-21, 1997.
150. C. Brooks, J. Hur, G. Fuller, C. Frank, C. Robertson, Surface Rheological Study of a Polymer Liquid Crystal Monolayer, AIChE 1997 Annual Meeting, Los Angeles, November 16-21, 1997.
151. G. Fuller, The Dynamics of Complex Fluid Interfaces, AIChE 1997 Annual Meeting, Los Angeles, November 16-21, 1997.
152. M. Lipp, C. Brooks, G. Fuller, J. Zasadzinski, Direct Measuremnt of the Effect of SP-B Protein on the Shear Viscosity of Model Lung Surfactant Monolayers, AIChE 1997 Annual Meeting, Los Angeles, November 16-21, 1997.
153. E. Wheeler, P. Fischer, G. Fuller, E. Shaqfeh, Flow-Induced Strcutres and Instabilites in Viscoelastic Micellar Solutions, AIChE 1997 Annual Meeting, Los Angeles, November 16-21, 1997.
A. Mosler, E. Shaqfeh, G. Fuller, An Experimental Investigation of Drop Breakup

in the Flow through a Fixed Bed of Fibers, AIChE 1997 Annual Meeting, Los Angeles, November 16-21, 1997.
154. E. Carlson, G. Fuller, R. Waymouth, Stereoblock Polypropylene Rheology, AIChE 1997 Annual Meeting, Los Angeles, November 16-21, 1997.
155. D. J. Olson, G. G. Fuller, Contraction/Expansion Flows of Non-Newtonian Monolayers, Society of Rheology Annual Meeting, Monterey, CA, Oct. 4-8, 1998.
156. K.-S. Yim, G. G. Fuller, C. W. Frank, C. R. Robertson, Isotropic-Nematic Transition in a Two-Dimensional Polymer Solution, Society of Rheology Annual Meeting, Monterey, CA, Oct. 4-8, 1998.
157. C. F. Brooks, J. Thiele, G. G. Fuller, C. W. Frank, W. Knoll, D. O'Brien, Surface Rheological Study of a Polymerizable Phospholipid Monolayer, Society of Rheology Annual Meeting, Monterey, CA, Oct. 4-8, 1998.
158. Structure and dynamics of polymer-tethered phospholipid membranes, Frank CW, Naumann C, Shen W, Brooks C, Fuller GG, Knoll W, ACS Meeting, New Orleans, LA, March 21, 1999.
159. G. Fuller, Dynamics of Complex, Nematic Interfaces, Eurorheo 99-1, Sophia-Antipolis, France, May 3-7, 1999.
160. Measurement of Particle Shape Distributions (Invited Poster), International Fine Particle Research Institute, Sommerset, NJ, June 9, 1999.
161. Flow-induced orientation of a flexible-chain polymer monolayer, David J. Olson, Gerald G. Fuller, Joke Hagting, and Arend Jan Schouten, 71st Annual Meeting of the Society of Rheology, Madison, WI, Oct. 17-21, 1999.
162. Study of rheological transition by photo-induced isomerization on Langmuir monolayers of azobenzene derivative, Kang Sub Yim, Gerald G. Fuller, and Curtis W. Frank, 71st Annual Meeting of the Society of Rheology, Madison, WI, Oct. 17-21, 1999.
163. PO35 First observation of the isotropic-nematic phase transition temperature of liquid crystalline polymers on two-dimensional Langmuir monolayers, Kang Sub Yim, Gerald G. Fuller, and Claus D. Eisenbach, 71st Annual Meeting of the Society of Rheology, Madison, WI, Oct. 17-21, 1999.
164. SF2 Birefringence and stress in uniaxial extension of polymer solutions, Tam Sridhar, D. A. Nguyen, and Gerald G. Fuller, 71st Annual Meeting of the Society of Rheology, Madison, WI, Oct. 17-21, 1999.
165. Surface rheology of a dendritic monolayer, J. Patrick Kampf, Carlton F. Brooks, Curtis W. Frank, Gerald G. Fuller, Craig Hawker, and Eva E. Malmström, 71st Annual Meeting of the Society of Rheology, Madison, WI, Oct. 17-21, 1999.
166. Contraction Flows of NonNewtonian Interfaces, G. G. Fuller and D. J. Olson, AIChE 1999 Annual Meeting, Dallas, TX, Oct. 31 - Nov. 5, 1999.
167. Order/Disorder Transitions in Polymer Interfaces, G. G. Fuller, K. S. Yim, AIChE 1999 Annual Meeting, Dallas, TX, Oct. 31 - Nov. 5, 1999.
168. Measurement of Interfacial Stress and Order in Flowing, Complex Interfaces, C. F. Brooks, G. G. Fuller, K. S. Yim, AIChE 1999 Annual Meeting, Dallas, TX, Oct. 31 - Nov. 5, 1999.
169. Non-newtonian Flows in 2D, D. Olson and G. Fuller, ACS Spring Meeting, San Francisco, Mar. 26-30, 2000.

170. Nematic Transitions in Polymer Monolayers, K. Yim, ACS Spring Meeting, San Francisco, Mar. 26-30, 2000.
171. Synthesis of well-defined long chain-branched polyolefins, Wiyatno W, Fox PA, Waymouth RM, Fuller GG, Hawker CJ, ACS Spring Meeting, San Francisco, Mar. 26-30, 2000.
172. Surface rheological transitions in Langmuir films of bicompetitive fatty acids, K. S. Yim, G. G. Fuller, ACS National Meeting, San Francisco, May 2000.
173. Dynamics of DNA adsorbed to fluid interfaces, D.J. Olson, J. M. Johnson, G. G. Fuller, S. G. Boxer, ACS National Meeting, San Francisco, May 2000.
174. Recent developments in patterning, manipulating, and interrogating supported bilayer membranes, Boxer SG, Kung L, Hovis J, Ajo C, Johnson J, Olson D, Fuller GG, ACS National Meeting, Washington, DC, Aug. 2000
175. Dynamics of Magnetic Fluids Subject to Rotating Magnetic Fields, S. Melle, G. Fuller, M. Rubio, XIIIth International Congress of Rheology, Cambridge, U. K., August 20-25, 2000
176. 2D Electrophoresis of DNA, D. Olson, G. Fuller, J. Johnson, S. Boxer, XIIIth International Congress of Rheology, Cambridge, U. K., August 20-25, 2000
177. Rheology of Complex Interfaces, G. Fuller, XIIIth International Congress of Rheology, Cambridge, U. K., August 20-25, 2000
178. Aggregation and Orientation of Magnetic Particles in Rotating Fields, S. Melle, G. Fuller, and M. Rubio, AIChE Annual Meeting, November 12-17, Los Angeles, CA.
179. Surface Gelation of Gelatin Solutions, K. Lim and G. Fuller, AIChE Annual Meeting, November 12-17, Los Angeles, CA.
180. 2D Electrophoresis of DNA, D. Olson, G. Fuller, J. Johnson, S. Boxer, AIChE Annual Meeting, November 12-17, Los Angeles, CA.
181. 2D electrophoresis and flow of DNA chains, Gerald G. Fuller, David J. Olson, and Ed Stancik, Society of Rheology, Hilton Head, SC, Feb 11 - 15, 2001.
182. Fluorescence microscopy experiments and Brownian dynamics simulations of flow behavior of DNA molecules confined to two dimensions, David J. Olson, Prateek D. Patel, Eric S. G. Shaqfeh, Steven G. Boxer, and Gerald G. Fuller, Society of Rheology, Hilton Head, SC, Feb 11 - 15, 2001.
183. Rheo-Optics and X-ray Scattering Study of Elastomeric Polypropylene, W. Wiyatno, J. Pople, A. P. Gast, R. M. Waymouth, and G. G. Fuller, ACS National Conference, Chicago, Aug 28, 2001
184. Mobility of DNA on cationic supported lipid bilayers, Marton A, Stancik EJ, Olson DJ, Johnson JM, Boxer SG, Fuller GG, ACS National Conference, Chicago, Aug 28, 2001.
185. Study of uniaxial extensional flow and morphology of elastomeric polypropylenes, Gerald G. Fuller, Willy Wiyatno, Holger Schonherr, John Pople, Robert M. Waymouth, Curtiss Frank, and Alice Gast, 73rd Annual Meeting of the Society of Rheology, October 21 - 25, 2001, Bethesda, MD.
186. Two-dimensional suspensions: Dynamics and rheology, Gerald G. Fuller, Alex Laschitsch, Martin Widenbrant, Ed Stancik, and Jan Vermant, 73rd Annual Meeting of the Society of Rheology, October 21 - 25, 2001, Bethesda, MD.
187. Flow-induced structures and rheology of concentrated latex suspensions, J.

Vermant, H. Hoekstra, J. Mewis, E. Stancik, A. Laschitsch, G.G. Fuller, Jülich Soft Matter Days 2001, 13 - 16 November , 2001 Congrescentrum Rolduc, Kerkrade, NL
188. Fibrous clay gels: extensional flow properties. Dichroism and SALS measurements, Frédéric Pignon, Albert Magnin, Jean-Michel Piau, Gerald G. Fuller, 2nd International Conference on Self-Assembled Fibrillar Networks, Autrans, France, November 24 - 28, 2001.
189. Two-dimensional suspensions : dynamics and rheology, J. Vermant, H. Hoekstra, J. Mewis, G G. Fuller, Annual Meeting of the Dutch Rheological Society, DSM Research, Geleen, The Netherlands, April 17, 2002.
190. Phase behavior of silicone copolymers swollen with water and oil. Hill RM, Fuller GG, Anseth J, 224th ACS National Meeting, August 18-22, 2002, Boston, MA
191. Orientation dynamics and crystallization of elastomeric polypropylenes. Fuller GG, Wiyatno W, Pople J, Gast AP, Waymouth R, ACS National Meeting, April, 2002, Orlando, FL.
192. Interfacial rheology of graft-type siloxane surfactants, Jay W. Anseth, Randal M. Hill, and Gerald G. Fuller, Society of Rheology Annual Meeting, Minneapolis, MN, Oct. 2002.
193. Complex fluid interfaces, Gerald G. Fuller, Society of Rheology Annual Meeting, Minneapolis, MN, Oct. 2002.
194. The structure and dynamics of particle monolayers at a liquid-liquid interface subjected to flow, Edward J. Stancik, Martin J. O. Widenbrant, Grant T. Gavranovic, Alex T. Laschitsch, Jan Vermant, and Gerald G. Fuller, Society of Rheology Annual Meeting, Minneapolis, MN, Oct. 2002.
195. Flow Induced Structure and Dynamics of Particle Monolayers Trapped at a Liquid-Liquid Interface, E. Stancik, M. Widenbrant, G. Gavranovic, A. Laschitsch, J. Vermant, G. Fuller, AIChE Annual Meeting, Indianapolis, IN, Nov. 2002.
196. Connect the Drops, E. Stancik, G. Fuller, AIChE Annual Meeting, San Francisco, Nov., 2003.
197. Rheology of Complex Siloxane Interfaces, J. Anseth, R. Hill, G. Fuller, AIChE Annual Meeting, Indianapolis, IN, Nov. 2002.
198. Interfacial Rheology of Lung Surfactants, J. Anseth, P. Kao, D. Upadhyay, G. Fuller, AIChE Annual Meeting, San Francisco, Nov., 2003.
199. Shear and Dilational Rheology of Protein Monolayers, E. Freer, K.S. Yim, G. Fuller, C. Radke, AIChE Annual Meeting, San Francisco, Nov., 2003.
200. Particle Laden Interfaces, E. Stancik, G. Fuller, AIChE Annual Meeting, San Francisco, Nov., 2003.
201. Surface gels of polyelectrolytes and surfactants, C. Monteux, O. Anthony, G. Fuller, C. Williams, V. Bergeron, MACRO 2004, 40th IUPAC World Polymer Congress, Paris, France, July 4-9, 2004.
202. Complex Fluid Interfaces, G. Fuller, International Congress on Rheology, Seoul, Korea, August 23 – 26, 2004.
203. Interfacial Rheology of Polymer Monolayers, G. Gavonovic, G. Fuller, International Congress on Rheology, Seoul, Korea, August 23 – 26, 2004.

204. Tracking Vesicles Bound to Phospholipid Monolayers, M. Wildenbrandt, G. Fuller, International Congress on Rheology, Seoul, Korea, August 23 – 26, 2004.
205. Particle Stabilized Emulsions, G. G. Fuller, E. Stancik, AIChE Annual Meeting, Austin TX, Nov. 7-12, 2004.
206. Two-Dimensional Gelation of Lung Surfactant Monolayers, J. Anseth, G. G. Fuller, P. Kao, D. Upadhyay, AIChE Annual Meeting, Austin TX, Nov. 7-12, 2004.
207. Surface Diffusion of Lipid Vesicles Attached to Membranes, M. Widenbrandt, G. Fuller, AIChE Annual Meeting, Austin TX, Nov. 7-12, 2004.
208. Two-Dimensional Polymer Melts, G. Gavranovic, J. Deutsch, G. Fuller, AIChE Annual Meeting, Austin TX, Nov. 7-12, 2004.
208. A. Goffin, J. Anseth, G. Fuller, D. Upadhyay, P. Kao, Viscoelasticity of lung surfactant responding to environmental stress, Soc. Rheology Annual Meeting, Lubbock, TX, Feb. 13-17, 2005.
209. M. Widenbrant, G. Fuller, Using single lipid tracking to investigate Langmuir monolayer properties, Soc. Rheology Annual Meeting, Lubbock, TX, Feb. 13-17, 2005.
210. G. Gavranovic, J. Deutsch, G. Fuller, Polymer films at the air/water interface: Rheology and simulation, Soc. Rheology Annual Meeting, Lubbock, TX, Feb. 13-17, 2005.
211. S. Melle, M. Lask, G. Fuller, Magnetic emulsions with tunable stability, Soc. Rheology Annual Meeting, Lubbock, TX, Feb. 13-17, 2005.
208. A. Goffin, J. Anseth, G. Fuller, D. Upadhyay, P. Kao, Gelation of lung surfactant responding to environmental stress, European Soc. Rheology, Grenoble, France, April 18-21, 2005.
209. M. Widenbrant, G. Fuller, Single lipid tracking of Langmuir monolayer properties, European Soc. Rheology, Grenoble, France, April 18-21, 2005.
210. G. Gavranovic, J. Deutsch, G. Fuller, Polymer melts at the air/water interface: Rheology and simulation, European Soc. Rheology, Grenoble, France, April 18-21, 2005.
211. G. Fuller, Solid-stabilized emulsions, European Soc. Rheology, Grenoble, France, April 18-21, 2005.
212. . Solid Stabilized Emulsions, Xu, H., Kirkwood, J., Fuller, G., Annual Meeting of the AIChE, Cincinnati, OH, October 30 – September 3, 2005.
213. Xu, H., Kirkwood, J, Fuller, G. Rheology of Particle-Laden Interfaces, Annual Meeting of the Society of Rheology, Vancouver, Canada, October 16-20, 2005.
214. Basavaraj, M. G., Fuller, G. G., Vermant, J., Packing, Flipping, and Buckling Transitions in Compressed Monolayers of Ellipsoidal Latex Particles, Annual Meeting of the Society of Rheology, Vancouver, Canada, October 16-20, 2005.
215. Golemanov, K., Kurtz, R., Fuller, G., Interfacial Rheology of Mixed Fatty Alcohol Monolayers, Annual Meeting of the Society of Rheology, Vancouver, Canada, October 16-20, 2005.
216. Xu, Hui, Kirkwood, J.,, Fuller, G., Buckling of Particle-Laden Fluid Interfaces, Materials Research Society, San Francisco, CA, April 17-20, 2006.
217. Xu, H. Kirkwood,, J., Fuller, G., Two Dimensional Polymer Melts and Glasses, Annual European Rheology Conference, Hersonisos, Crete, Greece, April 27-29, 2006.
218. Gavranovic, G., Fuller, G., Polymers in Two Dimensions: Spanning Solutions, Melts, and Glasses, International Workshop on Mesoscale and Multiscale Description of

Complex Fluids, Prato, Italy, July 5-8, 2006.
219. Wong, A., Miller, R., Fuller, G., Orientational Dynamics of Polydiacetylene Monolayers, Annual Meeting of the Society of Rheology, Portland, ME, October 8-12, 2006.
220. Gravranovic, G., Fuller, G., Effects of Temperature and Chemical Modification on Polymer Langmuir Films, Annual Meeting of the Society of Rheology, Portland, ME, October 8-12, 2006.
221. J. Kirkwood, G. Fuller, Amyloid-protein interactions with phospholipid membranes, AIChE Annual Meeting, San Francisco, CA, Nov. 12-16, 2006.
222. H. Xu, J. Kirkwood, G. Fuller, Buckling Transitions in Solid Stabilizing Emulsions, AIChE Annual Meeting, San Francisco, CA, Nov. 12-16, 2006.
223. M. Widenbrandt, G. Fuller, Lipid-Induced beta-Amyloid Peptide Assemblage and Fragmentationm, AIChE Annual Meeting, San Francisco, CA, Nov. 12-16, 2006.
224. A. Goffin, G. Fuller, Interfacial Flow Processing of Collagan Monolayers, AIChE Annual Meeting, San Francisco, CA, Nov. 12-16, 2006.
225. R. Kurtz, G. Fuller, Structure and Dynamics of mixures of straight and branched chain fatty acids, AIChE Annual Meeting, San Francisco, CA, Nov. 12-16, 2006.
226. A. Wong, G. Fuller, Interfacial Flow Processing of Organic Semiconductors, AIChE Annual Meeting, San Francisco, CA, Nov. 12-16, 2006.
227. J. Kirkwood, J. Rajadas, G. Fuller, Coupling of cell orientation to alignment of collagen substrates, Annual Meeting of the Society of Rheology, Salt Lake City, UT, Oct. 7-11, 2007.
228. R. Kurtz, M. Toney, A. Lange, G. Fuller, Interfacial Dynamics of Straight-Chain and Branched Hexadecanol and Eicosanol Mixtures, AIChE Annual Meeting, SLC, Nov. 4-8, 2007
229. J. Kirkwood, A. Goffin, G. Fuller, Deposition Of Oriented Collagen From A Nematic State: Orienting Fibroblasts, AIChE Annual Meeting, SLC, Nov. 4-8, 2007
230. S. Nishimura, H. Kettelson, G. Fuller, Development Of An Interfacial Rheological Model For Identification Of Stable Tear Films, AIChE Annual Meeting, SLC, Nov. 4-8, 2007
231. D. Leiske, G. Fuller, Use Of An Interfacial Tensiometer To Measure Response Of A Model Tear Film Under Extensional Strain, AIChE Annual Meeting, SLC, Nov. 4-8, 2007.
232. D. Leiske, G. Fuller, Use Of An Interfacial Tensiometer To Measure Response Of A Model Tear Film Under Extensional Strain, Association for Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL, May, 2008.
230. D. Leiske, G. Fuller, Development of an interfacial extensional rheometer with applications in model tear films, International Congress on Rheology, Monetery, CA, August 3-8, 2008.
231. J. Kirkwood, G. Fuller, Flow induced orientation of cholesteric collagen, a useful substrate for controlling cell orientation, International Congress on Rheology, Monetery, CA, August 3-8, 2008.
232. A. Goffin, G. Fuller, Interfacial flow processing of biological molecules, International Congress on Rheology, Monetery, CA, August 3-8, 2008.
233. Kristin Sommer, G. Fuller, Flow-induced morphologies of highly concentrated collagen solutions, International Congress on Rheology, Monterey, CA, August 3-8,

2008.
234. D. Auguste, J. Kirkwood, J. Kohn, G. Fuller, R. Prud'homme, Surface Rheology of Hydrophobically-Modified PEG Polymers Associating with a Phospholipid Monolayer at the Air-Water Interface, AIChE Annual Meeting, Philadelphia, Nov. 15-21, 2008.
235. Y. Shenghan, E. Shaqfeh, G. Fuller, An investigation of the collective behavior of colloidal particles trapped at a fluid-fluid interface, Annual Meeting of the Society of Rheology, Madison, WI, Oct. 18-22, 2009.
236. C. Anderson, E. Lai, G. Fuller, Oriented matrices of collagen for directed cellular growth, Annual Meeting of the Society of Rheology, Madison, WI, Oct. 18-22, 2009.
237. T. Hsu, G. Fuller, Fluid mechanics of rinsing flows, Annual Meeting of the Society of Rheology, Madison, WI, Oct. 18-22, 2009.
238. C. Wu, G. Fuller, Oriented monolayers of single-walled carbon nanotubes using interfacial flow processing, Annual Meeting of the Society of Rheology, Madison, WI, Oct. 18-22, 2009.
239. C. Anderson, E. Lai, G. Fuller, Oriented matrices of collagen for directed cellular growth, Annual Meeting of the AIChE, Nashville, TN, Nov. 10, 2009.
240. T. Hsu, G. Fuller, Fluid mechanics of rinsing flows, Annual Meeting of the AIChE, Nashville, TN, Nov. 11, 2009.

241. D. Leiske, G. Fuller, Interfacial Rheology of the Tear Film, 6th Annual European Rheology Conference, April 7-9, 2010, Göteborg – Sweden
242. T. Hsu, C. Frank, G. Fuller, Particle Removal: Turning Liquids into Soft Adhesives, 6th Annual European Rheology Conference, April 7-9, 2010, Göteborg – Sweden
243. Interfacial Rheology of the Meibomian Lipid Layer, 6th International Conference on the Tear Film and Ocular Surface, Florence, Italy, September 23-25, 2010.
244. Dynamic Contract Angle of Drops Supporting Monolayers of Meibomian Lipids, 6th International Conference on the Tear Film and Ocular Surface, Florence, Italy, September 23-25, 2010.
245. A Stress Rheometer for Living Mammalian Cells, C. Anderson, G. Fuller, Soc. Rheology Annual Mtg., Santa Fe, NM, Oct. 24-28, 2010.
246. Interfacial Rheology and Stability of the Tear Film, D. Leiske, G. Fuller, Soc. Rheology Annual Mtg., Santa Fe, NM, Oct. 24-28, 2010.
247. Rinsing Flows of Complex Liquids, T. Hsu, T. Walker, C. Frank, G. Fuller, Soc. Rheology Annual Mtg., Santa Fe, NM, Oct. 24-28, 2010.
248. Removal of Particles From Surfaces Using Non-Newtonian Fluids, T. Hsu, T. Walker, C. Frank, G. Fuller, A.I.Ch.E. Ann. Mtg., Salt Lake City, Nov. 2010.
249. Viscoelastic and Structural Changes of Human Meibomian Lipids with Temperature, D. Leiske, G. Fuller, A.I.Ch.E. Ann. Mtg., Salt Lake City, Nov. 2010.
250. Thin Film Formation of Silica Nanoparticle/Lipid Composite Films at the Fluid–Fluid Interface, M. Maas, G. Fuller, A.I.Ch.E. Ann. Mtg., Salt Lake City, Nov. 2010.
251. Rinsing Flows of Non-Newtonian Fluids, T. Walker, T. Hsu, G. Fuller, APS Div. Fluid Dynamics, Long Beach, Nov. 2010.
252. Interfacial Rheology of Monoclonal Antibody Solutions, M. Maas, G. Fuller, ACS Meeting, March 27-31, 2011 in Anaheim, California.
253. Porous media model and collective behaviour of colloidal particles trapped at a

fluidic interface, S. Yan, G. Fuller, E. Shaqfeh, Society of Rheology Meeting, Cleveland, OH, October 10-13, 2011.
254. Bulk and interfacial rheology of the tear film, L. Rosenfeld, D. Leiske, G. Fuller, Society of Rheology Meeting, Cleveland, OH, October 10-13, 2011.
255. Interfacial shear rheological behaviors of natural silk fibroin, X. Qiao, G. Fuller, Society of Rheology Meeting, Cleveland, OH, October 10-13, 2011.
256. Matrix-induced alignment and shear flow: effects on endothelial cells, E. Lai, M. Bynum, A. Dunn, G. Fuller, Society of Rheology Meeting, Cleveland, OH, October 10-13, 2011.
257. Rinsing flows using non-Newtonian fluids, T. Walker, T. Hsu, G. Fuller, Society of Rheology Meeting, Cleveland, OH, October 10-13, 2011.
258. Matrix-Induced Alignment and Shear Flow: Effects On Endothelial Cells, E. Lai, M. Bynum, A. Dunn, G. Fuller, AIChE Meeting, Minneapolis, MN, October 16-20, 2011.
259. Bulk and interfacial rheology of the tear film, L. Rosenfeld, D. Leiske, G. Fuller, AIChE Meeting, Minneapolis, MN, October 16-20, 2011.

Invited Seminars

1. Light Scattering and Flow Birefringence Studies of Flow Induced Macromolecular Deformation and Orientation in Solution, University of Wisconsin, Madison, Wisconsin, April, 1979.
2. Dynamics of Polymer Solutions Subjected to a Wide Range of Kinematic Conditions, Bell Telephone Laboratories, Murray Hill, New Jersey, October, 1980.
3. Dynamics of Polymer Solutions Subjected to a Wide Range of Kinematic Conditions, Raychem Corporation, Menlo Park, California, December, 1980.
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10. Dynamics of Dilute Suspensions Subject to Transient Flows by Conservative Dichroism, Department of Chemical Engineering, University of Delaware, Newark, Delaware, October 20, 1983.
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New York, October 25, 1983.
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15. Optical Methods in Micro-Rheology, Department of Chemical Engineering, University of Arizona, Tucson, Arizona, March 27, 1984.
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17. Optical Methods in Micro-Rheology, Celanese Research Laboratories, Summit, New Jersey, June 8, 1984.
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19. Dynamics of Iron Oxide Suspensions Subjected to Transient Flows Using Conservative Dichroism, IBM Research San Jose, California, August 15, 1984.
20. Optical Methods in Rheology, Department of Chemical Engineering, University of California, Davis, California, February 11, 1985.
21. Optical Methods in Rheology, AT&T Bell Laboratories, Murray Hill, New Jersey, March 1, 1985.
22. Optical Methods in Suspension Rheology, Laboratoire d'Aerothermique, C.N.R.S., Meudon, France, March 25, 1985.
23. Optical Methods in Suspension Rheology, Polymer and Colloid Laboratory, University of Bristol, Bristol England, March 27, 1985.
24. Optical Methods in Suspension Rheology, Department of Applied Mathematics, University College of Wales, Aberystwyth, Wales, March 29, 1985.
25. Optical Rheometry, American Cyanamid Research Laboratories, Stamford, Connecticut, August, 1985.
26. Optical Methods for Polymeric and Colloidal Liquid Fluid Dynamics, Dow Chemical Research Laboratories, Midland, Michigan, September, 1985.
27. Optical Rheometry, Owens-Corning Technical Center, Granville, Ohio, November 1985.
28. Optical Rheometry of Particles Suspended in Non Newtonian Liquids, Department of Chemical Engineering, University of Wisconsin, Madison, Wisconsin, February, 1986.
29. Flow Induced Particle Orientations by Optical Rheometry, 3M Center, St. Paul, Minnesota, February 1986.
30. Optical Rheometry of Colloidal and Polymeric Liquids, Eastman Kodak Company, Rochester, New York, May, 1986.
31. Optical Rheometry of Multicomponent Liquids, Department of Chemical Engineering, CALTECH, Pasadena, California October, 1986.
32. Optical Rheometry of Polymeric and Colloidal Liquids, Department of

Chemical Engineering, University of Pennsylvania, Philadelphia, Pennsylvania, February 1987.
33. Orientation of Colloidal Particles in Flowing Polymeric Liquids, Dupont Experimental Station, Wilmington, Delaware, February, 1987.
34. Optical Rheometry, Department of Chemical Engineering University of Delaware, Newark, Delaware, March, 1987.
35. Optical Rheometry, Fluid Mechanics Group, University of Toronto, Toronto, Ontario, April, 1987.
36. Optical Rheometry of Liquid Crystal Domain Structure, Department of Chemical Engineering, University of Leuven, Leuven, Belgium, May, 1987.
37. Optical Rheometry of Liquid Crystal Domain Structure Department of Chemical Engineering, VPI, Blacksburg, Virginia, May, 1987.
38. Orientation of Colloidal Particles in Polymeric Liquids Subjected to Flow, Department of Chemical Engineering, Cornell University, Ithaca, New York, June, 1987.
39. Guest Lecturer in Optical Rheometry, Rheology Short Course, University of Minnesota, Minneapolis, Minnesota, August, 1987.
40. Optical Rheometry of Polymeric Liquids, Dupont Research and Development, Brevart, North Carolina, March, 1988.
41. Rheo-optics of Polymeric and Colloidal Liquids, Department of Chemical Engineering, University of California, Berkeley, CA, September 12, 1988.
42. Rheo-optics of Bidisperse Polymer Melts, Institute for Chemical Research, Kyoto University, Kyoto, Japan, October 3, 1988.
43. Domain Structure of Polymer Liquid Crystals, Department of Polymer Chemistry, Kyoto University, Kyoto, Japan, October 4, 1988.
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45. Extensional Flow Properties of Flexible and Rigid Polymer Chains, Department of Mechanical Engineering, Niigata University, Niigata, Japan, October 7, 1988.
46. Flow Induced Structure in Dense Dispersions of Colloidal Spheres, Department of Physics, Tokyo Metrolpolitan University, Tokyo, Japan, October 11, 1988.
47. Determination of Liquid Crystalline Domain Size and Anisotropy, Dow Chemical, Research Center, Walnut Creek, CA, December 8, 1988.
48. Domain Structure of Polymer Liquid Crystals, Department of Chemical Engineering, University of Illinois, Urbana, IL, February, 16, 1989.
49. Optical Rheometry of Polymer Liquid Crystals, Physical Chemistry Laboratory, University of Utrecht, The Netherlands, May 24th, 1989.
50. Optical Rheometry of Bidisperse Polymer Melts, Corporate Research Laboratories, Dutch State Mining Company, May 25th, 1989
51. Dynamics of Polymeric Liquids at Intermediate Length Scales, Department of Polymer Chemistry, University of Mainz and Max Planck Institute for Polymer Science, Mainz, West Germany, May 29, 1989.
52. Optical Rheometry of Bidisperse Polymer Melts, Corporate Research Laboratories, BASF, Ludwigshafen, West Germany, May 30, 1989.
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54. Dynamics of Polymeric Liquids at Intermediate Length Scales, Polymer Science Department, University of Freiburg, Freiburg, West Germany, July 10, 1989.
55. Flow Induced Phase Separation in Polymer Solutions, Department of Chemical Engineering, Purdue University, West Lafayette, Indiana, September 13, 1989.
56. Rheo-optical Studies of Flow-Induced Phase Transition in Polymer Solutions, Department of Chemical Engineering, University of Connecticut, Storrs, CT, Nov. 15, 1989.
57. Rheo-optical Studies of Flow-Induced Phase Transition in Polymer Solutions, Department of Polymer Science, University of Massachusett, Amherst, MA, Nov. 17, 1989.
58. Optical Rheometry of Polymeric Liquids and Thin Films, Hoescht-Celanese Research Center, Summit, NJ, Jan. 8, 1990.
59. Infrared Polarimetry Studies for Multi-component Polymer Melts, Kodak Corporate Research Laboratories, Rochester, NY, August 14, 1990.
60. Electro-hydrodynamics of Dense Colloidal Suspensions, Department of Applied Physics, Nagoya University, Nagoya, Japan, September 18, 1990.
61. Rheo-optics of Flow-induced Phase Separation of Polymer Solutions, Department of Polymer Chemistry, Kyoto University, Kyoto, Japan, September 19, 1990.
62. Optical Rheometry, Department of Chemical Engineering, Brigham Young University, Provo, UT, November 29, 1990.
63. Optical Rheometry, Rhom & Haas Co., Spring House, PA, January 17, 1991.
64. Extensional Flow Properties of Solutions, Clorox Technical Center, Pleasanton, CA, April 23, 1991.
65. Rheo-Optics of Polymer Dynamics, 3M, St. Paul, MN, June 3, 1991.
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67. Optical Rheometry, BP Research, Middlesex, United Kingdom, July 22, 1991.
68. Optical Rheometry of Polymer Melts and Blends, Delft University of Technology, Delft, The Netherlands, September 9, 1991
69. Flow-Induced Phase Separation of Polymer Liquids, BP Research, Middlesex, United Kingdom, September 16, 1991
70. Optical Rheometry of Multicomponent Polymer Liquids, University of California, Santa Barbara, November 7, 1991.
71. Shear Induced Phase Transition and Electric-Field Induced Structures in Polymer Systems, Department of Physics, Kyoto University, January 16, 1992.
72. Optical Rheometry for Multicomponent Systems, University of Arizona, Tucson, January 21, 1992.
73. Optical Rheometry for Multicomponent Systems, Department of Chemical Engineering, University of Delaware, March 5, 1992.
74. Rheo-Optics of Polymer Dynamics, Shell Development Company, Houston, TX, April 23, 1992.
75. Optical Rheometry of Multicomponent Polymer Liquids, 3M Technical Center, St. Paul, MN, June 23, 1992.
76. Field Unduced Phase Separation in Polymer Liquids, Department of Polymer

Chemistry, University of Mainz, Germany, July 22, 1992.
77. Dynamics of Multicomponent Complex Liquids, Department of Material Science, EPFL, Lausanne, Switzerland, July 24, 1992.
78. Field Induced Phase Separation of Polymer Liquids, Institute for Problems in Mechanics of the Russian Academy of Sciences, Moscow, Russia, October 6, 1992.
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80. Extensional Viscometry of Low Viscosity Fluids, Polaroid Corporation, Boston, MA, October 21, 1993.
81. Dynamics of Polymer Mixtures, General Electric Co., Schenectady, NY, October 22, 1993.
82. Optical Rheometry of Complex Liquids, Department of Chemical Engineering, University of Florida, Gainesville, FL, November 12, 1993.
83. Optical Rheometry of Complex Liquids, Department of Chemical Engineering, University of Missouri-Rolla, Rolla, MO, November 14, 1993.
84. Optical Rheometry, Xerox Research Centre, Toronto, Canada, February 22, 1994.
85. Optical Rheometry of Complex Liquids, 3M Center, St. Paul, MN, February 23, 1994.
86. Dynamics of Multicomponent Polymer Liquids, Dept. of Chemical Engineering, University of Naples, Italy, March 30, 1994
87. Dynamics of Two Dimensional Liquid Crystals, Dept. of Chemistry, University of Mainz, Germany, April 26, 1994.
88. Optical Rheometry of Complex Liquids, Dept. of Chemical Engineering, University of Patras, Patras, Greece, May 9, 1994.
89. Optical Rheometry of Complex Liquids, Dept. of Polymer Science, F.O.R.T.H., University of Iraklion, Iraklion, Crete, Greece, May 19, 1994.
90. Optical Rheometry, Center for Materials Science, Ecole des Mines de Paris, Nice, France, June 7, 1994.
91. Introduction to Optical Rheometry, Bridgestone Corp., Tokyo, Japan, Sept. 21, 1994.
92. Dynamics and Structure of Wormlike Micelles, Procter and Gamble, Cincinati, OH, October 25, 1994.
93. Optical Rheometry of Complex Fluids, Chemical Engineering, Texas A&M University, College Station, TX, December 2, 1994.
94. Principles of Optical Rheometry, Technical University of Eindhoven, Eindhoven, The Netherlands, December 7, 1994.
95. Dynamics of Polymeric Liquids using Optical Rheometry, Department of Macromolecular Science, Case Western Reserve University, Cleveland, OH, February 3, 1995.
96. Dynamics of Multicomponent Polymer Liquids, DuPont Corp., Wilmington, DE, February 7, 1995.
97. Dynamics of Multicomponent Polymer Liquids, Union Carbide, New Brunswick, NJ, February 8, 1995.
98. Optical Rheometry of Polymer Liquids, Sunkyong Chemical Co., Yukong

Taeduk Research Center, Korea, March 29, 1995.
99. Gerald G. Fuller, Orientation Dynamics of Monolayers, The Levich Institute, City College of New York, March 26, 1996.
100. Gerald G. Fuller, Fluid Dynamics of Complex Interfaces, Department of Chemical Engineering, University of Colorado, Boulder, CO, April 10-11, 1996.
101. Gerald G. Fuller, Rheology of Monolayers, Laboratoire de Rheologie, University of Grenoble, Grenoble, France, April 26, 1996.
102. Gerald G. Fuller, Flow Orientation of Monolayers, Newton Institute, University of Cambridge, U.K., April 30, 1996.
103. Gerald G. Fuller, Series of three lectures: "Flow Induced Concentration Fluctuations in Polymeric Liquids", "Orientation Dynamics of Miscible Polymer Blends", "Interfacial Dynamics of Monolayers", Sadron Institute, University of Strasbourg, Strasbourg, France, June-July, 1996.
104. Gerald G. Fuller, Flow Orientation of Monolayers, Department of Material Science, EFPL, Lausanne, Switzerland, June 17, 1996.
105. Gerald G. Fuller, Flow Orientation of Langmuir Films, Department of Physics, Ecole Normale Superier, Paris, France, 1996.
106. Gerald G. Fuller, Flow Orientation of Langmuir Films, Department of Physics, Technical University of Berlin, July 2, 1996.
107. Gerald G. Fuller, Flow Orientation of Langmuir Films, Max Planck Institute for Colloid Science, Berlin, Germany, July 3, 1996.
108. Gerald G. Fuller, Rheology of Monolayers, Department of Chemistry, Tulane University, New Orleans, LA, Oct. 7, 1996.
109. Gerald G. Fuller, Optical Rheometry of Complex Liquids and Interfaces, Raychem, Menlo Park, CA, October 24, 1997.
110. Gerald G. Fuller, Fluid Dynamics of Langmuir Monolayers, Department of Chemical Engineering, Princeton University, Princeton, NJ, February 26, 1997.
111. Gerald G. Fuller, Interfacial Rheology of Monolayers, Chemical Engineering Department, Northwestern University, Evanston, IL, February 27, 1997.
112. Gerald G. Fuller, Rheology of Complex Interfaces, Rheology Research Center, University of Wisconsin, Madison, WI, February 28, 1997.
113. Gerald G. Fuller, Interfacial Rheology, Alza Corporation, Palo Alto, CA, June 18, 1997.
114. Gerald G. Fuller, Optical Rheometry of Complex Liquids, Hercules Inc., Wilmington, Deleware, July 15, 1997.
115. Gerald G. Fuller, Interfacial Rheology and Dynamics of Langmuir Films, Department of Chemistry, University of Essen, Essen, Germany, September 9, 1997.
116. Gerald G. Fuller, Optical Rheometry of Complex Fluids and Interfaces, Department of Chemical Engineering, Oklahoma State University, Stillwater, OK, September 23, 1997.
117. Gerald G. Fuller, Dynamics and Structure of Complex Interfaces, Department of Chemical Engineering, University of British Columbia, Vancouver, BC, September 26, 1997.
118. Gerald G. Fuller, Optical Rheometry of Polymer Melts, Blends, and

Copolymers, Elf Atochem, King of Prussia, PA, November 11, 1997.
119. Gerald G. Fuller, Optical Rheometry of Polymer Melts, Blends, and Stereoblock Polymers, Dow, Freeport, TX, November 12, 1997.
120. Gerald G. Fuller, Optical Rheometry of Complex Fluids and Interfaces, Chemical Engineering, NC State, Rayleigh, NC, November 24, 1997.
121. Optical Rheometry of Complex Liquids, Solvay Chemical Co., Brussels, Belgium, June 16, 1998.
122. Optical Rheometry of Complex Liquids, Dow-Corning, Midland, MI, July 13, 1998.
123. Optical Rheometry of Complex Liquids, Avery-Dennison, Cleveland, OH, July, 14, 1998.
124. Dynamics and Rheometry of Complex Interfaces, Carnegie-Mellon University, Pittsburg, PA, Nov. 10, 1999.
125. Structure and Dynamics of Complex Fluid Interfaces, UCSB, Santa Barbara, CA, 01/14/99
126. Structure and Dynamics of Complex Fluid Interfaces, UCLA, Los Angeles, CA, 01/14/99
127. Rheology of Complex Fluids and Interfaces, Procter and Gamble, Cincinatti, OH, 01/27/99.
128. Rheology of Complex Interfaces, Department of Chemistry, Colorado State University, Ft. Collins, CO, 04/15/99
129. Rheology of Complex Interfaces, Colorado School of Mines, Golden, CO, 04/16/99
130. Interfacial Rheology, Procter and Gamble, Brussels, Belgium, 05/07/99
131. Microrheology of Complex Liquids and Interfaces, Rohm and Haas Company, Spring House, PA, May 27, 1999.
132. Dynamics of Complex Liquids and Interfaces, Department of Polymer Chemistry, University of Bayreuth, Bayreuth, Germany, June 29, 1999.
133. Optical Rheometry, Enitechnologies, Milan, Italy, July 1-2, 1999.
134. Applied Rheology, National Starch and Chemical Company, Bridgewater, NJ, August 23-24, 1999.
135. Rheology in Two Dimensions, Chemical Engineering, UC Berkelely, Berkeley, CA, September 15, 1999.
136. Rheology of Complex Interfaces, Kodak Research Laboratories, Rochester, NY, Jan. 14, 2000.
137. Interfacial Rheology of Complex Systems, Merck Research, Rahway, NJ, Mar. 1, 2000.
138. Interfacial Rheology of Complex Systems, ExxonMobile Research and Engineering Company, Clinton, NJ, Mar. 2, 2000.
139. Rheology in Two Dimensions, Department of Polymer Engineering, University of Akron, Akron, OH, Mar. 3, 2000.
140. Dynamics of Complex Interfaces, Department of Polymer Science, Yamagata University, Japan, Mar. 14, 2000.
141. Rheology in Two Dimensions, Frontier Research System, RIKEN Laboratories, Tokyo, Japan, Mar. 16, 2000.
142. Rheology in Two Dimensions, Chemical Engineering, Texas Tech., Lubbock,

TX, Feb. 18, 2000.
143. Dynamics of Complex Interfaces, Department of Physics, Technical University of Munich, Germany, June 9, 2000.
144. Dynamics of Complex Interfaces, Department of Polymer Science, University of Bayreuth, Germany, June 12, 2000.
145. Rheology in Two Dimensions, Department of Chemical and Environmental Engineering, University of Arizona, January 23, 2001.
146. Dynamics of Chains Trapped in Two Dimensions, NIST, Gaithersburg, VA, March 6, 2001.
147. Interfacial Rheology, Department of Macromolecular Science, Case Western Reserve University, Cleveland, OH, January 18, 2002.
148. Dynamics of Polymer Interfaces, Deparment of Chemical Engineering, Wayne State University, Detroit, MI, February 15, 2002.
149. Complex Fluid Interfaces, Facultad de Ciencias de la UNED, E-28040 Madrid, Spain, March 4, 2002.
150. Complex Fluid Interfaces, Unilever Co., NJ, April 6, 2002.
151. Rheology of two-dimensional, mobile systems, University of Minho, Department of Polymer Engineering, Guimarães, Portugal, June 24, 2002.
152. Dynamics of Mobile Interfaces: Rheology on the Edge, Chemical Engineering, UC Davis, Davis, CA, Sept. 30, 2002.
153. Interfacial Rheology of Complex Interfaces, Chemical Engineering, Virginia Tech, October 18, 2002.
154. Dynamics of Mobile Interfaces: Rheology on the Edge, Miami Valley Research Laboratoies, Procter and Gamble, Cincinnati, OH, December 16, 2002.
155. Rheology of Complex, Mobile Interfaces, Department of Chemistry, Virginia Tech., Blacksburg, VA, April 18, 2003.
156. Rheology of Complex, Mobile Interfaces, Department of Chemistry, University of Sofia, Sofia, Bulgaria, May 9, 2003.
157. Rheology of Complex, Mobile Interfaces, Department of Materials Science, University of Crete, Heraklion, Greece, May 15, 2003.
158. Complex Fluid Interfaces, Chemical Engineering, University of Michigan, October 30, 2003.
159. Interfacial Rheology, KSV Corp., Helsinki, Finland, August 2, 2004.
160. Particle Stabilized Emulsions, University of Bordeaux, France, September 27, 2004.
161. Particle Stabilized Emulsions, BASF, Ludwigshafen, Germany, September 30, 2004.
162. Complex Fluid Interfaces, Mechanical Engineering, UC Berkeley, Oct. 20, 2004.
163. Rheology of Complex Fluid Interfaces, Physics Department, Emory University, Atlanta, GA, Dec. 3, 2004.
164. Complex Fluid Interfaces, Department of Chemistry, Oxford University, Oxford, England, Dec. 6, 2004.
165. Two-Dimensional Suspensions, Unilever Corporate Research, Colworth, England, Dec. 7, 2004.
166. Complex Fluid Interfaces, Department of Physics, Cambridge University, Cambridge, England, Dec. 8, 2004.

167. Dynamics of Complex Fluid Interfaces, Engineering and Applied Sciences, Harvard University, Cambridge, MA, Jan. 10, 2005.
168. Complex Fluid Interfaces, Department of Chemistry, University of Gronegin, Grongein, The Netherlands, Jan. 17, 2005.
169. Solid-Stabilized Emulsions, Department of Physics, Free University of Amsterdam, Amsterdam, The Netherlands, Jan. 18, 2005.
170. Interfacial Rheology, Chemical Engineering, Ecole Polytechnique, Montreal, Canada, March 31, 2005.
171. Complex Fluid Interfaces, Chemical Engineering, Laval University, Quebec City, Quebec, Canada, April 1, 2005.
172. Complex Fluid Interfaces, Department of Physics, UC Santa Cruz, Santa Cruz, CA, April 8, 2005.
173. Dynamics of Biological Films, Guidant, Mountain View, CA, June 3, 2005.
174. Dynamics of Biological Films, Nellcor, Pleasanton, CA, June 6, 2005.
175. Particle Stabilized Droplets, Rheology Research Center, University of Wisconsin, October 28, 2005.
176. Complex Fluid Interfaces, Chemical Engineering, University of Pittsburg, November 11, 2005.
177. Complex Fluid Interfaces: Applications in Consumer Products and the Life Sciences, Department of Chemistry, UCLA, April 1, 2006.
178. Complex Fluid Interfaces, Department of Chemical Engineering, Univesity of Calabria, May 30 2006.
179. Interfacial Rheology, Institute of Bioengineering and Nanotechnology, Singapore, August 7, 2006.
180. Interfacial Rheology, King's Mongkut Institute of Technology North Bangkok, Department of Mechanical Engineering, Bangkok, Thailand, August 9, 2006.
181. Recent Advances in Interfacial Rheology, Shanghai Jiao Tong University, Shanghai, China, December 13, 2006.
182. The Rheology of Complex, Biological Interfaces, Manchester Interdisciplinary BioCentre, Manchester, England, July 1-6, 2007.
183. Short Course on Rheology, Shanghai Jiao Tong University, Shanghai, China, July 23 – 27, 2007
184. Washington University, October 28, 2007
185. IIT Delhi, November 21, 2007.
186. IIT Kanpur, November 22, 2007.
187. National Chemical Laboratories, Pune, India, November 23, 2007.
188. Interfacial Rheology, IIT Mumbai, India, October 3, 2008.
189. Interfacial Rheology, National Chemical Laboratories, Pune, India, October 4, 2008.
190. Interfacial Rheology, IIT Delhi, India, October 15, 2008.
191. Interfacial Rheology, Indian Institute of Science, Bangalore, India, October 17, 2008.
192. Oriented collagen substrates for directed cell growth, Department of Chemical Engineering, University of Queensland, Brisbane, Australia, August 10, 2009.
193. Surface Cleaning using Non-Newtonian Fluids, Departmental Seminar, Chemical Engineering, ASU, Tempe, AZ, April 24, 2010
194. Interfacial Rheology, Petrobras Research Laboratories, Rio de Janeiro, Brazil, July

12, 2010.
195. Extensional Rheometry and Surface Cleaning, Departmental Seminar, Chemical Engineering, University Federal Rio de Janeiro, July 13, 2010.
196. Protein-Surface Interactions, Cabot Industries, Billerica , MA, July 11, 2010.
197. Interfacial Rheology: Emulsion Stability, Coalescence, and Adhesion, Cape Town University, Cape Town, SA, Sept. 7, 2010.
198. Rinsing Flows and Particle Removal, ESPCI, Paris, France, September 28, 2010.
199. Protein-Surface Interactions, Medimmune, Gaithersburg, MD, Oct. 11, 2010.
200. Rinsing Flows and Surface Cleaning by Complex Liquids, Chemical Engineering, University of Leuven, Leuven, Belgium, December 8, 2010.
201. Rinse and Repeat: Turning Polymeric Liquids into Soft Adhesives, Chemical Engineering, Queen's University, Kingston, Ont., Canada, January 20, 2011.
202. Surface Cleaning by non-Newtonian Fluid Rinsing, Clorox Corp., Pleasonton, CA, January 28, 2011.
203. Rinse and Repeat: Turning Polymeric Liquids into Soft Adhesives, Mechanical Engineering, U. Washington, Seattle, March 1, 2011.
204. Rinse and Repeat: Turning Polymeric Liquids into Soft Adhesives, Mechanical Engineering, Georgia Tech, April 11, 2011.
205. Short Course on Rheology, Brazilian Society of Rheology, Rio de Janeiro, Brazil, July 4-5, 2011.
206. Short Course on Rheology, Golden Gate Polymer Forum, July 13-15, 2011, Mountain View, CA.
207. Short Course on Rheology, University of Leuven, Leuven, Belgium, September 5-9, 2011.
208. Short Course on the Rheology of High Interface Systems, Society of Rheology Meeting, Cleveland, OH, October 8-9, 2011.
209. Short Course on Rheology, South African Society of Rheology, Johannesburg, SA, November 21-22, 2011.

APPENDIX II

Why molecules move along a temperature gradient

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Molecules drift along temperature gradients, an effect called thermophoresis, the Soret effect, or thermodiffusion. In liquids, its theoretical foundation is the subject of a long-standing debate. By using an all-optical microfluidic fluorescence method, we present experimental results for DNA and polystyrene beads over a large range of particle sizes, salt concentrations, and temperatures. The data support a unifying theory based on solvation entropy. Stated in simple terms, the Soret coefficient is given by the negative solvation entropy, divided by *kT*. The theory predicts the thermodiffusion of polystyrene beads and DNA without any free parameters. We assume a local thermodynamic equilibrium of the solvent molecules around the molecule. This assumption is fulfilled for moderate temperature gradients below a fluctuation criterion. For both DNA and polystyrene beads, thermophoretic motion changes sign at lower temperatures. This thermophilicity toward lower temperatures is attributed to an increasing positive entropy of hydration, whereas the generally dominating thermophobicity is explained by the negative entropy of ionic shielding. The understanding of thermodiffusion sets the stage for detailed probing of solvation properties of colloids and biomolecules. For example, we successfully determine the effective charge of DNA and beads over a size range that is not accessible with electrophoresis.

DNA | fluorescence | microfluidic | Soret | thermodiffusion

Thermodiffusion has been known for a long time (1), but its theoretical explanation for molecules in liquids is still under debate. The search for a theoretical understanding is motivated by the fact that thermodiffusion in water might lead to powerful all-optical screening methods for biomolecules and colloids. Equally well, thermodiffusion handles and moves molecules all-optically and therefore can complement well established methods: for example, electrophoresis or optical tweezers. For the latter, forces of optical tweezers scale with particle volume and limit this method to particles of only >500 nm. Electrophoresis does not suffer from force limitations but is difficult to miniaturize because of electrochemical reactions at the electrodes.

On the other hand, thermodiffusion allows the microscale manipulation of small particles and molecules. For example, 1,000-bp DNA can be patterned arbitrarily in bulk water (Fig. 1). The temperature pattern "DNA," heated by 2 K, was written into a water film with an infrared laser scanning microscope. The concentration of 1,000-bp DNA was imaged by using a fluorescent DNA tag. In an overall cooled chamber at 3°C, DNA accumulates toward the heated letters "DNA" (negative Soret effect), whereas at room temperature DNA is thermophobic (positive Soret effect) as seen by the dark letters.

In the past, the apparent complexity of thermodiffusion prevented a full theoretical description. As seen for DNA in Fig. 1, molecules characteristically deplete from regions with an increased temperature, but they can also show the inverted effect and accumulate (2, 3). Moreover, the size scaling of thermodiffusion recorded by thermal field flow fractionation showed fractional power laws with a variety of exponents that are hard to interpret (4, 5). The latter effect might be resolved by revealing nonlinear thermophoretic drift for the strong thermal gradients used in thermal field flow fractionation (our unpublished observations).

A variety of methods were used to measure thermodiffusion, mostly in the nonaqueous regime, ranging from beam deflection (2, 3, 6), holographic scattering (7–9), electrical heating (10), to thermal lensing (11). Recently we have developed a fluorescence microfluidic imaging technique (12, 13) that allows the measurement of thermodiffusion over a wide molecule size range without artifacts induced by thermal convection. Highly diluted suspensions can be measured; therefore, particle–particle interactions do not have an influence. We only apply moderate temperature gradients. In the following study, we used this method to confirm a straightforward theoretical explanation of thermodiffusion.

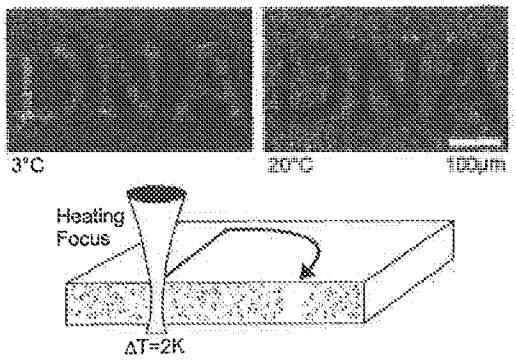

Fig. 1. Thermodiffusion manipulates the DNA concentration by small temperature differences within the bulk solution. A thin water film is heated by 2 K along the letters "DNA" with an infrared laser. For a cooled chamber at 3°C, fluorescently tagged DNA accumulates at the warm letters. However, at room temperature, DNA moves into the cold, showing reduced fluorescence. The chamber is 60 μm thin, containing 50 nM DNA in 1 mM Tris buffer. Every 50th base pair is labeled with TOTO-1 (for details, see supporting information).

Theoretical Approach

For diluted concentrations, it is generally assumed (14) that the thermodiffusive drift velocity $\vec{v}$ depends linearly on the temperature gradient ∇T with a proportionality constant which equals the thermodiffusion coefficient D_T: $\vec{v} = -D_T \nabla T$. In steady state, thermodiffusion is balanced by ordinary diffusion. Constant diffusion and thermodiffusion coefficients both lead to an exponential depletion law (15) $c/c_0 = \exp[-(D_T/D)(T - T_0)]$, with the concentration c depending on the temperature difference $T - T_0$ only. The concentration c is normalized by the boundary condition of the concentration c_0 with temperature T_0. The Soret coefficient is defined as ratio $S_T = D_T/D$, which determines the magnitude of thermodiffusion in the steady state. Although the above exponential distribution could motivate an approach based on Boltzmann equilibrium statistics, it is commonly argued that thermodiffusion without exception is a local nonequilibrium effect that requires fluid dynamics, force fields, or particle–solvent potentials (16–20). However, in a previous paper (15), we demonstrated that for moderate temperature

Author contributions: D.B. designed research; S.D. and D.B. performed research; S.D. and D.B. analyzed data; and S.D. and D.B. wrote the paper.

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gradients the thermal fluctuations of the particle are the basis for a local equilibrium. This allows the description of the thermodiffusive steady state by a succession of local Boltzmann laws, yielding $c/c_0 = \exp[-(G(T) - G(T_0))/kT]$, with G being the Gibbs-free enthalpy of the single particle–solvent system. Such an approach is valid only if the temperature gradient ∇T is below a threshold $\nabla T < (aS_T)^{-1}$, which is given by the particle fluctuations with the hydrodynamic radius a and Soret coefficient S_T, as shown recently (15). In the present study, temperature gradients below this limit were used so that thermodiffusion is measured at local thermodynamic equilibrium conditions.

Local thermodynamic equilibrium allows the derivation of a thermodynamic foundation of the Soret coefficient. The local Boltzmann distribution relates small concentration changes δc with small Gibbs-free energy differences: $\delta c/c = -\delta G/kT$. We equate this relation with a locally linearized thermodiffusion steady state given by $\delta c/c = -S_T \delta T$ and thus find the Soret coefficient by the temperature derivative of G:

$$S_T = D_T/D = (kT)^{-1} \times \partial G/\partial T. \qquad [1]$$

Whereas the above relation is sufficient for the following derivation, it can be generalized by locally applying the thermodynamic relation $dG = -SdT + Vdp + \mu dN$. For single particles at a constant pressure we find that the Soret coefficient equals the negative entropy of the particle–solvent system S according to $S_T = -S/kT$. This relation is not surprising given that the entropy is by definition related with the temperature derivative of the free enthalpy.

The above general energetic treatment is inherent in previously described approaches based on local equilibrium (14, 21, 22), including the successful interpretation of thermoelectric voltages of diluted electrolytes (23, 24), which are described by energies of transfer. Recently, the nonequilibrium approach by Ruckenstein (25) was applied to colloids (26) with the characteristic length l assigned to the Debye length λ_{DH}. If instead one would assign the characteristic length according to $l = 2a/3$ with the particle radius a, the Ruckenstein approach would actually confirm the above local equilibrium relation (1) for the Soret coefficient. Measurements on SDS micelles (26) appeared to confirm this nonequilibrium approach, but for the chosen particles the competing parameter choices $l = 2a/3$ and $\ell = \lambda_{DH}$ yielded comparable values. Thus, the experiments could not distinguish between the competing theories.

We will use the above local equilibrium relations to derive the Soret coefficient for particles larger than the Debye length in aqueous solutions and put the results to rigorous experimental tests. Two contributions dominate the particle entropy S in water (Fig. 2*a*): the entropy of ionic shielding (Fig. 2a *Left*) and the temperature-sensitive entropy of water hydration (Fig. 2*a Right*). The contribution from the entropy of ionic shielding is calculated with the temperature derivative of the Gibbs-free enthalpy (26, 27) $G_{ionic} = Q_{eff}^2 \lambda_{DH}/[2A\varepsilon\varepsilon_0]$ with the effective charge Q_{eff} and particle surface A. Alternatively, this enthalpy can be interpreted as an electrical field energy $G_{ionic} = Q_{eff}^2/[2C]$ in the ionic shielding capacitor C. We neglect the particle–particle interactions because the fluorescence approach allows the measurement of highly diluted systems. To obtain the Soret coefficient, temperature derivatives consider the Debye length $\lambda_{DH}(T) = \sqrt{\varepsilon(T)\varepsilon_0 kT/(2e^2 c_S)}$ and the dielectric constant $\varepsilon(T)$. Both temperature derivatives give rise to a factor $\beta = 1 - (T/\varepsilon)\partial\varepsilon/\partial T$. The effective charge Q_{eff} is largely temperature-insensitive, which was confirmed by electrophoresis independently (28). Such a dependence would be unexpected because the strongly adsorbed ions dominate the value of the effective charge. Experimentally, we deal with colloids exhibiting flat surfaces, i.e., the particle radius is larger than λ_{DH}. In this case, charge renormalization does not play a role and we can introduce an effective surface charge density $\sigma_{eff} = Q_{eff}/A$ per molecule area A. From the temperature derivation according to Eq. 1, the ionic contribution to the Soret coefficient is $S_T^{(ionic)} = (A\beta\sigma_{eff}^2\lambda_{DH})/(4\varepsilon\varepsilon_0 kT^2)$. A similar relation was derived for charged micelles recently (22), although without considering the temperature dependence of the dielectric coefficient ε. Next, the contribution to the Soret coefficient from the hydration entropy of water can be directly inferred from the particle-area-specific hydration entropy $s_{hyd} = S_{hyd}/A$, namely $S_T^{(hyd)} = -As_{hyd}(T)/kT$. Finally, the contribution from the Brownian motion is derived as $S_T = 1/T$ by inserting the kinetic energy of the particle $G = kT$ into Eq. 1. However, this contribution is very small ($S_T = 0.0034$/K) and can be neglected for the molecules under consideration. The contributions from ionic shielding and hydration entropy add up to

$$S_T = \frac{A}{kT}\left(-s_{hyd} + \frac{\beta\sigma_{eff}^2}{4\varepsilon\varepsilon_0 T} \times \lambda_{DH}\right). \qquad [2]$$

The Soret coefficient S_T scales linearly with particle surface A and Debye length λ_{DH}. We tested Eq. 2 by measuring S_T versus salt concentration, temperature, and molecule size. In all cases, thermodiffusion is quantitatively predicted without any free parameters. We used fluorescence single-particle tracking to follow carboxyl-modified polystyrene beads (catalog no. F-8888, Molecular Probes, Eugene, OR) with diameters of 1.1 and 0.5 at 25 aM dialyzed into 0.5 mM Tris·HCl at pH 7.6. Thermodiffusion of particles ≤ 0.2 μm is measured by the fluorescence decrease that reflects the bulk depletion of the particles (12). The chamber thickness of 20 μm damped the thermal convection to negligible speeds (15). The experimental design also excludes thermal lensing and optical trapping (15). Debye lengths λ_{DH} were titrated with KCl (see the supporting information, which is published on the PNAS web site).

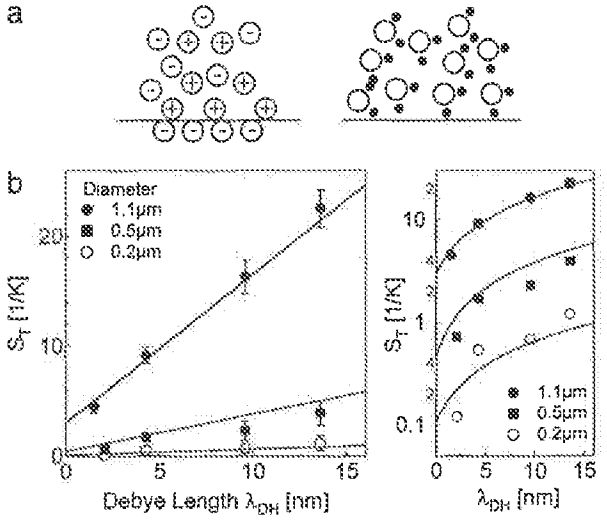

Fig. 2. Salt dependence. (*a*) Thermodiffusion in water is dominated by ionic shielding (*Left*) and water hydration (*Right*). (*b*) Soret coefficient S_T versus Debye length for carboxyl-modified polystyrene beads of diameter 1.1, 0.5, and 0.2 μm. Linear plot (*Left*) and logarithmic plot (*Right*). The Soret coefficients are described by Eq. 2 with an effective surface charge of $\sigma_{eff} = 4{,}500$ e/μm^2 known from electrophoresis. The intercept $S_T(\lambda_{DH} = 0)$ is fitted with a hydration entropy per particle surface of $s_{hyd} = -1{,}400$ J/(mol·K·μm^2).

Salt Dependence. Fig. 2*b* shows the Soret coefficients of polystyrene beads with different sizes versus λ_{DH}. The Soret coefficients

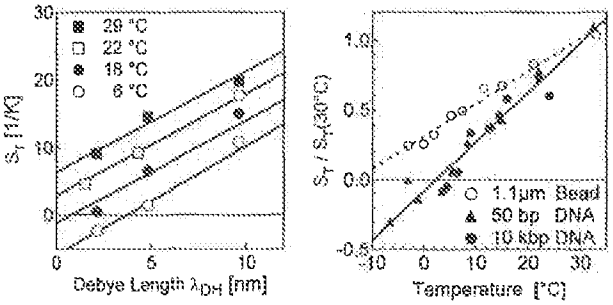

Fig. 3. Temperature dependence. (*a*) The temperature dependence is dominated by the linear change in the hydration entropy S_{hyd}. It shifts the salt-dependent thermodiffusion $S_T(\lambda_{DH})$ to lower values. The particle size is 1.1 μm. (*b*) The Soret coefficient S_T increases linearly with the temperature as expected for a hydration entropy S_{hyd}(7). It depends on the molecule species, not its size, as seen from the rescaled Soret coefficients for DNA with different lengths.

scale linearly with a small intercept at $\lambda_{DH} = 0$ and confirm the λ_{DH}-dependence of Eq. 2. For smaller-diameter beads, the Soret coefficients scale with the particle surface area A (Fig. 2), as expected from Eq. 2. To check whether Eq. 2 also quantitatively explains the measured Soret coefficients, we inferred the effective charge of the beads by electrophoresis (see supporting materials). By using 40-nm beads with identical carboxyl surface modifications at $\lambda_{DH} = 9.6$ nm, we fluorescently observed free-flow electrophoresis and corrected for electroosmosis, finding an effective surface charge density of $\sigma_{eff} = 4{,}500 \pm 2{,}000$ $e/\mu m^2$. This value is virtually independent from the used salt concentrations (28). With this inferred effective charge, Eq. 2 fits the Soret coefficient for various bead sizes and salt concentrations well (Fig. 2*b*, solid lines).

The intercept $S_T(\lambda_{DH} = 0)$, where ionic contributions are zero, also scales with particle surface and is described by a hydration entropy per particle surface of $s_{hyd} = -1{,}400$ J/(mol·K·μm^2). The value matches the literature values for similar surfaces reasonably well (29–31). For example, dansyl-alanine, a molecule with surface groups comparable with polystyrene beads, was measured to have a hydration entropy (29) of -0.13 J/(mol·K) at a comparable temperature. Linear scaling with its surface area by using a radius of $a = 2$ nm results in a value of $s_{hyd} = -2{,}500$ J/(mol·K·μm^2), in qualitative agreement with our result. The hydration entropy is a highly informative molecule parameter that is notoriously difficult to measure, yielding an interesting application for thermodiffusion.

Temperature Dependence. Hydration entropies S_{hyd} in water are known to increase linearly with decreasing temperatures (29–31). Because the slope of the ionic contribution of S_T versus λ_{DH} is with high-precision temperature insensitive for water [$\beta(T)/(\varepsilon T^2) \approx$ const], only the intercept is expected to decrease as the overall temperature of the chamber is reduced. This is indeed the case, as seen from the temperature dependence of beads with diameters of 1.1 μm ($T = 6$–29°C) (Fig. 3*a*). We infer from the intercept $S_T(\lambda_{DH} = 0)$ that the hydration entropy changes sign at ≈20°C. As seen for DNA in Fig. 1, hydration entropy can dominate thermodiffusion at low temperatures and move molecules toward the heat ($D_T < 0$).

The properties of hydration entropy lead to a linear increase of S_T over temperatures at a fixed salt concentration as measured for 1.1-μm beads and DNA (Fig. 3*b*). We normalized S_T by dividing by S_T(30°C) to compensate for molecule surface area. The slopes of S_T over temperature differ between beads and DNA. However the slope does not differ between DNA of different size (50 bp versus 10,000 bp). Based on Eq. 2, this is to be expected because the temperature dependence of the hydration entropy depends only on the type of surface of the molecule, not its size. We measured the diffusion coefficients of the DNA species at the respective temperature independently. Within experimental error, changes in the diffusion coefficient D match with the change of the water viscosity without the need to assume conformational changes of DNA over the temperature range. Please note that the change of the sign of the DNA Soret coefficient is situated near the point of maximal water density only by chance. There, the two entropic contributions balance. For polystyrene beads at $\lambda_{DH} = 2$ nm for example, the sign change is observed at 15°C (Fig. 3*a*). An increased Soret coefficient over temperature was reported for aqueous solutions before (3), however with a distinct nonlinearity that we attribute to remnant particle–particle interactions.

Size Dependence of the Beads. The Soret coefficient was measured for carboxyl-modified polystyrene beads in diameters ranging from 20 nm to 2 μm. Beads with diameters of 0.2, 0.1, 0.04, and 0.02 μm were diluted to concentrations of 10 pM, 15 pM, 250 pM, and 2 nM, and their bulk fluorescence was imaged over time to derive D_T and D (12, 15) from the depletion and subsequent back-diffusion. Larger beads with diameters of 1.9, 1.1, and 0.5 μm were diluted to concentrations of 3.3 aM, 25 aM, and 0.2 pM and measured with single-particle tracking. The solutions were buffered in 1 mM Tris (pH 7.6) with $\lambda_{DH} = 9.6$ nm. In all cases, interactions between particles can be excluded. Care was taken to keep the temperature gradient in the local equilibrium regime.

We find that the Soret coefficient scales with particle surface over four orders of magnitude (Fig. 4*a*). The data are described well with Eq. 2 with an effective surface charge density of $\sigma_{eff} = 4{,}500$ $e/\mu m^2$ and neglected hydration entropy contribution. The 5-fold too-low prediction for the smallest particle (20 nm in diameter) can be explained by charge renormalization because its radius is smaller than λ_{DH}.

The diffusion coefficient D for spheres is given by the Einstein relation and scales inversely with radius $D \propto 1/a$. Inserting Eq. 2 into $S_T = D_T/D$, the thermodiffusion coefficient D_T is expected to scale with particle radius a. This is experimentally confirmed over two orders of magnitude (Fig. 4*b*). These findings contradict several theoretical studies claiming that D_T should be independent of particle size (16–20, 26), based on ambiguous experimental results from thermal field flow fractionation (4) that were probably biased by nonlinear thermodiffusion in large thermal gradients (15).

Size Dependence of DNA. Whereas polystyrene beads share a very narrow size distribution as a common feature with DNA molecules, beads are a much less complicated model system. Beads are rigid spheres that interact with the solvent only at its surface. In addition, the charges reside on the surface, where the screening takes place. Thus, the finding that thermodiffusion of flexible and homogeneously charged DNA is described equally well with Eq. 2 is not readily expected and quite interesting (Fig. 4 *c* and *d*).

We measured DNA with sizes of 50–48,502 bp in 1 mM Tris buffer ($\lambda_{DH} = 9.6$ nm) at low molecule concentrations between 1 μM (50 bp) and 1 nM (48,502 bp). Only every 50th base pair was stained with the TOTO-1 fluorescent dye. The diffusion coefficient was measured by back-diffusion after the laser was turned off and depends on the length L of the DNA in a nontrivial way. The data are well fitted with a hydrodynamic radius scaling $a \propto L^{0.75}$. This scaling represents an effective average over two DNA length regimes. For DNA molecules longer than ≈1,000 bp, a scaling of 0.6 is found (32), whereas shorter DNA scales with an exponent of ≈1 (see the supporting information).

We can describe the measured Soret coefficient over three

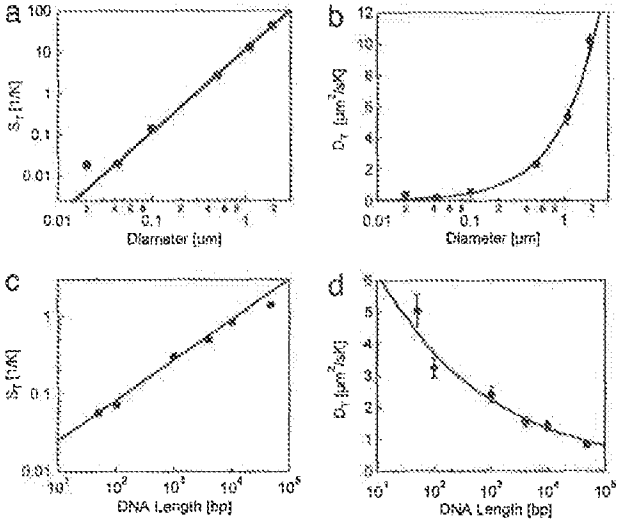

Fig. 4. Size dependence. (*a*) For polystyrene beads, the Soret coefficient scales with the particle surface over four orders of magnitude. Measurements are described by Eq. 2 with an effective surface charge density of $\sigma_{eff} = 4{,}500$ e/μm^2 (2) and negligible hydration entropy. The deviation for the bead with a diameter of 20 nm can be understood from an increased effective charge due to the onset of charge normalization for $a \approx \lambda_{DH}$. (*b*) Accordingly, the thermodiffusion coefficient D_T scales linearly with bead diameter. (*c*) The Soret coefficient of DNA scales according to $S_T \propto \sqrt{L}$, with the length L of the DNA based on Eq. 2 with an effective charge per base pair of 0.12 e. (*d*) Thermodiffusion coefficient D_T decreases over DNA length with $D_T \propto L^{-0.25}$, caused by the scaling of diffusion coefficient $D \propto L^{-0.75}$.

orders of magnitude of DNA lengths with Eq. 2 if we assume that effective charge of the DNA is shielded at the surface of a sphere with the hydrodynamic radius a. Because of the low salt concentration ($\lambda_{DH} = 9.6$ nm), such globular shielding is reasonable. Not only is the experimentally observed scaling of the Soret coefficient with the square root of its length correctly predicted based on Eq. 2 ($S_T \propto Q_{eff}^2/a^2 \propto L^2/L^{1.5} \propto L^{0.5}$), but the Soret coefficient also is fully described in a quantitative manner (Fig. 4*c*, solid line), with an effective charge of 0.12 e per base, matching well with literature values (33) ranging from 0.05 e/bp to 0.3 e/bp.

As shown in Fig. 4*d*, the thermodiffusion coefficient for DNA drops with DNA length according to $D_T = DS_T \propto Q_{eff}^2/a^3 \propto L^2/L^{2.25} \propto L^{-0.25}$. Thus, shorter DNA actually drifts faster in a temperature gradient than longer DNA. It is important to point out that this finding is in no way contradictory to experimental findings of a constant D_T over polymer length in nonaqueous settings (8). According to Eq. 1, the thermodynamic relevant parameter is the Soret coefficient, which is determined by the solvation energetics. The argument (19) that polymers have to decouple into monomers to show a constant D_T merely becomes the special case where the solvation energetics determine both S_T and D with equal but inverted size scaling. In accordance with our local energetic equilibrium argument, S_T and not D_T dominates thermodiffusion also for nonaqueous polymers near a glass transition (8). Here, S_T is constant, whereas D_T and D scale according to an increased friction. However, for a system of DNA in solution, for which long-ranging shielding couples the monomers, a constant D_T over polymer length cannot be assumed *a priori* (Fig. 4*d*).

Effective Charge. The effective charge Q_{eff} is a highly relevant parameter for colloid science, biology, and biotechnology. So far it only could be inferred from electrophoresis, restricted to

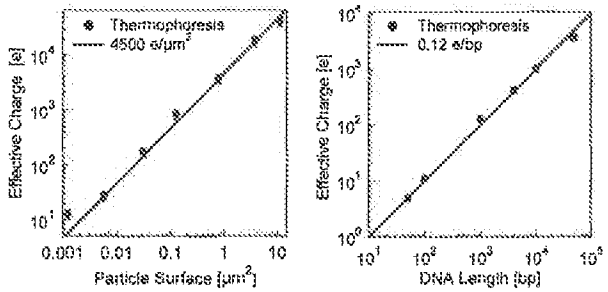

Fig. 5. Effective charge from thermodiffusion. Effective charge is inferred from thermodiffusion using Eq. 3. Polystyrene beads (20–2,000 nm) (*a*) and DNA (50–50,000 bp) (*b*) were measured over a large size range, which is impossible with electrophoresis. As expected, the effective charge of the beads scales with particle surface and linearly with the length of DNA.

particles smaller than the Debye length ($a \leq 3\lambda_{DH}$) (34). Unfortunately, many colloids are outside this regime. As shown before, a similar size restriction does not hold for thermodiffusion. In many cases, the hydration entropy s_{hyd} contributes <15% (Fig. 2) and can be neglected at moderate salt levels. Thus, we can invert Eq. 2 to obtain the effective charge Q_{eff} for spherical molecules from

$$Q_{eff} = \frac{2T^2}{3\eta D}\sqrt{\frac{\varepsilon\varepsilon_0\kappa^3 S_T}{\beta\pi\lambda_{DH}}}. \qquad [3]$$

The effective charge derived from thermodiffusion measurements of polystyrene beads and DNA is plotted in Fig. 5 over several orders of magnitude in size. The effective charge of beads scales linearly with particle surface, with a slope confirming the effective surface charge density of $\sigma_{eff} = 4{,}500$ e/μm^2, which was inferred from electrophoresis only for small particles. Average deviations from linear scaling are <8% (Fig. 5*a*). The effective charge inferred from thermodiffusion measurements of DNA using Eq. 3 scales linearly with DNA length with an effective charge of 0.12 e/bp. The length scaling is confirmed over four orders of magnitude with an average error of 12% (Fig. 5*b*). Thus, thermodiffusion can be used to infer the effective charge with low errors for a wide range of particle sizes. This is even more interesting for biomolecule characterization because measurements of thermodiffusion can be performed all-optically in picoliter volumes.

Conclusion

We describe thermodiffusion, the molecule drift along temperature gradients, in liquids with a general, microscopic theory. Applied to aqueous solutions, this theory predicts thermodiffusion of DNA and polystyrene beads with an average accuracy of 20%. We experimentally validate major parameter dependencies of the theory: linearity against screening length λ_{DH} and molecule hydrodynamic area A, quadratic dependence on effective charge, and linearity against temperature. Measurements of thermodiffusion can be miniaturized to the micrometer scale with the all-optical fluorescence technique and permit microscopic temperature differences to manipulate molecules based on their surface properties (Fig. 1). The theoretical description allows the extraction of solvation entropy and the effective charge of molecules and particles over a wide size range.

Materials and Methods

Infrared Temperature Control. The temperature gradients used to induce thermodiffusive motions were created by aqueous absorption of an infrared laser (Furukawa Electric, Tokyo, Japan) at a wavelength of 1,480 nm and 25 mW of power. Water strongly

absorbs at this wavelength with an attenuation length of $\kappa = 320$ μm. The laser beam was moderately focused with a lens of 8-mm focal distance. Typically, the temperature in the solution was raised by 1–2 K in the beam center with a $1/e^2$ diameter of 25 μm, measured with the temperature-dependent fluorescence signal of the dye 2′,7′-bis(carboxyethyl)-5(6)-carboxyfluorescein (12). Thin chamber heights of 10–20 μm and moderate focusing removed possible artifacts from optical trapping, thermal lensing, and thermal convection (12). For temperature-dependent measurements, both the objective and the microfluidic chip were tempered with a thermal bath. Imaging was provided from an AxioTech Vario fluorescence microscope (Zeiss, Oberkochen, Germany), illuminated with a high-power light-emitting diode (Luxeon, Calgary, Canada), and recorded with the CCD camera SensiCam QE (PCO, Kelheim, Germany).

Molecules. Highly monodisperse and protein-free DNA of 50, 100, 1,000, 4,000, 10,000, and 48,502 bp (Fast Ruler fragments and λ-DNA; Fermentas, St. Leon-Rot, Germany) were diluted to 50 μM base pair concentration, i.e., the molecule concentration was between 1 μM (50 bp) and 1 nM (48,502 bp). DNA was fluorescently labeled by the intercalating TOTO-1 fluorescent dye (Molecular Probes) with a low dye/base pair ratio of 1:50. Carboxyl-modified polystyrene beads with diameters of 2, 1, 0.5, 0.2, 0.1, 0.04, and 0.02 μm (catalog nos. F-8868, F-8823, F-8827, F-8888, F-8795, F-8823, and F-8827; Molecular Probes) were dialyzed (Eluta Tube mini; Fermentas) in distilled water and diluted in 1 mM Tris (pH 7.6) to concentrations between 3.3 aM (2 μm) and 2 nM (0.02 μm).

Concentration Imaging Over Time. Either the method of concentration imaging (12) or single-particle tracking was used to measure thermodiffusion at low concentrations, namely <0.03 g/liter for DNA and 10^{-5} g/liter for beads. At higher concentrations, we found profound changes of thermodiffusion coefficients. DNA and polystyrene beads of <0.5 μm in diameter were imaged over time (12) by bright-field fluorescence with a ×40 oil-immersion objective. Concentrations inferred after correcting for bleaching, inhomogeneous illumination, and temperature-dependent fluorescence (12) were fitted with a finite element theory. The model captures all details of both thermodiffusive depletion and back-diffusion to measure D_T and D independently (see supporting information). Measurements were performed in microfluidic chips 10 μm in height with polydimethylsiloxane on both sides.

Single-Particle Tracking. Polystyrene particles of >0.5 μm in diameter were measured by single-particle tracking due to the slow equilibration time and risk that steady-state depletion is disturbed by thermal convection. The thermodiffusive drift was imaged with a ×32 air objective at 4 Hz at an initial stage of depletion in a 20-μm-thick chamber. Averaging over the z position of the particles removed effects from thermal convection. The drift velocity versus temperature gradient of 400 tracks were linearly fitted by $v = -D_T \nabla T$ to infer D_T. The diffusion coefficients D of the particles were evaluated based on their squared displacement, matching within 10% the Einstein relationship.

We thank Klaus Stierstadt, Jan Dhont, and Werner Köhler for discussions and Julia Morfill and Veronica Egger for comments on the manuscript. Our Emmy-Noether Group is funded by the Deutsche Forschungsgemeinschaft and hosted by Hermann Gaub.

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EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

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Signed: Michael I. Chakansky /Michael I Chakansky/

REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111

Madame:

In compliance with the Notice Re Defective Paper in *Inter Partes* Reexamination, mail date February 26, 2013, Patent owner MonoSol Rx, LLC ("Patentee" and/or "MonoSol") hereby presents its re-drafted response to the Office Action in the above-identified *Inter Partes* Reexamination, dated November 29, 2012 ("Office Action"), a reply to which is due March 13, 2013. Please amend U.S. Patent No. 7,897,080 ("the '080 Patent") in reexamination as set forth hereinbelow. The present amendments are being made in accordance with 37 C.F.R. §1.530(d)–(j). Patentee has previously paid fees for the addition of 4 new independent claims and 324 new dependent in connection with this reexamination. Accordingly, no claim fees are believed to be due with this submission. If, however, there are any fees due in connection with this submission, authorization to charge such fees, including any claim fees, and authorization to credit any overpayments, to Deposit Account No. 08-2461 are hereby provided.

Amendment to the Claims begins on page 2 of this paper.

Remarks begin on page 42 of this paper.

Amendment to the Claims

1. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

2. (Original) The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl

cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group

consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (Cancelled)

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-

spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15. (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Cancelled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (Amended) The process of claim 1, wherein said active is an anti-diarrhea preparation.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H_2-antagonist.

35. (Original) The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (Original) The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. (Original) The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. (Original) The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. (Original) The process of claim 72, wherein said second film layer is extruded onto said resulting film. .

77. (Original) The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. (Original) The process of claim 72, wherein said second film is laminated onto said resulting film.

79. (Original) The process of claim 72, further comprising laminating said resulting film to another film.

80. (Original) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim [72]80, wherein said active in said second film is different than said active in said resulting film.

82. (Amended) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives[, drugs, medicaments] and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected

from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol

copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Cancelled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management

agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Cancelled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (Amended) The process of claim 82, wherein said active is an anti-diarrhea preparation.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (Amended) The process of claim [82]113, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step of providing a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (Original) The process of claim 151, wherein said second film comprises an active.

160. (Amended) The process of claim [151]159, wherein said active in said second film is different than said active in said resulting film.

161. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; [and]

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and

[(e)](f) administering said resulting film to a body surface.

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic

acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (Cancelled)

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,

]vitamins and combinations thereof.

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Cancelled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (Amended) The process of claim 161, wherein said active is an anti-diarrhea preparation.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H_2-antagonist.

196. (Original) The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition

provides a sustained release.

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step of providing a second film layer.

234. (Original) The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. (Original) The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. (Original) The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. (Original) The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. (Original) The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. (Original) The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. (Original) The process of claim 233, further comprising laminating said resulting film to another film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim [233]241, wherein said active in said second film is different than said active in said resulting film.

243. (Original) The process of claim 1, said active is an anti-nauseant.

244. (Amended) The process of claim 1, said active is an erectile dysfunction drug.

245. (Original) The process of claim 1, said active is a vasoconstrictor.

246. (Original) The process of claim 1, said active is a stimulant.

247. (Original) The process of claim 1, said active is a migraine treatment.

248. (Original) The process of claim 1, said active is granisetron hydrochloride.

249. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. (Original) The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. (Original) The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. (Cancelled)

255. (Cancelled)

256. (Original) The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. (Cancelled)

258. (Original) The method of claim 1, wherein said resulting film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Original) The method of claim 1, wherein said matrix comprises a dispersion.

261. (Original) The process of claim 82, said active is an anti-nauseant.

262. (Amended) The process of claim 82, said active is an erectile dysfunction drug.

263. (Original) The process of claim 82, said active is a vasoconstrictor.

264. (Original) The process of claim 82, said active is a stimulant.

265. (Original) The process of claim 82, said active is a migraine treatment.

266. (Original) The process of claim 82, said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (Original) The process of claim 82, wherein said resulting film provides administration of said active through gingival application of said individual.

269. (Original) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (Cancelled)

273. (Cancelled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (Cancelled)

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (Original) The process of claim 161, said active is an anti-nauseant.

280. (Amended) The process of claim 161, said active is an erectile dysfunction drug.

281. (Original) The process of claim 161, said active is a vasoconstrictor.

282. (Original) The process of claim 161, said active is a stimulant.

283. (Original) The process of claim 161, said active is a migraine treatment.

284. (Original) The process of claim 161, said active is granisetron hydrochloride.

285. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. (Original) The process of claim 161, wherein said resulting film provides administration of said active through gingival application of said individual.

287. (Original) The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (Cancelled)

291. (Cancelled)

292. (Original) The method of claim 161, wherein said resulting film contains less than about 6% by weight solvent.

293. (Cancelled)

294. (Original) The method of claim 161, wherein said resulting film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

301. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

302. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

303. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

304. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

305. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

306. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

307. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

308. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

309. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

310. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

311. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

312. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

313. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

314. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

315. (New) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes

by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

317. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said

active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

318. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus at a temperature of about 60 °C and using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-

elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

REMARKS

I. Description of the Patent and the Applicant's Reply

The above-identified U.S. Patent No. 7,897,080 (" '080 Patent") is presently under reexamination. Claims 1-299 were issued in the '080 Patent. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 16, 95 and 177, have been canceled herein as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Claims 12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293 have also been canceled purely for clarity. Claims 300 through 318 are new.

While the Examiner's rejection of all the claims is respectfully traversed in all respects, claims 1, 82 and 161 of the '080 Patent have been amended in an effort to advance the prosecution of the present reexamination. Claims 1, 82 and 161 are hereby amended in accordance with 37 C.F.R. §1.530(d) (2) and (f). In accordance with 35 U.S.C. § 314(a), the amendments to claims 1, 82 and 161, new independent claims 315-318, and new dependent claims 300-314 do not enlarge the scope of the claims of the '080 Patent. Explanation of the support for these claims appears below. Entry of this amendment and reconsideration is respectfully requested.

II. Status of Claims and Support for Claim Changes Pursuant to 37 C.F.R. §1.530(e)

The status of the claims as of the date of this amendment is as follows: Claims 1-299 were issued in the '080 Patent and are subject to reexamination. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 300 through 318 are new and are subject to examination. Please cancel claims 16, 95 and 177, as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Please cancel Claims 12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293, for clarity, including some limitations which now appear in the independent claims from which some depend.

In compliance with 37 C.F.R. § 1.530(j), the amendments to claims 1, 82 and 161 do not enlarge their scope or the scope of the original claims or introduce new matter, nor do the

amendments adding new claims 300 through 318 enlarge the scope of the original claims or introduce new matter.

Support for the amendments to claims 1, 82 and 161 and new claims 300 through 318 may be found throughout the '080 Patent, including, the Abstract, Specification, Figures and Claims, for example, at col. 13, ll. 23-36, col. 16, l. 62 through col. 17, l. 3, col. 28, l. 66 through col. 29, l. 6; col. 29, ll. 20-35 and 38; col. 32, ll. 34-41; col. 2, ll. 27-46; col. 15, ll. 28-43, and the Abstract; quoted in detail below; col. 3, ll. 58-60 ("the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval"); col. 19, l. 30 through col. 21, l. 31 (actives including pharmaceutical actives, bioactive actives, and combinations thereof); col. 6, ll. 49-52 ("These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process."); Figures 6, 7, 8, 35 and 36 and col. 14, ll. 20-25 ("drying" and "drying apparatus"); col. 11, ll. 17-19 ("Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition"); col. 11, ll. 21-23 ("yield values . . . force"); col. 12, ll. 20-36, col. 13, ll. 37-38 ("After mechanical mixing, the film may be placed on a conveyor"); col. 29, ll. 11-13 ("As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus"); col. 33, l. 10 through col. 34, l. 24 (example M); col. 44, 11. 9-13 ("the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the 'locking-in' of uniformity of content throughout the film"); col. 4, l. 8; col. 6, ll. 46-52; col. 13, ll. 36-43; col. 26, ll. 9-27; col. 28, ll. 24-58; col. 29, ll. 8-10; col. 20, ll. 65-66 ("Erectile dysfunction . . . drugs"); col. 19, l. 55 ("anti-diarrhea preparations"); col. 6, ll. 52-60 ("Examples of controlled drying processes include . . . hot air impingement across the bottom substrate and bottom heating plates . . . controlled radiation drying . . . such as infrared and radio frequency radiation . . . ."); col. 7, lines 5 through 16 ("This may be achieved by applying heat to the bottom surface of the film . . . or alternatively by the introduction of controlled microwaves to evaporate the water . . . . air currents directed at the bottom of the film should desirably be controlled"); col. 27, ll. 53-55 ("The temperature at which the films are dried is about 100°C. or less"); col. 41, ll. 49-50 ("films were dried in an oven at approximately 60° C."). Support for new claims may also be found throughout the '080 Patent, including, the Figures, Tables and

Claims, for example at col. 19, ll. 10-25, col. 19, l. 30 through col. 22, l. 28, col. 25, ll. 53-60, col. 22, ll. 24-28; col. 28, ll. 1-2; col. 14, ll. 63-65; Tables 17 and 18; Figures 6-8, 33, 34 and 35. Many of the claim elements of the new independent claims can be found in original independent claims 1, 82, and 161 of the '080 patent.

> "Temperatures that approach 100° C. will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of 70° C. for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature.
>
> "Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component."
>
> '080 Patent. col. 12, ll. 20-36.
>
> "For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80° C. for 10 minutes produces a temperature differential of about 5° C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5° C. less than the outside exposure temperature. In many cases, however, drying times of less than 10 minutes are sufficient, such as 4 to 6 minutes. Drying for 4 minutes may be accompanied by a temperature differential of about 30° C., and drying for 6 minutes may be accompanied by a differential of about 25° C. Due to such large temperature differentials, the films may be dried at efficient, high temperatures without causing heat sensitive actives to degrade."
>
> '080 Patent. col. 13, ll. 23-36.
>
> "The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process."

'080 Patent, col. 16, l. 62 through col. 17, l. 3 (emphasis supplied).

"It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and overall appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."

'080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

"The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s). . . . After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples."

'080 Patent, col. 29, ll. 20 through 35 (emphasis supplied).

"An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."

'080 Patent, col. 32, ll. 34-41 (emphasis supplied).

"The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage

units based on films, this virtually mandates that uniformity in the film be present."

'080 Patent, col. 2, ll. 27-46 (emphasis supplied).

"Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. "

'080 Patent, col. 15, ll. 28-43 (emphasis supplied).

III. Declarations Submitted With This Reply

Along with this Reply, the Patentee is submitting the Declarations of Dr. B. Arlie Bogue (Exhibit A) ("Bogue Declaration") and Dr. David T. Lin (Exhibit B) ("Lin Declaration") under 37 C.F.R. §1.132. The Bogue Declaration provides technical results regarding Patentee's commercial pharmaceutical films manufactured in accordance with the '080 Patent and it should not be counted toward the page limit of 37 C.F.R. §1.943. The Lin Declaration provides Dr. Lin's background information, information relating to FDA uniformity of content dosage requirements, and has six (6) numbered paragraphs of statements (¶¶ 17-22) relating to a prior art disclosure at pages 5-6, which might at most be counted as two (2) pages toward the page limit of 37 C.F.R. §1.943.

IV. Background of the '080 Patent

The '080 Patent is a continuation of U.S. application Ser. No. 10/856,176, filed May 28, 2004 now U.S. Pat. No. 7,666,337 (" '337 Patent"), which claims the benefit of U.S. Provisional Application No. 60/473,902, filed May 28, 2003 and is a continuation-in-part of U.S. application Ser. No. 10/768,809, filed Jan. 30, 2004 now U.S. Pat. No. 7,357,891 (" '891 Patent"), which claims benefit to U.S. Provisional Application No. 60/443,741 filed Jan. 30, 2003 and is a continuation-in-part of:

(a) PCT/US02/32575 filed Oct. 11, 2002, which claims priority to: (1) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002 which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (2) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002;

(b) PCT/US02/32594, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and

(c) PCT/US02/32542, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002.

There are pending applications claiming the benefit of the priority of all and/or some of the above.

The '891 Patent is involved in a U.S. litigation wherein Patentee has alleged that the Third Party Requester, BioDelivery Sciences International, Inc. ("BDSI") has infringed its '891 Patent. The litigation is Civil Action No. 10-cv-5695 in the U.S. District Court in the District of New Jersey. In the litigation, Patentee also alleged that the Third Party Requester infringed two other of Patentee's patents, U.S. 7,425,292 (" '292 Patent") and U.S. 7,824,588 (" '588 Patent").

Third Party Requester requested reexamination of the '891 Patent (90/012,098), the '292 Patent (90/012,097) and the '588 Patent (95/001,753) as well. Both the '292 and the '891 Patent successfully exited reexamination. The Examiner on January 23, 2013 issued a Right of Appeal Notice ("RAN") for the '588 Patent reexamination. In response, Patentee filed a Notice of Appeal, a Petition Under 37 C.F.R. § 1.183 Requesting Waiver of the Prohibition of an Extension of Time for Filing an Appeal Brief and for an Extension of Time for Filing an Appeal Brief, and a Petition Under 37 C.F.R. § 1.182 Requesting Continued Reexamination.

Third Party Requester requested reexamination of another of Patentee's related patents namely U.S. Pat. No. 7,666,337 (Control No. 95/002,171), reexamination was ordered, an Office Action issued, Patentee Replied, and Third Party Requester submitted its Comments.

Finally, Third Party Requester requested the reexamination herein of the '080 Patent. .

The '080 Patent has not been and is not currently involved in litigation.

'080 Patent Office Action Statements

In connection with the Order Granting Request for Inter Partes Reexamination of the '080 Patent, Control No. 95/002,170 ("Order Granting IPR Request '080 Patent"), noted above, certain comments were made by the Examiner with respect to Claim 25 of the '337 Patent. The statements were made when the Examiner addressed Third Party Requester's request to find that claim 82 of the '080 Patent should be rejected under 35 U.S.C. § 101 double patenting over claim 25 of the '337 Patent. Patentee supports the Examiner's finding that the Third Party Requester had failed to demonstrate a reasonable likelihood of success of arriving at the subject matter of at least one claim of the '080 Patent. However, Patentee respectfully disagrees with the Examiner's statements interpreting "uniform" and "substantially uniform" therein. In particular, Patentee disagrees that "the active is uniformly distributed (i.e. no variance of active)" in the matrix. Certainly a uniform distribution does not require a state of "no variance". See pages 21 and 22 of the Order Granting IPR Request '080 Patent. "Uniform" and "substantially uniform" are indeed different, but "uniform" from a practical standpoint must of necessity allow for some variance, albeit less than "substantially uniform".

V. The Patented Invention

The present invention is directed to novel and non-obvious processes for manufacturing pharmaceutical and bioactive active containing films, suitable for commercialization and U.S. Food and Drug Administration ("FDA") approval. As noted in the Bogue Declaration, ¶ 4, one manufactured lot of such resulting film can contain 2,000,000 individual dosage units. The claimed processes accomplish this feat while providing the necessary narrow ranges in the amount of active in individual dosage units. As claimed, the '080 Patent, at least, requires a uniformity of content in amount of active (i) in individual dosage units sampled from a resulting film of 10% or less (independent claims 1, 82, 161, and 316-318, see Appendix A, Bogue Declaration), and (ii) in individual dosage units sampled from two or more resulting films of

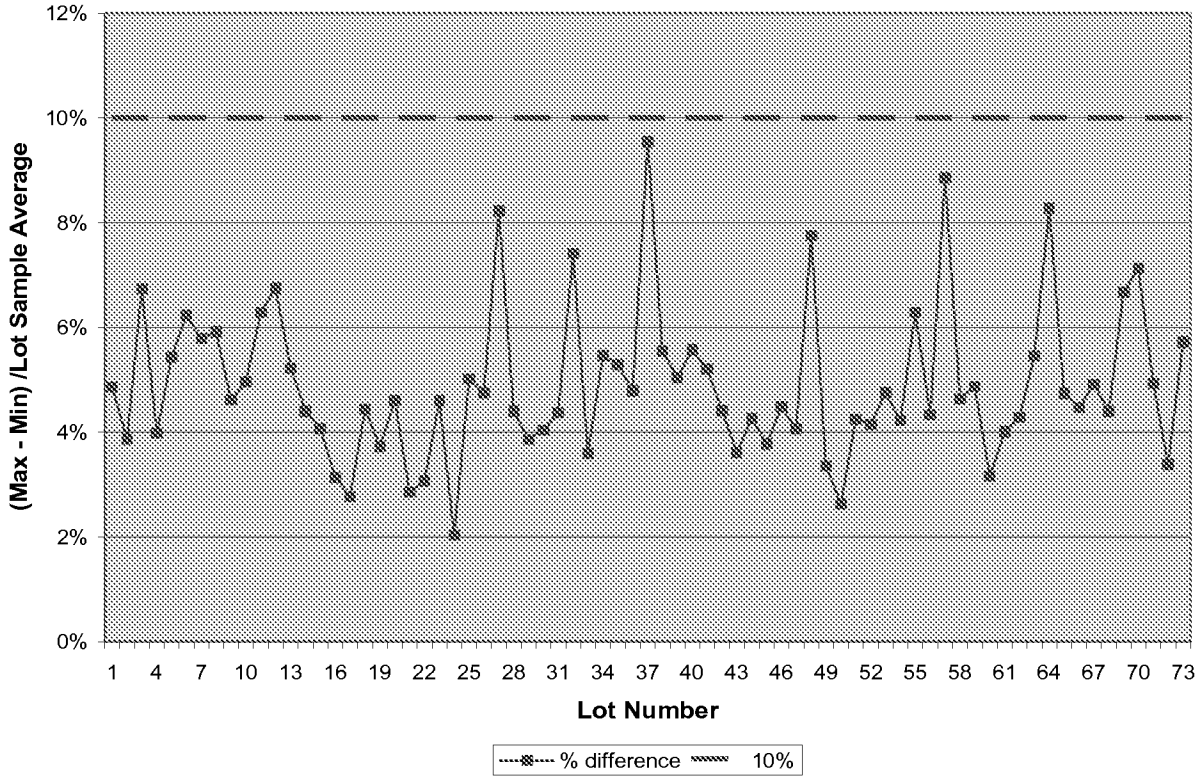
10% or less as a percent difference from a desired amount (independent claim 315, see Appendix B, Bogue Declaration).

One conceptual approach to understanding (i) and (ii) is as follows. A baker has a good recipe or process for making bread. The recipe includes the ingredients and the controlled baking conditions. On Monday the baker bakes a loaf of bread strictly following the recipe. On Friday the baker bakes a loaf of bread again strictly following the recipe. The loaves are cut into individual slices. When tasted, all the slices from Monday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Monday's loaf. In the same fashion, when tasted, all the slices from Friday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Friday's loaf. However, when a slice from Monday's loaf is compared to a slice from Friday's loaf, the difference in taste is more pronounced than between individual slices from the same loaf. Since the baker follows the same recipe for all his/her bread the baker expects that all slices from all loaves should taste alike or almost alike. However, the difference in taste between slices from Monday and slices from Friday is greater than the difference between slices in the same loaf. Indeed, the taste difference is now about 10% from what the baker believes all his/her bread should be expected to taste like-- that is, 10% from the high quality standard ("desired amount" and/or "target amount") for all the bread baked.

In a similar fashion, the "recipe" of Patentee's claimed processes keep differences between individual dosage units from one manufactured lot very small-- e.g. smaller than 10% in amount of pharmaceutical active. See, independent claims 1, 82, 161 and 316-318. The "recipe" of Patentee's claimed processes also keeps differences between individual dosage units between different manufactured lots small as well, just not necessarily as small-- e.g. smaller than a 10% difference from the standard, i.e. desired amount. See, independent claim 315.

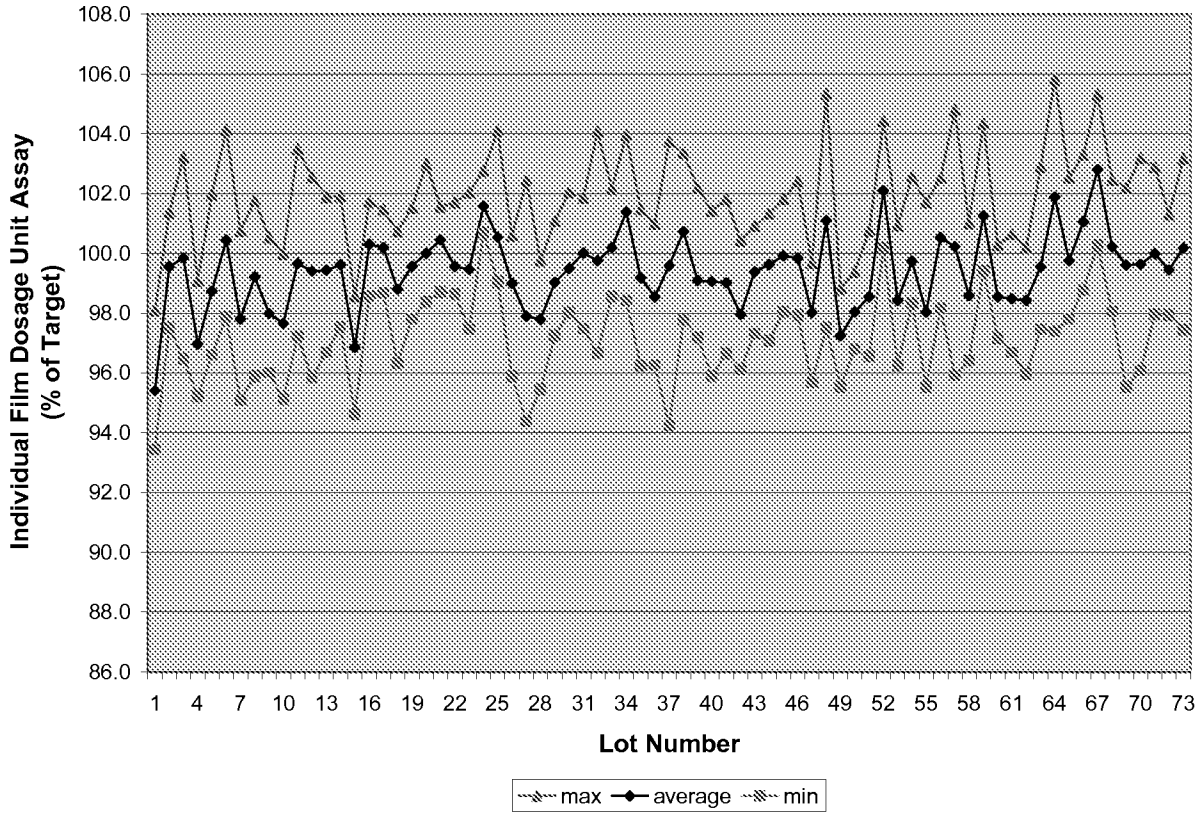
Thus, in the case of a resulting film from one manufacturing lot, the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active in substantially equal sized individual dosage units sampled from the resulting film varies by no more than 10%. See Appendix A from Bogue Declaration copied below and Bogue Declaration, ¶ 9, where this is shown to be true for 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention.

APPENDIX A (Bogue Declaration)



In the case of resulting films from different manufacturing lots the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active varies by no more than 10% from a desired amount. See Appendix B from Bogue Declaration copied below and Bogue Declaration, ¶ 10, where this is shown to be true across 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention. 100.0% indicating the desired amount.

APPENDIX B (Bogue Declaration)



Hence, the manufacturing process of the '080 Patent as claimed is a commercially viable processes which yields commercial viable products meeting FDA regulations, including active assaying requirements.

This should be compared to the laboratory produced films described in the prior art relied on by the Examiner. In the cited prior art, terms such as uniformity, substantial uniformity, and homogeneity are all accepted without real support. They cannot be relied upon. What is missing is the support for the statements -- that is, having had the amount of active tested by analytical chemical testing, including assaying. *See* Lin Declaration, ¶¶ 17-22 (statements about insufficient disclosure in cited prior art reference). Patentee uses the '080 Patent invention to manufacture commercially acceptable products for which Patentee must establish uniformity of content in the amount of active in its products by such analytical chemical testing as required by regulatory agencies, such as the FDA. Dr. Bogue's Declaration describes such testing on

Patentee's products produced in accordance with the invention and the results which are consistent with the '080 Patent's claims for uniformity of content in the amount of active (i) in individual dosage units sampled from a resulting film of 10% or less, and (ii) in individual dosage units sampled from two or more resulting films of 10% or less as a percent difference from a desired amount. Bogue Declaration, ¶¶ 4-11.

PATENTEE'S CLAIMS

Patentee's instant claims recite additional details about its processes for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval. Some of the details include: forming a flowable polymer matrix comprising a polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less; forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film from one lot, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and, in the case of more than one resulting film lot, repeating the process for forming one film lot such that uniformity of content in the amount of said active across all said resulting film lots varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

Additional claim limitations can be found in some of Patentee's narrower independent claims, for example claims 317-318. These claims generally add to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising continuing evaporation to a water content of said resulting film of 10% or less.

As defined in the '080 Patent, a visco-elastic film is one that has been controllably dried to lock its components into a substantially uniform distribution throughout the film while avoiding problems associated with conventional drying methods. By providing a visco-elastic film product having this compositional uniformity or uniformity of content, the user can be assured that the product includes the proper amount of components, such as an active contained therein. Further, the process can be used to make commercially viable large-scale film products, such as large rolls of film from which smaller individual dosage units are cut, the user can feel confident that no matter where the large roll of film is cut, the resulting pieces (e.g., individual unit dosages) will have a substantially uniform composition. As noted above, Patentee successfully manufactures pharmaceutical films containing 2,000,000 individual dosage units meeting FDA requirements using the claimed processes. Bogie Declaration, ¶ 4. As claimed, the uniformity of content as a percent difference will be no more than 10% and in some cases less. The need for providing a process for obtaining the desired uniformity of content of the desired amount of active in the resulting products is critically important, particularly for regulated products, such as the claimed pharmaceuticals.

Prior to the present invention, it was known to prepare films. However, in many cases the end product was merely assumed to be homogeneous, either because the initial components were blended together or because after the blending step the physically observable properties of the resulting film product, for example, its appearance or weight, were satisfactory. However,

these physical properties do not indicate or establish that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units varies by no more than 10% for a particular film. By contrast, for example, in one instance, "the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix." '080 Patent, col. 18, ll. 37-40.

Nor do physical properties indicate or establish that that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units from one film to another film varies by no more than 10% from a desired amount. This range of uniformity is disclosed in connection with, for example, the uniformity of content disclosed in the '080 Patent when referencing the FDA and other regulatory requirements. "Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present." '080 Patent, col 2, ll. 43-45. In these cases, the FDA and/or other regulatory agency sets the amount of active that must be present in an individual dosage unit (or dosage form), *i.e.,* the desired amount, and provides for the necessary uniformity of content, in this case the active may vary by 10% from the desired amount. A "desired amount" is an essential concept, as the FDA indicates the required dosage for each drug, and each drug has its own specified dosage amount. Essential to any pharmaceutical and related product is a viable means of actually testing for the amount of the active present in individual dosage unit samples, and that is to use analytical chemical testing and actually test for the presence of the desired amount of active and thereby determine whether the prescribed uniformity of content of active is present. *See* Lin Declaration, ¶¶ 9-16.

Importantly, the process of forming a proper film product with the claimed levels of uniformity of content in, for example, the amount of active does not end at the mixing stage. Patentee has discovered that the various steps post-mixing play a very important role in ensuring that the resulting product complies with the stringent requirements for uniformity of content. For example, one key step in the formation of a film product is the drying step, particularly when heat and/or radiation is used to dry the film. Patentee has discovered that controlled drying methods is essential in meeting these claimed requirements. Controlled drying includes methods that avoid, for example, the formation of bubbles, or uncontrolled air currents that may cause

movement of particles within the visco-elastic film forming matrix. Controlled drying, as required by the invention as claimed, may be effectuated through evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less.

It is important to understand that compositional uniformity or uniformity of content is not the same as having a surface that appears free of defects. Importantly, having a glossy surface does not equate to a uniform film, because the bottom side of a film product formed on a substrate will take the surface features of the substrate. If the substrate is smooth, the resulting bottom surface will also be smooth and possibly glossy. A product that has a surface that appears free of defects may have experienced significant non-uniformity below the surface, for example due to aggregation and agglomeration of components. It is important to note that just because the surface of a resulting product looks glossy or free of defects does not inherently mean that the actives within the film product exhibit the level of uniformity of content necessary to satisfy regulatory requirements and/or deliver the desired amount to the patient.

The '080 Patent discloses in a section entitled "Testing Films for Uniformity" (col. 28, l. 65 through col. 29, l. 53) that "[i]t may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process". '080 Patent, col. 28, l. 66 through col. 29, l. 1. In particular:

> "It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and over all appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."
>
> '080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

Thus disclosed are two general types of testing, one for physical uniformity, and one for chemical uniformity. The disclosure goes on to provide different ways to test for each.

> "After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art. If the testing results show non-uniformity between film samples, the manufacturing process may be altered. This can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions, mixing conditions, compositional components and/or film viscosity may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others."
>
> '080 Patent, col. 29, ll. 33-38 (emphasis supplied).

In this way the '080 Patent provides multiple tests for non-uniformity, which are extremely useful in guiding the commercial manufacture of films. For example, manufacturing runs of films which appear to exhibit "non-uniformity" may be adjusted early in the run with less waste of materials, thus saving time and expense associated with the possibility of a non-uniform film. Physical tests, such as observational tests, are insufficient to determine the level of uniformity of content disclosed and claimed by the '080 Patent-- they do not determine the actual amount of active in samples.

The '080 Patent discloses testing to determine the appropriate degree of uniformity of content of the resulting film involving sampling substantially equal sized individual dosage units of the resulting film, dissolving the active in the sampled resulting film, and testing for the amount of active present in the sampled resulting film. Thus, the '080 Patent discloses that uniformity of the active is demonstrated through testing.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."
>
> '080 Patent, col. 32, ll. 36-41 (emphasis supplied).

In this respect the Examiner, in his Scope of Claims section has mistakenly included physical uniformity type tests, used to quickly and/or easily suggest non-uniformity, with chemical uniformity type tests involving analytic equipment, that is, the actual testing of the uniformity of content for the amount of active. In the Scope of Claims section of the Office Action (pp. 3-7), the Examiner refers to two different portions of the '080 Patent's "EXAMPLES" section as follows:

> "An alternative means for evaluating uniformity is to cut the films into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39)."
>
> Office Action, p. 7.

Significantly, the two sentences are not related to each other, other than that both deal with examples and with cutting the film into dosage forms. The first is from a physical test, the second, relating to actives, is from an analytical chemical test for uniformity of content of active.

First is the physical test which refers to uniformity in mass.

> "Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:
>
> [Table omitted.]
>
> "The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. **Therefore,** when the components of different densities are combined in a uniform manner in a film, as in the present invention, **individual dosages forms from the same film of substantially equal dimensions, will contain the same mass**."
>
> '080 Patent, col. 31, l. 46 through col. 32, l. 34 (emphasis supplied).

In accordance with this test, if the masses are unequal that would be an indication of mass non-uniformity.

Immediately after the above quoted disclosure, the '080 Patent discloses essentially that to demonstrate uniformity of content for active, the amount of active in each substantially similarly sized sample must be determined.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. **The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active**."
>
> '080 Patent, col. 32, ll. 35-40 (emphasis supplied).

The Examiner also relies on the paragraph at '080 Patent, col. 31, ll. 38-45 for support that physical type tests, in this case observational tests, are sufficient to establish uniformity of content of active.

> "The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film."
>
> '080 Patent, col. 31, ll. 38-45

However, it is one thing to have films which appear to be substantially free of aggregation and rely on that to say there is substantially no disparity among the amount of active in any portion of the film, and it is a totally different thing to demonstrate the presence of the required level of uniformity of content in the amount of active by analytical chemical testing and determining the actual amount of active in samples.

This paragraph, again, from the '080 Patent's section on "EXAMPLES", sets the stage for disclosing both the physical and chemical type tests referred to above at '080 Patent, col. 31, l. 46 through col. 32, l. 40, which follows this paragraph (see citation). Moreover, this paragraph

itself follows the manufacture of the film of Examples A-I and starts with what would be an expected quick and inexpensive procedure of looking at the film right after making it to see if it appears non-uniform or uniform. Such an observational test is at a macro level and does not indicate the degree of uniformity. Even if the film appears uniform, analytical chemical tests must then be conducted to verify uniformity of content at the prescribed level. What followed next were the two other tests discussed above.

Importantly, the first test is obviously a physical type test needed to rely on assumptions to reach its conclusion of substantially no disparity among the amount of active found in any portion of the film. Namely, by "viewing the films it was apparent that they were substantially free of aggregation . . . . Therefore, there was substantially no disparity among the amount of active found in any portion of the film." Based on physical observations a conclusion was drawn. The second, another physical test, concluded "individual dosages forms from the same film of substantially equal dimensions will contain the same mass;" again, referring to mass not uniformity of content of active. Again, no simple declarative statement that the amount of active in each sample was substantially the same or that the actual amount of active was determined.

It was only the third test, the analytical chemical type test that could directly establish that "films of substantially similar size cut from different locations on the same film contain substantially the same amount of active". This is to be expected as only the chemical based tests could provide the necessary assurance for the statement that substantially the same amount of active was present in each dose. Thus, one cannot solely rely on physical tests in prior art disclosures to "establish" that the prior art films actually possessed the levels of uniformity of content as claimed by the '080 Patent. However, analytical chemical testing is used in the '080 Patent to establish the actual amount of active in samples. In one example, in the '080 Patent analytical chemical testing was used to test for the amount of one component, a red dye, and in so doing established that the uniformity of content of the component fell well within the 10% level, particularly, it was 4%. See, '080 Patent, col. 33, l. 10 through col. 34, l. 24 (example M).

VI. Arriving at the Invention

The inventors of the '080 Patent are the first to not only identify the problems associated with manufacturing commercially and pharmaceutically viable active containing film individual

dosage units or forms, but also to solve those problems, especially as same relate to obtaining required levels of uniformity of content. Although many prior publications discussed the use of film as a dosage form for drugs, none of the publications identified nor solved the problems and complications associated with their manufacture. These early publications focused on the compositional and qualitative aspects of the films only and merely treated the manufacturing, if mentioned at all, as being simple, such as exposing the cast wet film to a conventional hot air circulating oven. However, especially in a commercial manufacturing setting, drying an active-containing cast wet film (even if the wet film is homogenous), in a conventional hot air circulating oven does not necessarily produce a film that is commercially viable, or deliver a film with the prescribed degree of uniformity of content in said setting. The '080 Patent does. *See* Bogue Declaration, ¶¶ 4-11.

A. Recognition of the Problem

The inventors discovered that it is not commercially viable to manufacture therapeutic–active-containing films using conventional drying methods. Even when a wet film matrix is properly formed so as to have a substantially uniform distribution of active within it, there are numerous factors which can destroy that uniformity of content during later processing such as casting and drying. The present specification describes many of these problems, which include (i) self-aggregation and agglomeration of active; (ii) skinning of the surface (a barrier through which remaining solvent must penetrate) before the thickness of the film is sufficiently dried, resulting in ripping and re-forming of the surface; (iii) forming of ripples on the surface; (iv) formation of air bubbles, which result in voids or air spaces within the film product; (v) maintaining the active in a substantially stable and uniformly dispersed state; (vi) movement of active particles due to uncontrolled air currents during drying; (vii) using air currents which create forces which overcome the yield value of the polymer matrix, or which would disturb or break the surface of the polymer matrix, or which overcome the inherent viscosity of the polymer matrix. See, for example, col. 3, l. 33 through col. 4, l. 6, and col. 11, ll. 14-25, the '080 Patent.

B. Solving the Problem

The inventors not only were the first to identify all the problems described above, but the first to solve them. Failure to solve one or more of these problems results in a film product that lacks the desired degree of uniformity of content of active per unit dose of film and therefore when equal dosage sizes are cut from the bulk film product, the desired amount of active per dosage lacks the desired and/or required degree of uniformity of content of active. The inventive methods and processes of the '080 Patent maintain the desired uniformity of content of active by, *inter alia*, controlling polymer matrix viscosity and controlling the drying processes so as to avoid the aforementioned problems, thereby forming a visco-elastic film that locks-in the substantially uniform distribution of active(s) during the drying steps. As described in the specification and claims, the present invention maintains the claimed levels of uniformity of content of active from the formation of the initial matrix through the final drying process, such that the pharmaceutical active varies by no more than 10% within a film lot, and by no more than 10% when sampled from different film lots.

The Examiner has cited several references, which will be discussed in further detail below. For ease of understanding, the Patentee will briefly discuss the primary cited references herein. During the discussion, it is important to keep in mind that statements from these sources regarding uniformity of content of components, especially actives, are not based on analytical chemical testing for the amount of active present in equally sized samples, but are at best assumptions, generally based on physically observable properties of the film in its intact state. The below discussion is supported by the Bogue Declaration and the Fuller Declaration.

VIII. The Claim Rejections.

The Examiner's rejection of the claims begins on page 7 of the Office Action.

A. Claims 1-299 were improperly rejected.

Claims 1-299 were rejected as allegedly anticipated under 35 U.S.C. §102(b), or, in the alternative under 35 U.S.C. § 103(a), as obvious over, each of the following references: Chen (WO 00/42992) ("Chen"), Staab (U.S. 5,393,528) ("Staab"), Le Person (*Chemical Engineering and Processing*, Vol. 37, pp. 257-263 (1998)) ("Le Person") and Horstmann (U.S.

5,629,003) ("Horstmann") or some combination thereof as set forth in the Office Action. These rejections relied on the Examiner's findings that material claim elements of the '080 Patent's only independent claims in reexamination, Claims 1, 82 and 161, were inherent in the cited references. Two limitations were of paramount importance, namely the limitations of "substantially uniform distribution of components" and of "locking-in or substantially preventing migration of" active.

Patentee maintains that the foregoing claim limitations are sufficent in themselves to establish patentability. Nevertheless, to advance prosecution, Patentee has explicitly added to all the independent claims herein presented specified levels of uniformity of content in the amount of active. Either a 10% limitation on the amount by which an active can vary between individual dosage units sampled from a particular film, and/or a 10% limitation by which the amount of active can vary from a desired amount among individual dosage units sampled from more than one film, which specificed levels of uniformity of content in the amount of active are not disclosed expressly nor are they inherent in the art of record. Patentee has also explicitly required manufacturing resulting pharmaceutical and/or bioactive active-containing films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units. Additional aspects not present in the art of record include, *inter alia*, viscosity ranges, controlled drying, conveying, applying air currents which have forces below the yield value of the polymer matrix during drying, forming a visco-elastic film in about 4 minutes, keeping the polymer matrix temperature below 100 °C, wherein resulting film has a water content of 10% or less. And the foregoing was just a partial listing of new claim elements. Hence, independent claims 1, 82 and 161, as amended, and all the new independent claims, claims 315-318, are not disclosed and/or made obvious, explictly or inherently, in the cited prior art.

The Examiner relies on the Declaration of Edward D. Cohen, Ph.D. under 37 C.F.R. § 1.132, dated September 6, 2012 ("Cohen Declaration) to support the assumption that it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active. Office Action, pp. 14 and 43. However, Dr. Cohen's assumption is dead wrong on its face or does not apply to the '080 Patent. Importantly, Dr. Cohen does not discuss

the degree of uniformity of content. He refers generally to "substantial uniformity of content of active" and "uniform content of active" per unit dosage. Cohen Declaration, ¶¶ 8-10. Dr. Cohen's statement about uniform content of active, without providing the degree of uniformity of content cannot be applied to the '080 Patent's invention. Especially now that the claims of the '080 Patent expressly require a degree of uniformity of content, namely, that uniformity of content of the resulting film(s) varies (i) no more than 10% with respect to the amount of active within a film (claims 1, 82, 161, 316-318) and/or (ii) no more than 10% from a desired amount with respect to the amount of active; said active sampled from different films in substantially equally sized individual dosage units sampled from different locations of the relevant film(s) (claim 315).

Moreover, as set forth in the Bogue Declaration, ¶¶ 4-11, 730 samples of individual dosage units, ten each from 73 separately manufactured lots of resulting films produced in accordance with Patentee's invention, were tested for active content. The results were that the active content of each individual dosage unit remained well within the control limits of 90% to 110% of the desired amount.

> "The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A. Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.."
>
> Bogue Declaration, ¶ 11.

As noted, the FDA requires that the amount of active vary from dose to dose by no more than a prescribed percentage from the desired amount of active, essentially prescribing a degree

of uniformity of content in the amount of active which must be met. *See* Lin declaration, ¶¶ 9-16. Dr. Cohen provides no support for any prescribed degree of uniformity, and certainly not for the prescribed degree of uniformity of content in the amount of active explicitly recited by Patentee's claims under examination to meet commercial and/or regulatory requirements, or the degree of uniformity present in resulting films manufactured in accordance with Patentee's invention, as clearly demonstrated by the Bogue Declaration.

As held by the Court of Appeals for the Federal Circuit ("Federal Circuit") inherency requires much more than probabilities, possibilities, or for that matter assumptions. In *Crown Operations Intern., Ltd. V. Solutia Inc.*, 289 F.3d 1367 (Fed.Cir. 2002) ("*Crown*"), the patents at issue related to layered films used to create safety and solar control glass. The multi-layer film added properties to the glass assembly, such as impact resistance. An inner layer had solar control properties to reflect, absorb (and thus convert to heat), or transmit defined percentages of certain wavelengths of light. *Crown*, at 1370. The district court had held the only relevant independent claim of one of the patents, the '511 patent, not invalid on the grounds of anticipation and obviousness. It claimed a composite solar/safety film, comprised of a solar control film "wherein said solar control film contributes no more than about 2% visible reflectance". *Crown*, at 1372.

> "Crown [the declaratory judgment plaintiff] argued that U.S. Patent No. 4,017,661 to Gillery (the "Gillery patent") anticipates the '511 patent. The district court held otherwise, because, while the Gillery patent discloses the first three limitations of claim 1 of the '511 patent, it does not disclose the two percent visible reflectance limitation. The court found that neither the Gillery patent claims nor its description expressly disclose a two percent limit on reflectance contribution from the solar control film layer. Crown argued that the two percent limitation was inherently present in the Gillery patent's teachings because the Gillery patent disclosed an assembly with PVB layers, substrate layer, and substrate metal-coating — arguably of the same composition and thickness of the films disclosed by the '511 patent. Thus, Crown argued, because the structure, thickness and materials of the assembly were the same or within the same range(s), the Gillery patent must inherently disclose a two percent limitation. The district court rejected this argument because it found that none of the embodiments disclosed by the Gillery patent meet the two percent visible light reflectance limit."
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> *Crown*, at 1372.

The Federal Circuit, in upholding the decision of the District Court as well as the validity of the '511 patent, discussed the application of inherency to validity that is most relevant here.

> "Regarding alleged anticipation by the Gillery patent, on its face the Gillery patent does not disclose or discuss a two percent limitation for the reflectance contribution of the solar control film. Crown maintains that the '511 patent merely claims a preexisting property inherent in the structure disclosed in the prior art. Crown urges us to accept the proposition that if a prior art reference discloses the same structure as claimed by a patent, the resulting property, in this case, two percent solar control film reflectance, should be assumed. We decline to adopt this approach because this proposition is not in accordance with our cases on inherency. If the two percent reflectance limitation is inherently disclosed by the Gillery patent, it must be necessarily present and a person of ordinary skill in the art would recognize its presence. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed.Cir.1999); *Continental Can*, 948 F.2d at 1268, 20 USPQ2d at 1749. **Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient**." *Id.* at 1269, 20 USPQ2d at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)) (emphasis supplied)."

The alleged inherency of the art cited by the Examiner and discussed below has not been established other than by statements of probabilities and/or possibilities and/or just statements that things are uniform without providing any degree of uniformity that must be present. For example, the assumption that by starting with so-called "uniform" mix of materials, stirring them, then casting and drying as alleged to be disclosed in the prior art is insufficient to establish inherency. Again, inherency requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. Importantly, the mere possibility that some of the films produced as disclosed by the art cited might result in some type of "uniform" film is not sufficent.

1. Chen's alleged inherency.

> "The claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" of the active in independent claims 1, 82 and 161, and the variation of active content of 10% or less in dependent claims 254-255,272-273 and 290-291, are inherent in Chen's exemplified films and process. Inherency is based on the following: As discussed above, Chen uses the

> same materials and method as here claimed. Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection."
>
> Office Action, p. 13.

The criteria used by Chen as cited by the Examiner for evaluation of "substantial uniform distribution" are physical observations. Such "observations" cannot be used, either inherently or otherwise, to establish the uniformity of content in the actual amount of active in equally sized samples in Chen's examples. Absent statements or data based on analytical chemical testing, not weighing or visual inspection, for the amount of active present in the film, Chen does not and cannot inherently disclose Patentee's resulting film having the claimed levels of uniformity of content. Moreover, even if Chen disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra*, at 1378.

Moreover, Third Party Requester has not provided any proof that Chen's process examples when followed exactly, with all the components exactly as listed, and all other conditions of Chen exactly met, will provide a process suitable for commercial manufacture, a process which produces products which are regulatory approvable by the FDA, and which exhibit the levels of uniformity of content in actual amount of active claimed by Patentee's processes. Indeed, FIG. 5 of Chen describes a release profile of almost 120% of active from a film, which certainly exceeds the levels of uniformity of content in the amount of active that Patentee claims. This single active content result voids all claims to Chen's alleged inherency regarding same.

> "Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity

between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film."

Lin Declaration, ¶ 22.

The Examiner states that the films made in accordance with the claims as issued are inherent in Chen. This conclusion is based on the belief that Chen uses the "same materials and method" as the Patentee, but even if true, much more is required. Patentee respectfully submits that this conclusion is incorrect, and particularly incorrect in light of the claims as amended. The Examiner erroneously states that Chen "uses the same criteria" as the '080 Patent that issued in evaluating substantial uniform distribution, i.e. weights of dosages and visual inspection." Although, a number of ways to test films in the patent are disclosed, in order to test content uniformity of an FDA regulated film product, it is necessary to assay using analytical chemical tests for drug or therapeutic active content of unit film doses. *See*, Lin declaration, ¶¶ 9-16. This is necessary to ensure the amount of active is within acceptable guidelines. Visual observation and physical measurements such as weight is insufficient to determine the active amount in equally sized dosage units at the level of uniformity of content required.

All of Patentees' claims now require analytical chemical testing and that the films have levels of uniformity in the amount of active which varies by no more than 10% from film to film and/or no more than 10% from a desired amount across several films. The Examiner's assumption that visual inspection and weight measurements establish these levels of uniformity of content in and by themselves is therefore incorrect, in so far at least as is required by the FDA, for example. Moreover, "Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products." Lin Declaration, ¶ 21.

Finally, there is a misplaced reliance on the physical terms "glossy" and "transparent" in the Office Action, which the Examiner use to establish the presence of "uniformity" in Chen's films. However, the term "glossy" is purely a visual characteristic ("surface luster or brightness") and is not interchangeable with nor equivalent to the uniformity of content of components of a film, nor the content uniformity of an active in the film. *See,* www.merriam-

webster.com/dictionary/glossy. It is also not interchangeable with specified levels of uniformity of content in amount of active in individual dosage units sampled from a film or sampled from different films. The term transparent is also a purely visual appearance characteristic ("transmitting light without appreciable scattering …"). *See,* www. merriam-webster.com/ dictionary/transparent. It is not indicative of the uniformity of content of the film. As such, Chen can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

2. Staab's alleged inherency.

> "Staab also discloses that "[t]he device of the invention thus is composed of a biologically-compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Accordingly, Staab's films inherently have the instantly claimed substantially uniform distribution of components and active. Also, in view of the fact that each film contains 19 mg of benzalkonium chloride and in view of said homogeneous blending, the variation of active in the dosage units is 0% (*sic* 10%), as per claims 254, 255, 272, 273, 290 and 291."
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> Office Action, p. 29.
>
> "In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. Accordingly, Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, after drying for about 10 minutes, a viscoelastic film having less water that before drying is formed."
>
> Office Action, p. 30.
>
> "While Staab does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process."
>
> Office Action, p. 31.

Again, as with Chen, absent statements based on testing to determine the actual uniformity of content in the amount of active present in the film, so as to meet FDA approval, Staab does not and cannot inherently disclose Patentee's resulting film having the claimed levels of uniformity of content, with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film and/or of different resulting films. Staab does not and cannot inherently form a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content within the recited levels of uniformity of content.

Moreover, even if Staab disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra*, at 1378. Moreover, Staab just states that there is 19 mg of benzalkonium chloride present in each sample weighing 190 mg. However, Staab does not disclose testing to determine the amount of benzalkonium chloride present in the final film product or even how each and every sample turned out to be 19 mg. Staab, col. 11, l. 35 - col. 12, l. 3. Staab's resulting structure is a foam rather than the recited visco-elastic film formed within 4 minutes and Staab also would not inherently have the recited degree of uniformity of amount of active in substantially equal sized dosage units. Moreover, Staab starts with a composition having 10% by weight of benzalkonium chloride (50% aqueous) yet allegedly obtains a resulting film with 19 mg benzalkonium chloride in a 190 mg film, to once again obtain a 10% benzalkonium chloride resulting composition. A perfect yield must must always be considered suspect. Inherency should never be based on a suspect disclosure. As such, Staab can neither anticipate, explicitly nor inherently, nor make obvious the '080 Patent claims, see discussion below.

3. Le Person's alleged inherency.

> "Le Person discloses that after 5 min of the drying, 'the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates.' (See p. 262, col. 2, third full paragraph.) Le Person also teaches that '[b]etween the 5th and 10th min of drying the heavy solvent migrates... active substance, slowed down in its migration, stays in the bottom of the layer.' (See the

> last four lines at page 262, col. 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that, inherently, a substantial uniform distribution of the active is locked-in and migration is substantially prevented within the film, as here claimed. The active material homogenizes and a quasi-equilibrium is obtained for the components of the Page 38 active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13), and thus, there is a variation of active content of less than 10%, as per claims 272, 273, 290 and 291.
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> Office Action, pp. 37-38.
>
> "While Le Person does not discuss viscoelasticity or that the films in its process have a 'substantially uniform distribution of components' or disclose 'locking-in or substantially preventing migration' of the active, Le Person, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 82, 89-91,161,171-173, 272-274 and 290-292, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, p. 38.

Le Person is entirely devoid of any details with respect to its process and materials. For example, nowhere does Le Person discuss what type of acrylic polymer he uses nor the molecular weight of the polymer. Thus, Le Person allows for materials which may have such a low molecular weight that forming a visco-elastic film may not be possible. Moreover, Le Person lacks sufficient enabling disclosure to be an effective reference as applied in view of the amended claims. Such deficiencies cannot be used in support of an inherency argument. Again, absent statements and data based on testing for the amount of active present in the film with results establishing a substantial uniformity of content at the claimed levels and suitable for FDA approval, Le Person does not and cannot inherently disclose Patentee's resulting film. Moreover, Le Person does not and cannot inherently form a viscoelastic film in about 4 minutes which locks-in the claimed uniformity of content in the amount of active.

Le Person discloses very little about the acrylic polymer, such as the molecular weight. If the molecular weight was low enough it may not become a viscoelastic material. Patentee asks, how could Le Person anticipate and/or make obvious the '080 Patent which is directed to the commercial manufacture of a regulatory approvable resulting film meeting required specified

levels of uniformity of content in the amount of the active, where Le Person's goal, as noted in its abstract, was devoted to determining "cases of maldistribution of the active substance," in connection with different drying methods, and not to providing a process for manufacturing films with uniformity of content of the desired amount of an active. Importantly, Patentee has added several additional process steps not in the prior art. These new process steps present in the amended independent claim, as well as the new independent claims, further distance Patentee's patent from the prior art. As such, Le Person can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

4. Horstmann's alleged inherency.

> "The claimed substantially uniform distribution of components and active, and locking-in or substantially preventing migration of active, and the variance of active content of 10% or less in dependent claims 254, 272 and 290 are also inherent in Horstmann's Examples 1, 3 and 4. In particular, Horstmann's films before drying are described as being uniform and homogeneous (see col. .3, line 11-19, 29-34 and 37-41; col. 5, lines 1 and 50), and as noted above, Horstmann uses the same components and process steps as here claimed. The '080 patent notes that Horstmann addressed the problem of self-aggregation and nonuniformity by increasing the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film (see col. 2, line 60 through col. 3, line 1).
>
> Office Action, p. 43.
>
> "While Horstmann does not discuss viscoelasticity, water content of its dried films or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the, active, Horstmann, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1, 5,7-10,12-1423,63,64,82,84,86-89,91-93,102,142,143,161, 166, 168-171, 173-175, 184,224,225,249,254,267,272,285 and 290, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, pp. 43-44.

Horstmann forms a gel, rather than a solid film as in the present invention. Thus the gel rheological properties of Horstmann are very different than a solid visco-elastic film having a

water content of 10% or less. Moreover, Horstmann specifically teaches protecting the gels from drying up by placing the cut out gel shapes in a water vapor impermeable sealing material. See Horstmann, col. 5, ll. 11-13. This is a direct teaching away from drying to a water content of 10% or less. Horstmann at col. 2, ll. 25-29, suggests drying may not be necessary.

Again, absent statements based on testing for the amount of active present in the film with results establishing a the claimed levels of uniformity of content in the amount of active, suitable for FDA approval, Horstmann does not and cannot inherently disclose Patentee's resulting film claiming the specified levels of uniformity of content in the amount of active.

Additionally, as the Examiner admits, Horstmann discloses only that its film is alleged to be uniform at a point prior to drying. Horstmann, col. 3, ll. 37-41. Horstmann says nothing about the uniformity of the product during or after drying. Again, *Crown* holds that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* A disclosure of some unspecified degree of uniformity of a film prior to drying in Horstmann does not establish that the product after drying is uniform, let alone the degree of uniformity as claimed by the '080 Patent. As noted throughout the '080 Patent, controlled drying is required for ensuring the claimed levels of uniformity of content. As such, Horstmann can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

Importantly, Patentee has added several additional process steps also not in the prior art. See above. These new process steps present in the amended independent claims, as well as the new independent claims, further distance Patentee's patent from the prior art, by negating any anticipation and obviousness assertions. Even without the additional process steps, even if it were possible that a resulting film with the proper levels of uniformity of content in the amount of active might possibly result from some manipulations of the disclosures given in any of Chen, Staab, Le Person and/or Horstmann, it is incorrect to rely on these references in an attempt to show they inherently disclosed Patentee's resulting film. See *Crown*, at 1377-1378, *supra*.

As the absence of inherency in and of itself removes Chen, Staab, Le Person and Horstmann as viable prior art for rejecting Patentee's claims under 35 U.S.C. § 102, the Examiner should withdraw his rejections of Patentee's claims 1, 82 and 161 based on same. For the same reasons new independent claims 315-318 are allowable. Moreover, these references for

the same reasons discussed above, as well as the reason discussed below, do not support any finding of obviousness, and thus the rejections of claims 1, 82, and 161 based on 35 U.S.C. § 103 should be withdrawn as well. For the same reasons new independent claims 315-318 are not obvious in light of the prior art. Finally, Patentee's claims 2 through 81, 83 through 160, 162 through 299 and 300 through 314 as they depend from independent claims 1, 82, 161 should all be allowed as well, with any rejections withdrawn.

B. Third Party Requester's Wherein Argument is Wrong

Patentee finds it necessary to address Third Party Requester's attempt to vitiate the '080 Patent's claim language beginning with "wherein". Third Party Requester cites to the Federal Circuit for the premise that "a whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed.Cir.2003). Third Party Requester's Request for Inter Partes Reexamination ("The Request"), p. 16.

However, the Federal Circuit has also strongly held that "when the 'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F. 3d 1326, 1329 (Fed. Cir. 2005). Essentially, Requester proposes that with elimination of the "whereby" clauses, the claims 1, 82 and 161 (before the amendments herein) would not require "wherein said resulting film has a water content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained." The Request, p. 20.

As noted above, "when the whereby clause states a condition that is material to patentability, it cannot be ignored to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326 (Fed. Cir. 2005); *see also Fantasy Sports Properties, Inc. v. Sportsline.com, Inc.*, 287 F.3d 1108, 1111-16 (Fed. Cir. 2002); *Griffin v. Bertina*, 285 F.3d 1029, 1034 (Fed. Cir. 2002). In *Griffin*, for example, the court found that "wherein" clauses were claim limitations "because they relate back to and clarify what is required by the count. Each 'wherein' clause ... expresses the inventive discovery [and] ... elaborates the meaning of the preamble." *Griffin*, 285 F. 3d at 1033-34. Further, "the allegedly inherent properties of the 'wherein clauses' provide the necessary purpose to the steps." *Id.* See also, MPEP, § 2111.04.

The '080 Patent independent claims' wherein clause limitations cannot be disregarded. The '080 Patent claims processes for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films. The ability to make such films with the required level of uniformity in content of active is the essence of Patentee's invention. Thus, such wherein clauses which express the inventive discovery and elaborates the meaning of the preamble cannot be ignored for purposes of patentability.

Finally, Third Party Requester has made many allegations about the '080 Patent and its specifications and claims, and the prior art in The Request. Patent owner believes that the amendments to claims 1, 82 and 161 herein clarifying the scope of same and thereby advancing the prosecution of same, obviate the need to address Third Party Requester's allegations or the Examiner's statements made without the benefit of the amendments. Nevertheless, to the extent that any are not explicitly addressed herein, Patentee hereby asserts they are wrong and unsupported in either fact or law.

C. Claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84,87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen.
Claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Chen, WO 00/42992 ("Chen") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Chen. Patentee incorporates its previous discussions in sections A. and B. above. Chen is a primary reference relied upon by the Examiner in the Office Action. Patentee

respectfully traverses the above rejections on the basis, among others, that Chen does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of a lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Chen also fails to disclose, explicitly or inherently, the additional elements found in Claim 317. Claim 317 generally adds, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Chen discloses two methods of forming a film product, a solvent casting method and an extrusion method. The extrusion method does not rely upon putting a hydrocolloid in a solvent, nor does the extrusion method use a drying oven and is apparently preferred by Chen over the solvent method. Chen, page 15, lines 9-21. In the solvent casting method, Chen states that a hydrocolloid is dissolved or dispersed in water, and mixed to form a homogeneous solution. The active agent and other ingredients may be added and dispersed or dissolved uniformly in the hydrocolloid solution. The coating solution with a solid content of 5-50% and a viscosity of 500-15000cps is degassed and coated onto a polyester film and "dried under aeration" at a temperature between 40-100°C to avoid destabilizing the agents. Chen, p. 15, ll. 19- 29. The dry

film formed by this process is described to be a "glossy, stand alone, self supporting, non-tacky and flexible film". Chen, p. 15, ll. 30-31. These very general statements are all that are given by Chen as to the formation and drying of Chen's film product. These statements cannot support either anticipation or obviousness rejections.

Chen's drying process is so general and devoid of detail so as to provide no guidance other than that to dry, one places a film in a conventional hot air circulating oven at temperatures of from 40-100°C and leaves it for a period of time. Chen does not disclose any other drying methods beyond drying "under aeration", nor does Chen disclose any controlled drying processes whatsoever. Chen showed no recognition of the complexities involved in the commercial manufacturing of films, as Chen's focus relates solely to the ingredients and mechanical properties, not the process. Without any recognition of the problems, and without any appreciation of the difficulties in preventing the settling, migration and/or aggregation or agglomeration of active(s) in the cast flowable mass, Chen neither sought nor found the solution to creating commercial scale films having uniformity of content of pharmaceutical and bioactive actives per individual dosage unit and meet FDA requirements regarding same. Chen lacks substantial disclosure in view of the '080 Patent. Among its deficiencies, Chen lacks any disclosure as to specific processing means (beyond generally drying in a generic oven) or the formation of a visco-elastic film state. Chen only discloses the apparent homogeneity of a blended matrix, and this is prior to the addition of actives. There is no disclosure or suggestion as to how to create a substantially uniform distribution of the pharmaceutical or biological active in the blended matrix and then cast that matrix to maintain uniformity, and then control drying through among other processes conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 to maintain said uniform distribution of said pharmaceutical or biological active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film and then test it to establish the substantially uniform distribution of pharmaceutical or biological active content, in compliance with FDA regulations.

Among other things, the '080 Patent claims are directed to locking-in an active such as a pharmaceutical or biological active, by controlling drying to form a viscoelastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes. The Examiner has stated in the Reexamination, Reasons for Patentability/ Confirmation ("RFP/C"), in connection with both the '292 Patent and the '891 Patent reexaminations that "Chen does not discuss what happens within the first 4 minutes of drying." Moreover, in the '891 Patent RFP/C the Examiner goes on to state that: "Chen does not discuss uniformity of pharmaceutical or biological active components in its doses. Table 4 of Chen gives the grams per unit dosage film and density for Example 1 with standard deviation based on three or four measurements, but does not give compositional uniformity." Additionally, Chen's Example 1 contains only food flavorings and a sweetener.

Chen does not disclose that the resulting products are compositionally uniform, but only that they are "glossy". As stated above, glossy does not imply or establish compositionally uniformity. In fact, Chen's Figure 5 (Examples 5-8) clearly shows a lack of compositional uniformity of active. Although statistics are not defined in the text, the error bars represent either high or low values, standard deviation or some measure of variation. Given that the compositions of Examples 5-8 are the same, except for the amount of active, it is reasonable to conclude that the active is not uniformly present in the individual films due to the wide variation of release of active from the same film compositions. For example, with regard to the release of nicotine in the same film compositions, the release reaches in excess of 118%. Certainly there is neither disclosure of, nor inherency in, the that the level uniformity of content in the amount of active as sampled in individual dosage units of the same film be 10% or less. "The release profile data presented in Figure 5 show a high degree of variability at each data point. This indicates that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film." Lin Declaration, ¶ 22.

As defined in the specification for the '080 Patent as filed, a visco-elastic solid is one that has been sufficiently dried to lock its active components into a substantially uniform distribution throughout the film. The '080 Patent claims require that this be done within about the first 4

minutes or less. The Examiner has previously acknowledged that Chen does not disclose that the resulting film product has any compositional uniformity of pharmaceutical or biological active at that point in time. See '891 Patent RFP/C. Neither Chen nor the other references teach this step.

As explained throughout the '080 Patent and as summarized above, the present invention is based upon the discovery that certain process parameters, such as, viscosity and controlled drying methods to avoid non-uniformity of content in the amount of active must be employed to provide a commercially and FDA viable film product. Chen does not disclose or suggest such a resulting product. *See* Lin Declaration, ¶¶ 17-22. Chen discloses that various components (absent the active) are combined and that the mixture is blended to form a "uniform" solution. (Chen, p. 20, ll. 19-20). although even the formation of a uniform solution in a blender is beneficial, it is not the end of the process by any means. Further, as explained above, conventional drying methods do not inherently provide uniform films and, in fact, would not be expected to provide resulting films having the claimed uniformity of content in the amount of active.

Patentee's claimed processes are not present in Chen, either expressly or inherently, and Chen cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited Chen reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Chen does not render obvious the pending claims .

D. Claims 2, 3, 16, 32, 55, 72-81, 95, 111, 134, 151-160, 177, 193, 216 and 233-242 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

The Office Action rejected the above claims under 35 U.S.C. § 103(a), as being unpatentable over the combined teaching of Chen and Staab, U.S. 5,393,528 ("Staab"). Patentee incorporates its previous discussions in sections A., B. and C., above, and E., below and traverses all said rejections thereon. As all the above claims depend from one of the independent claims, claims 1, 82 and 161, they are allowable for all the reasons provided in the sections dealing with Chen, above, and Staab, below and even combined Chen and Staab do not render obvious the pending claims of this rejection.

E. Claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78- 84, 89, 91-95, 100, 103, 104,111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171,173-177,182,185,186,193,205-207,215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Staab.
Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 were rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Staab, or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Staab. Patentee incorporates its previous discussions in sections A., B., C. and D., above, Patentee respectfully traverses the rejection on the basis, among others, that Staab does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the pharmaceutical and/or bioactive active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Staab certainly does not disclose, explicitly or inherently, the additional claim elements of Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising

drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Moreover, Staab teaches the benefits of using a "gas foamed film" or films. Staab, col. 5, ll.33-35; col. 8, ll. 33. Staab thus teaches away from the '080 Patent by teaching that air bubbles are necessary, which are contraindicated in Patentee's invention requiring a substantially uniform distribution of active. Staab instead teaches that gas bubbles must be added to the polymer/drug mixture prior to casting.

> "It should be noted that heretofore, the significance of the addition of gases in the formation of the film to alter the texture and solubility of the film has not been recognized."
> Staab, col. 3, ll. 15-20.

> "**The fine tuning of dissolution rates and delivery of agent material, by the addition of gases and by altering the grades or mixtures of polymer materials or layers, is an important aspect of the present invention.**
>
> * * * *
>
> **"The gases, for example, air or nitrogen are introduced near the point of application of the liquid polymer material to the stainless steel casting sheet. The gases are added in a closed system by mixing with whipping blades or a motor driven homogenizer to homogenize the mixture of polymer, active material and gas to form a frothy foam. The final mixture then sets up or gels as a foam.** It is also possible to pour the frothy foam mixture into a mold. The mold is then deformed and the formed device such as a diaphragm, is removed."
> Staab, col. 8, ll. 29-64 (emphasis supplied).

In direct conflict with Staab's teaching, the '080 Patent teaches the use of anti-foaming agents to **prevent** gas bubble formation and thereby promote uniformity. Importantly, Patentee's processes, in many cases, avoid the formation of bubbles, without the need to use anti-foaming agents.

> **" Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product."**
>
> '080 Patent, col. 4, ll. 5-21 (emphasis supplied).

> "A number of techniques may be employed in the mixing stage to **prevent bubble inclusions in the final film. To provide a composition mixture with**

substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed.."

'080 Patent, col. 9, ll. 56-65 (emphasis supplied).

See also section of '080 Patent entitled "Anti-foaming and De-foaming Compositions" ('080 Patent, col. 22, l. 47 through col. 23, l. 53).

Staab addresses the fine tuning of dissolution rates and delivery of active agent, by teaching the addition of gases as an important aspect of his invention (Staab, col. 8, ll. 30-34). Staab is silent with respect to the recited levels of uniformity of content. The '080 Patent in connection with achieving uniformity of content in the amount of active teaches avoiding bubble formation and the removal of such gases and bubbles ('080 Patent, col. 9, ll. 56-65). Moreover, Staab uses conventional drying (Staab, col. 11, ll. 64-65) rather than the particular drying methods used to ensure the uniformity of content claimed by the '080 Patent.

The presently claimed process is not disclosed in Staab, either expressly or inherently, and Staab does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Staab does not render obvious the pending claims of the above rejections.

F. Claims 82, 89-91, 161, 171-173, 272-274 and 290-292 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Le Person.
Claims 92 and 174 were rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Le Person, Chemical Engineering and Processing, Vol. 37, pp. 257-263 (1998) ("Le Person") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Le Person. Patentee incorporates its previous discussions in sections A., B., C., D. and E., above, Patentee respectfully traverses the rejection on the basis, among others, that Le Person does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by

locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Le Person certainly does not disclose, either explicitly or inherently, the additional claim elements found in Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Le Person does disclose that the drying step used plays a role in the final product, but fails to disclose or suggest how to achieve a uniform final product. In fact, Le Person discloses methods that result in a non-uniform product prior to and at 10 minutes. According to Le Person, the resulting product dried in 9 minutes would not have claimed uniformity of content of active.

Le Person's goal was to determine "cases of maldistribution of the active substance," in connection with different drying methods, said maldistribution having consequences on storage and delivery of a drug and proposes the use of Laser Scanning Confocal Microscopy on the active substance and the heavy solvent to determine same. (Le Person, Abstract). Le Person acknowledges that in the formation of a film product, "drying is the essential unit operation necessary to form the final product." (Le Person, p. 257). Le Person's experimental set-up was composed of two parts, "the drying cell and the wind tunnel. . . . [wherein] the wind tunnel is a conventional drying rig. . . ." Le Person, p. 258, col. 2 & Fig. 1. Le Person's disclosure of the

use of a wind tunnel further negates any argument that Le Place inherently anticipates or makes obvious Patentee's invention.

It is important to note that Le Person simply recognized the overall, general difficulty in obtaining films with a substantially uniform distribution of active. Le Person did not try to solve this problem, only to determine means to identify it. Thus, Le Person did not recognize the specific reasons therefor, nor did Le Person recognize the solutions needed to overcome this difficulty. Le Person's goal was to find ways to best determine whether or not there was homogeneity of film product.

However, the point of Le Person is that, in the time period (i.e., less than 10 minutes), there is non-uniformity of the product. Le Person even states that "intense moisture removal through the exposed surface of the layer to the radiation, during the first 3 min of drying (Le Person, Fig. 7) produces a stress on the polymer skeleton … and as a result the acrylic polymer becomes more and more dense in the upper part of the layer (exposed surface)." (Le Person, p. 261). As a result, this "intense" shrinkage results in displacement of the active phase. As such, Le Person's disclosure is not directed towards achievement of a film having a substantially uniform distribution of an active through drying, and in fact, if anything, teaches away from achieving uniformity of content in the amount of an active.

The presently claimed processes are not present in Le Person, either expressly or inherently, and Le Person does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Le Person does not render obvious the pending claims.

G. Claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hortsmann.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Horstman, et al. U.S. 5,629,003 ("Horstmann") or, in the alternative under 35 U.S.C. § 103(a), as obvious over Horstmann. Patentee incorporates its previous discussions in sections A., B., C., D., E. and F., above, Patentee respectfully traverses the rejection on the basis, among

others, that Horstmann does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, by no more than 10% from the desired amount across different resulting films, and is in compliance with FDA regulations governing same.

Horstmann certainly does not disclose, either explicitly or inherently, the additional claime elements of Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Moreover, the '080 Patent's description of the differences between Horstmann and Patentee's invention claimed in the '080 Patent is relevant to the Examiner's current rejections as well. For example:

> "In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann . . . incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other

such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. " '080 Patent, col. 2, l. 63 to col. 3, l. 9.

Horstmann's use of conventional drying methods and need for gel formers teaches away from obtaining a resulting film with the desired levels of uniformity of content in the amount of active. Horstmann does not disclose the degree of uniformity of content, merely, for example, in Example 2, referring to film sections containing "approximately" 3 mg of active and a weight of "approximately" 80 mg. Horstmann, col. 5, ll. 15-36. Horstmann does not disclose that these amounts are based on any testing, or for that matter what they are based upon, or that they comply with FDA requirements relating to drug products.

The presently claimed process is not present in Horstmann, either expressly or inherently, and Horstmann cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Horstmann does not render obvious the pending claims.

IX. Conclusion

No reference, either alone or in combination with other references, teaches the processes claimed by the '080 Patent. Entry of the amendments herein is respectfully requested. Patentee traverses all rejections of its claims. For at least the reasons set forth above, independent claims 1, 82, 161, and 315-318 are allowable. Claims 2 - 81, 83 - 160, 162 - 314 are allowable at least based on their dependencies, whether direct or indirect, from independent Claims 1, 82, 161 . Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections to same. Should the Examiner have any questions regarding this response, the undersigned would be pleased to address them.

Respectfully submitted,

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CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

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EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

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March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation,

processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. I have read the '080 Patent and the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Office Action") and the references cited therein, and I have also reviewed the amendment as to the independent claims set forth in Patentee's Reply to the Office Action concurrently filed herewith.

II. Producing resulting films in accordance with the '080 Patent

4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

5. Additionally, the uniformity of content in the amount of active as sampled from the 73 lots of resulting film varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests from 4(e) above. [See Appendix B]

III. Analytical Chemical Testing for Uniformity of Content of Patentee's Resulting Films

6. To demonstrate the uniformity of individual dosage unit films, I compiled individual dosage unit assay data for individual Lots 1- 73, all of which were disclosed in MonoSol's 2012 Annual Product Review to the FDA.

7. Ten (10) individual dosage units all having the same dimensions were cut out from different locations of each of the 73 lots of resulting films using a commercial packaging machine, thus providing 730 randomly sampled individual dosage units, ten each from the 73 separate lots. All samples were analyzed by a validated method, in compliance with FDA guidelines and regulations regarding same, using analytical chemical testing, in which the pharmaceutical active

was extracted and analyzed by High Performance Liquid Chromatography (HPLC) against an external standard to quantify the amount of active present in each individual dosage unit.

8. According to the inventive process set forth and claimed in the '080 Patent, and in accordance with FDA nomenclature, I have prepared tables shown as Appendices A, B and C, reflecting the uniformity of content of active of individual dosage units within particular lots and across different lots.

9. First, the uniformity of content of active in a lot is determined through establishing the amount of active ($A_{N(i)}$) actually present in each sampled individual dosage unit from the same lot (N) as determined by taking the difference between the amount of active in the sample with the most active ($Max_{LOT(N)}$) minus the amount of active in the sample with the least amount of active ($Min_{LOT(N)}$) and dividing the difference by the average amount of active in the lot samples ($Lot_{(N)}$ Sample Average). That is: $(Max_{LOT(N} - Min_{LOT(N)}) / ((A_{N(1)} + A_{N(2)} + + + A_{N(10)})/10)$. The results are shown in Appendix A.

10. Second, the uniformity of content across different lots is determined through establishing the amount of active actually present in each sampled individual dosage unit from all 73 lots and comparing that amount of active with a "target" or "desired" amount of active contained therein. The target amount of active, when it is a pharmaceutical, is referred to as the "Label Claim", thus identifying the amount of pharmaceutical active in the film to a user. The desired amount is 100% of the target amount. Each individual dosage unit film cut from any individual lot must have the desired content of pharmaceutical active, varying no more that 10% from the target or desired amount. See Appendix B.

IV. '080 Patent Process Produces Films With Required Uniformity of Content of Active

11. The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A.

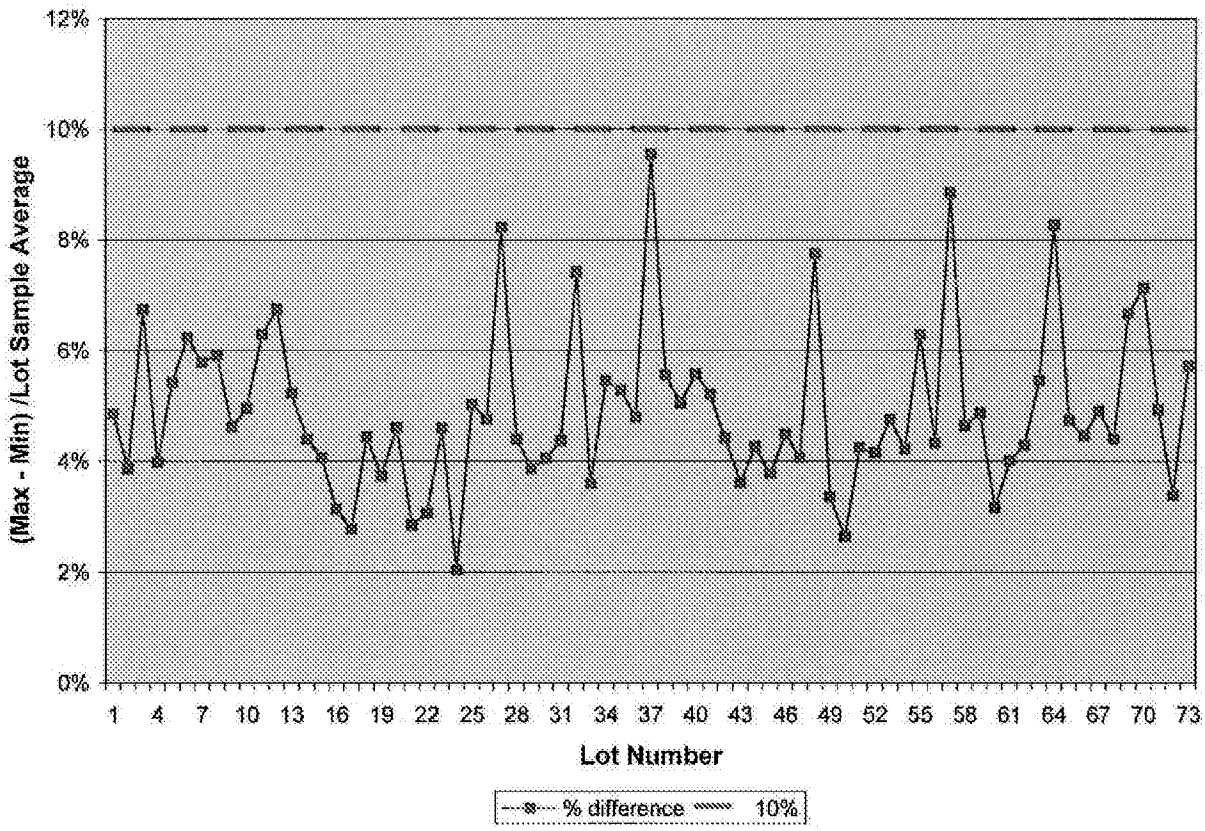
Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

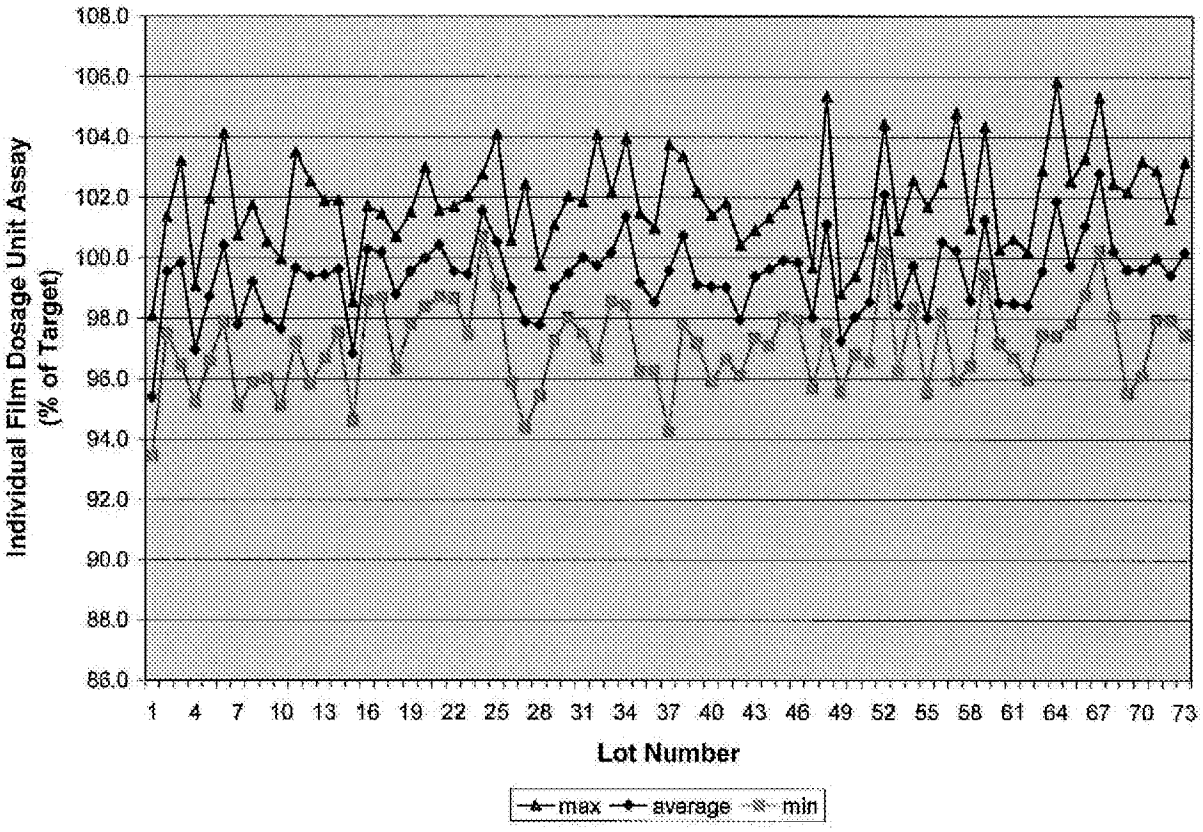
Dated this 13th day of March, 2013

B. Arlie Bogue

APPENDIX A



APPENDIX B



APPENDIX C

Lots less than 5%			lots 5% to 10%	
Lot #	% Difference		Lot #	% Difference
24	2.0%		10	5.0%
45	2.6%		25	5.0%
17	2.8%		39	5.0%
21	2.8%		41	5.2%
22	3.1%		13	5.2%
16	3.1%		35	5.3%
60	3.2%		5	5.4%
50	3.4%		63	5.5%
72	3.4%		34	5.5%
33	3.6%		38	5.6%
43	3.6%		40	5.6%
19	3.7%		73	5.7%
46	3.8%		7	5.8%
29	3.9%		8	5.9%
2	3.9%		6	6.2%
4	4.0%		11	6.3%
61	4.0%		55	6.3%
30	4.0%		69	6.7%
48	4.1%		3	6.7%
15	4.1%		12	6.7%
52	4.2%		70	7.1%
54	4.2%		32	7.4%
51	4.2%		49	7.8%
44	4.3%		27	8.2%
62	4.3%		64	8.3%
56	4.3%		57	8.9%
31	4.4%		37	9.5%
28	4.4%			
14	4.4%			
68	4.4%			
42	4.4%			
18	4.4%			
66	4.5%			
47	4.5%			
23	4.6%			
20	4.6%			
9	4.6%			
58	4.6%			
65	4.7%			
26	4.8%			
53	4.8%			
36	4.8%			
1	4.9%			
59	4.9%			
67	4.9%			
71	4.9%			
total	46		total	27

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

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Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF DAVID T. LIN, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, David T. Lin, Ph.D. do hereby make the following declaration:

I. SUMMARY OF CREDENTIALS AND EXPERIENCE

1. Since January 2005, I have served as a Senior Consultant to Biologics Consulting Group, Inc. ("BCG"), a team of consultants who provide national and international regulatory and product development advice on the development and commercial production of small molecular weight synthetic drug, biotechnological and biological products.

2. While BCG is being paid for my time, I am not an employee of, nor do I have any financial interest in, MonoSol Rx, LLC ("Patentee" and/or "MonoSol").

3. Before joining BCG, I held various positions with the United States Food and Drug Administration ("FDA"). From 1997-2001, I was a Chemistry Reviewer in the Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research ("CDER"). In 2001, I became the Team Leader in the same Division and served in that role until 2003 when I was promoted to the position of acting Deputy Division Director in the Division of New Drug Chemistry III, Office of New Drug Chemistry (currently referred to as Office of New Drug Quality Assessment). In 2004, I was promoted to the position of acting Division Director.

4. As a Chemistry Reviewer at CDER, I was responsible for the comprehensive review of Chemistry, Manufacturing and Controls ("CMC") data for drugs being investigated during Phase 1, 2, and 3 clinical studies. I was also responsible for the review of CMC data in New Drug Applications and provided regulatory input to CMC reviewers responsible for review of Abbreviated New Drug Applications. This included providing scientific and regulatory guidance during development of small molecular weight drugs and biotechnological/biological drugs across a wide variety of dosage forms. I have reviewed CMC data submitted with respect to over 100 Investigational New Drug Applications and New Drug Applications (original and supplemental) as a chemistry reviewer, contributed to decisions regarding the approval of drugs, made presentations before scientific and regulatory conferences and participated in a variety of special FDA projects and committees, including serving as the co-Chair of the CMC Good Review Practices Committee.

5. As Team Leader, acting Deputy Division Director and acting Division Director in the Office of New Drug Chemistry, I was actively involved in directing the content of FDA guidances that pertained to CMC topics. As acting Deputy Division Director and Division Director, I was directly involved in discussions, regarding the content of the 2003 FDA draft guidance on Drug Product-Chemistry, Manufacturing, and Controls Information, with the committee responsible for writing this guidance. I had signatory authority for this draft guidance prior to public issuance by FDA. As acting Deputy Division Director and Division Director, I was involved in regular meetings with the supervisory staff in the Office of Generic Drugs to discuss regulatory and review policy issues that are common to both New Drug Applications and Abbreviated New Drug Applications.

6. I consider myself an expert in the fields of FDA practice and procedure as applicable to the testing requirements for drugs and review of Investigational New Drug Applications (INDs) and New Drug Applications (NDAs).

7. I received my B.A. in Biochemistry from the University of Pennsylvania in 1984, my Ph.D. in Organic Chemistry from the University of Maryland in 1989 and my M.B.A. from the University of Maryland's RH Smith School of Business in 2002. Attached hereto as Exhibit A is my curriculum vitae, including a list of my publications for the past ten years.

8. I have carefully reviewed Chen (WO 00/42992) ("Chen").

II. U.S. STATUTORY AND REGULATORY BACKGROUND FOR TESTING DRUGS FOR POTENCY AND DOSAGE UNITS FOR UNIFORMITY

9. From a US regulatory perspective, for a drug to be approved for commercial marketing and distribution, specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product must be provided in a New Drug Application.[1] In addition, reference to the current U.S. Pharmacopeia (USP) may satisfy these requirements.

10. Section 501(b) of the Food, Drug, and Cosmetic Act (the Act) deems an official drug (i.e., a drug represented as a drug which is recognized in the U.S. Pharmacopeia) to be adulterated if it fails to conform to compendial standards of quality, strength or purity. Compendial tests or assay methods are used when determining such conformance under 501(b); the standards are stated in individual monographs as well as portions of the General Notices section of the USP/NF. Standards and test methods have been established for such characteristics as potency and content uniformity.

11. Section 501(c) of the Act deems a drug that is not recognized in the USP to be adulterated if it fails to meet the strength, purity or quality which it is represented to possess.

[1] 21 CFR 314.50(d)(1)(ii)(a)

The applicable quality standards for a drug not recognized in the USP can be determined from such sources as the labeling of the drug (or drug product), the manufacturer's written specifications, and new drug applications.

12. The current good manufacturing practice (cGMP) regulations include the minimum requirements for the preparation of drug product for administration to humans. One of the requirements is that the strength[2] of the drug (active ingredient) in the drug product must be determined for each batch of drug product manufactured for commercial distribution.[3] Strength is taken to mean content or assay of the drug.

13. Batch uniformity of the drug products is ensured with procedures that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.[4] FDA also describes in guidance that it is expected the sampling plan for drug product is representative of the batch.[5]

14. Controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that the drug product conform to appropriate standards of identity, strength, quality, and purity.[6]

15. Regulatory specifications must be established to ensure that the dosage form will meet acceptable therapeutic and physicochemical standards throughout the shelf-life of the marketed product.[5] These specifications include tests for strength (content or assay) and uniformity of dosage units.

---

[2] 21 CFR 210.3(b)(16)

[3] 21 CFR 211.165(a)

[4] 21 CFR 211.110(a)

[5] FDA Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products, February 1987

[6] 21 CFR 211.160(b)

16. Testing to establish uniformity of dosage units is defined in the USP under the USP general chapter <905>.[7]

III. CHEN'S DISCLOSURE IS INSUFFICIENT

17. I have been asked to review Chen and render an opinion as to whether there is sufficient information contained within to allow regulatory FDA approval and commercialization of a drug product that is manufactured as described. After review of the patent in light of FDA practice and procedure, it is my opinion that there is insufficient disclosure to allow FDA to determine that a drug product as described can be manufactured for commercial distribution, manufactured in a consistent manner and meet specifications that will ensure the identity, strength, quality, purity, and potency of the drug product. In particular, Chen lacks any disclosure which would necessarily lead to the manufacture of films with uniformity of content (strength) of drug active required for FDA approval.

18. As would be required for FDA approval Chen does not disclose sufficient information that films containing drug can be produced consistently with respect to uniformity of content of the drug. No information was disclosed that demonstrated uniformity of content in the amounts of drug in individual dosage units. Chen discloses no specific test methods, and hence no test results, that could allow for the determination of the actual amount of drug (active) in individual dosage units.

19. As required for FDA approval, Chen's patent did not disclose sufficient information regarding the manufacturing process and process controls. The information disclosed by Chen would not ensure that films containing drug could be manufactured to meet specifications that ensure consistent strength.

20. Even if the information disclosed in Chen could be utilized to develop a manufacturing process for films containing drug, there is no information regarding the test methods that are necessary to determine the amount of drug in individual dosage units.

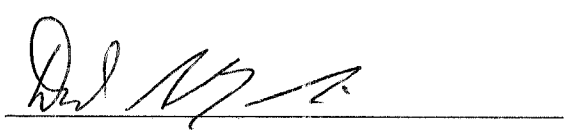
[7] USP General Chapter <905> Uniformity of Dosage Units

21. Therefore, Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products. It is my understanding that an inherent disclosure may not be established by probabilities or possibilities and that the mere fact that a certain thing may result from a given set of circumstances is not sufficient and that to be inherent requires that the missing disclosure is necessarily present.

22. Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film.

23. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 13th day of March, 2013



David T. Lin

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF DAVID T. LIN, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

EXHIBIT A

DAVID TSOCHUNG LIN

9121 Fall River Lane, Potomac, MD 20854 (301) 299-2853 dlin@bcg-usa.com

EXPERTISE

- 18+ years pharmaceutical regulatory experience.
  - 7+ years regulatory chemistry, manufacturing and controls (CMC) experience at CDER/FDA on small molecular-weight drugs, botanical drugs, peptide drugs, and protein drugs formulated in a broad range of sterile and non-sterile dosage forms.
  - 3+ years research experience at CBER/FDA.
  - 8+ years experience as regulatory CMC consultant.
- Unique combination of biologic/biotechnological and small molecular-weight drug regulatory experience, including device/drug and device/biologics combination products.
- Understanding of FDA regulatory requirements and expectations for drug development and marketing approval.
- Performed primary CMC review and assessment of drug products for treatment of reproductive and urologic disorders and diseases.
- Supervised CMC review activities in 7 CDER medical reviewing divisions including Reproductive/Urologic, Anti-viral, Dermatologic/Dental, Anti-inflammatory/ Analgesic/Ophthalmologic, Anti-infective, Special Pathogen/Immunologic, and Over-the-Counter drug products.
- Understanding of drug substance and drug product analytical method development and validation.
- Understanding of drug substance and drug product stability protocol development and stability data analysis.
- Understanding of current Good Manufacturing Practices (cGMPs)
- Experienced in chemical synthesis, small-scale and pilot-scale fermentation, biologics/ biotechnology, and protein chemistry.
- Experienced working in cross-functional teams (i.e., Pharmacology/toxicology, Clinical, Biostatistics, Biopharmaceutics, and Analytical).
- Ph.D. in Organic Chemistry; M.B.A. degree and training for managers.

EXPERIENCE

BIOLOGICS CONSULTING GROUP, INC. Alexandria, VA
January 2005 – Present
Senior Consultant

- Evaluate and provide advice on client CMC scientific and regulatory strategies for a wide range of therapeutic drug products (biologic and non-biologic) in dosage forms that include tablets, topicals, injectables, transdermals, implants, sprays, and inhalation, at all stages of product development, from pre-IND through post-NDA/BLA approval.
- Review and provide advice on IND and NDA/BLA submissions for suitability relative to FDA expectations for CMC data.
- Perform gap analysis audits for deficiencies relative to FDA expectations.
- Conduct regulatory and scientific due diligence audits for business acquisitions and licensing partnerships. Provide assessment of strengths and deficiencies.
- Represent clients in interactions with FDA.
- Prepare and write submissions to FDA, with focus on CMC sections.
- Represent client as FDA regulatory expert in legal proceedings.
- Advise clients on manufacturing contractor and vendor evaluation and selection.
- Provide management and technical oversight of contract manufacturing organizations (CMOs).
- Involved in business development to increase client base.
- Provide scientific and regulatory training and presentations at pharmaceutical/biopharmaceutical conferences.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF NEW DRUG CHEMISTRY, DIVISION OF NEW DRUG CHEMISTRY III. Rockville, MD
July 2003 – December 2004
Division Director (acting) *March 2004 – December 2004*
Deputy Division Director (acting) *July 2003 – March 2004*

- Supervised 34 employees in 9 therapeutic product classes, includes 6 Team Leaders, review chemists and administrative staff. Responsible for employee work performance review and career development.
- Planned and set long-range plans and schedules for Division work. Directed and coordinated workload, and assured implementation of Division policies, goals and objectives.
- Evaluated budget and fiscal controls to manage Division functions.
- Made critical decisions and provided expert advice concerning regulatory, scientific and compliance approaches and options consistent with Office policies and objectives.
- Represented FDA in dealing and negotiating with the regulated industry, and professional and industry organizations.
- Participated as invited speaker at regulatory and scientific conferences on behalf of FDA.
- Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
October 2001-July 2003
Lead Chemist (Team Leader)

- Managed a team of 4 review chemists in 2 therapeutic product classes.
- Responsible for secondary review, consistency of CMC reviews and adherence to FDA/ONDC policies and guidances.
- Coordinated reviewers' workload of IND and NDA submissions to ensure that reviews were conducted in timely manner.
- Interacted extensively with the regulated industry to provide regulatory direction during IND drug development and NDA post-approval activities.
- Active in the development of FDA guidances for industry and internal good review practices. Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
April 1997-October 2001
Chemistry Reviewer

- Evaluated the quality of new drug products submitted to the FDA for approval.
- Integral part of a cross-functional review team responsible for evaluating the quality and effectiveness of reproductive and urologic drug products being investigated in clinical studies.
- Major contributor to committees responsible for establishing drug product quality standards and publishing guidances for pharmaceutical companies.
- Provided regulatory guidance to pharmaceutical company representatives during drug development.
- Mentored new reviewers.
- Served as computer focal point to facilitate and troubleshoot computer issues.

FOOD & DRUG ADMINISTRATION, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, LABORATORY OF PARASITIC BIOLOGY AND BIOCHEMISTRY. Bethesda, MD
February 1994-April 1997
National Research Council Fellow

- Investigated the biological role of specific proteins in the sexual differentiation of the malaria parasite. Published three research papers in peer-reviewed journals.
- Presented research data at three separate scientific conferences.
- Supervised the research projects of college students.
- Responsible for the coordination of instrument repairs and the ordering of laboratory supplies.

GENERAL ELECTRIC CO., CORPORATE RESEARCH & DEVELOPMENT, BIOLOGICAL SCIENCES LABORATORY. Schenectady, NY
July 1989-January 1994
Staff Scientist

- Developed recombinant biphenyl-metabolizing microorganisms capable of degrading environmental contaminants. Marketed this technology to the GE business units and government agencies responsible for environmental clean-up.
- Investigated the factors affecting aerobic biodegradation of indigenous PCBs in Hudson River sediment by various bacterial strains.
- Isolated and conducted mechanistic studies of the dioxygenase enzymes involved in biodegradation.
- Investigated the scientific and economic feasibility of biologically synthesizing aromatic monomers for use as a feedstock to produce biodegradable polymers.
- Supervised research projects of summer interns.
- Published research in peer-reviewed journals.
- Recruited at major East Coast universities. Interviewed and screened graduating science Ph.D. students for second round interviews at the Research Center.

UNIVERSITY OF MARYLAND, Dept. of Chemistry/Biochemistry. College Park, MD
May 1985-May 1989
Research Assistant

- Investigated mechanism of action of two bacterial enzymes, mandelate racemase and D-amino acid oxidase.
- Synthesized and tested novel halogenated aromatic hydroxy- and amino- acid analogs as potential irreversible inhibitors.
- Published research in peer-reviewed journals and co-authored one chapter in a biotechnology book. In addition, the research data was presented at two national scientific conferences.
- Served as the computer expert for the laboratory group.

EDUCATION

ROBERT H. SMITH SCHOOL OF BUSINESS. College Park, MD
University of Maryland
Master of Business Administration (MBA), *2002*
Concentration: Finance

UNIVERSITY OF MARYLAND. College Park, MD
Department of Chemistry and Biochemistry
Ph. D. -- Organic Chemistry, *1989*
Research Advisor -- Dr. John W. Kozarich

UNIVERSITY OF PENNSYLVANIA. Philadelphia, PA
Bachelor of Arts with Honors – Biochemistry, *1984*
Dean's List, Phi Lambda Upsilon Chemical Honor Society

TRAINING

- Facilitation Skills, CDER/FDA (Fall 2002)
- Six Sigma Strategy and Methods, Univ. of MD (Summer 2002)
- Group Decision-Making Techniques, CDER/FDA (Feb. 2002)
- Managing Written Communications for Team Leaders, CDER/FDA (Spring 2002)
- Organizational Behavior and Human Resources, Univ. of MD (Fall 1999)
- Management of Human Resources, Univ. of MD (Fall 1999)
- Introduction to Drug Law and Regulation, CDER/FDA (Nov. 1998)
- Basic Statistical Methods, CDER/FDA (Fall 1998)

HONORS/AWARDS

- CDER's Team Excellence Award (Nov 2004)
- FDA's Group Recognition Award (May 2004)
- CDER's Special Recognition Award (Nov 2002)
- CDER's Team Excellence Award (Nov 2002)
- OPS/ONDC Special Recognition Award (Dec 2001)
- CDER's Team Excellence Award (Nov 2000)
- OPS/ONDC Special Recognition Award (Jun 2000)
- CDER's Excellence in Mentoring Award (Nov 1999)

PRESENTATIONS

- Conducting Effective & Compliant Stability Programs for Pharmaceuticals & Biologics, "Stability Studies During Development", "Stability of Biopharmaceuticals", "Development of Specifications for Biopharmaceuticals", and "Extractables, Leachables, and Particulates – Safety Concern for Biotechnology Products", Dubai, UAE (Sep 2012).
- 4th DIA China Annual Meeting, "ICH Guidelines Q1D, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products", and "Q1E, Evaluation of Stability Data", Shanghai, China (May 2012).
- IPA's Current Trends and Practices in Stability Testing, "Stability Testing Requirements for Biopharmaceutical Products", Montreal, Canada (Oct 2011)
- IPA's Current Trends and Practices in Stability Testing, "Stability Program for Combination Products", Montreal, Canada (Oct 2011)
- 3rd DIA China Annual Meeting, "Thinking About Comparability for Biosimilar Proteins", Beijing, China (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Stability Challenges for Combination Products", Boston, MA (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Country Specific Stability Requirements", Boston, MA (May 2011).
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Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Stephen J. Brown
Attorney Docket Number:	117744-00023

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Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
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Application Number:	95002170
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Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
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1	Response after non-final action-owner timely	FINAL080REPLYTOOA.pdf	653223 8fc8f0e3f49f5bcf46d57581b8d7765071574da1	no	86

Warnings:	
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2	Response after non-final action-owner timely	Declarations.pdf	9066001 fa617de5bca4c8f01850c9912482145029fb095c	no	26
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30246 0f8873435e13b90bd937cd3b03eb008e2ed9e7c7	no	2
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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

EXHIBIT C

EXHIBIT C
Comparison of Supplemental Response filed March 13, 2013
with Reply filed January 29, 2013

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.:	6418
Filed:	September 10, 2012	H&B Docket:	119-26 RCE/CON/REX
Dated:	~~January 29~~March 13, 2013	M&E Docket:	117744-00023

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Attn: Central Reexamination Unit
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Alexandria, VA 22313-1450

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I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on ~~January 29~~March 13, 2013
Signed: Michael J. Chakansky /Michael J. Chakansky/

REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111

Madame:

In compliance with the Notice Re Defective Paper in *Inter Partes* Reexamination, mail date February 26,2013, Patent owner MonoSol Rx, LLC ("Patentee" and/or "MonoSol") hereby presents its re-drafted response to ~~an~~the Office Action in the above-identified *Inter Partes* Reexamination, dated November 29, 2012 ("Office Action"), a reply to which is due ~~January 29~~March 13, 2013~~, please~~. Please amend U.S. Patent No. 7,897,080 ("the '080 Patent") in reexamination as set forth hereinbelow. The present amendments are being made in accordance with 37 C.F.R. §1.530(d~~) (j). If~~)G). Patentee has previously paid fees for the addition of 4 new independent claims and 324 new dependent in connection with this reexamination. Accordingly, no claim fees are believed to be due with this submission. If, however, there are any fees due in connection with this submission, authorization to charge such fees, including any claim fees, and authorization to credit any overpayments, to Deposit Account No. 08-2461 ~~is~~are hereby provided.

Amendment to the Claims begins on page 2 of this paper.

Remarks-begin on page ~~79~~42 of this paper.

EXHIBIT C
Comparison of Supplemental Response filed March 13, 2013
with Reply filed January 29, 2013

Claim Amendments[1]

1. (Amended) A process for manufacturing a resulting ~~pharmaceutical~~ film suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said [making a]film having a substantially uniform distribution of **components ~~a pharmaceutical active~~** [of components] **comprising a substantially uniform distribution of said active in individual dosage units of said resulting film**, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]**said ~~a pharmaceutical~~** active**, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof,** to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) **controlling drying through a process comprising** conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent **from said flowable polymer matrix** [from said flowable polymer matrix] to **~~rapidly~~** form a visco-elastic film, having said **~~pharmaceutical~~** active **substantially** uniformly distributed throughout **~~by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying,~~** within

[1] The claim amendments show the original amendments filed in the January 2013 Reply in underlining and brackets, and the NEW amendments filed in the March 13, 2013 reply in bold, underlining and strikethrough.

about the first [10]4 minutes [or fewer]**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said ~~**pharmaceutical**~~ active by locking-in or substantially preventing migration of said ~~**pharmaceutical**~~ active within said visco-elastic film**,** wherein **during said drying said flowable** ~~**the**~~ polymer matrix temperature is 100°C or less; [and]

(e) forming [a]**said** ~~**the**~~ resulting ~~**pharmaceutical**~~ film from said visco-elastic film, wherein said resulting ~~**pharmaceutical**~~ film has a water content of 10% or less and said substantially uniform distribution of ~~**pharmaceutical**~~ active by said locking-in or substantially preventing migration of said ~~**pharmaceutical**~~ active is maintained; and

(f) ~~**forming a plurality of individual dosage unit samples of substantially the same size from said resulting pharmaceutical film; and**~~

~~(g)~~ performing analytical chemical tests for ~~**content**~~ uniformity ~~**on said plurality**~~ of **content of said active in substantially equal sized** individual dosage units **sampled** ~~**samples**~~ from **different locations of** said resulting ~~**pharmaceutical**~~ film, said tests indicating ~~**said substantially uniform distribution of the pharmaceutical active, in that the amount of the pharmaceutical active in the individual dosage unit samples**~~ **that uniformity of content in the amount of the active** varies by no more than 10% **and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration**.

2. (Original) The process of claim 1, wherein said pre-determined amount ofmaster batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and

combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (~~Original~~ Cancelled) ~~The process of claim 1, wherein said active is selected from the group consisting ofbioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.~~

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti -convulsants, anti -depressants, anti -diabetic agents, anti -diarrhea preparations, antidotes, anti -histamines, anti -hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-

thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and nonsystemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, antithrombotic drugs, hypnotics, anti -emetics, anti -nauseants, [anti -convulsants,]neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, antispasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15 (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Cancelled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (~~**Original**~~ **Amended**) The process of claim 1, wherein said active is an anti-diarrhea **preparation**.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H2-antagonist.

35. (Original) The process of claim 34, wherein said H2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides

a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (~~Amended~~ **Original**) The process of claim 72, wherein said second film layer is coated onto said resulting ~~pharmaceutical~~ film.

74. (~~Amended~~ **Original**) The process of claim 72, wherein said second film layer is spread onto said resulting ~~pharmaceutical~~ film.

75. (~~Amended~~ **Original**) The process of claim 72, wherein said second film layer is cast onto said resulting ~~pharmaceutical~~ film.

76. (~~Amended~~ **Original**) The process of claim 72, wherein said second film layer is extruded onto said resulting ~~pharmaceutical~~ film.

77. (~~Amended~~ **Original**) The process of claim 72, wherein said second film layer is sprayed onto said resulting ~~pharmaceutical~~ film.

78. (~~Amended~~ **Original**) The process of claim 72, wherein said second film is laminated

onto said resulting **~~pharmaceutical~~** film.

79. (**~~Amended~~** **Original**) The process of claim 72, further comprising laminating said resulting film to another **~~pharmaceutical~~** film.

80. (**~~Amended~~** **Original**) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim **~~72~~80**, wherein said active in said second film **~~layer~~** is different than said active in said resulting **~~pharmaceutical~~** film.

82. (Amended) A process for manufacturing resulting films suitable for commercialization and regulatory approval**,** said **regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said** [making a]film**s** having a substantially uniform distribution of **components** **~~an active~~** [of components], **comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films,** comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and **~~an~~** **said** active**, said active** selected from the group consisting of bioactive actives, pharmaceutical actives**~~, drugs, medicaments~~** and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising** conveying said flowable polymer matrix

through a drying apparatus and evaporating at least a portion of said solvent from **said flowable polymer matrix** [said flowable polymer matrix] to ~~**rapidly**~~ form a visco-elastic film**,** having said active **substantially** uniformly distributed throughout ~~**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying,**~~ within about the first [10]4 minutes [or fewer]**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein **during said drying said flowable ~~the~~** polymer matrix temperature is 100°C or less, and wherein ~~**content**~~ uniformity **of content** of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a] ~~**the**~~ **said** resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) ~~**forming a plurality of individual dosage unit samples of substantially the same size form said resulting film: and**~~

~~**(f)**~~ performing analytical chemical tests for ~~**content**~~ uniformity ~~**on said plurality**~~ **of content of said active in substantially equal sized** individual dosage units ~~**samples**~~ **sampled** from **different locations of** said resulting film, said tests indicating ~~**said substantially uniform distribution of the active, in that the amount of the active in the individual dosage unit samples**~~ **that uniformity of content in the amount of said active** varies by no more than 10% **and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and**

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said

analytical chemical tests.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting ofmethylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum,

acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting ofwater, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Cancelled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti -convulsants, anti -depressants, anti -diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid

preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and nonsystemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, antithrombotic drugs, hypnotics, anti -emetics, anti -nauseants, [anti -convulsants,]neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, antispasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Cancelled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (~~Original~~ **Amended**) The process of claim 82, wherein said active is an anti-diarrhea **preparation**.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (~~Original~~ **Amended**) The process of claim ~~82~~ **113**, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step ofproviding a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (~~Amended~~ **Original**) The process of claim 151, wherein said second film ~~layer~~ comprises an active.

160. (Amended) The process of claim ~~151~~**159**, wherein said active in said second film ~~layer~~ is different than said active in said resulting film.

161. (Amended) A process for manufacturing a resulting ~~pharmaceutical~~ film suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of **a** ~~pharmaceutical active~~[components] **components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film**, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and **a**[n] ~~pharmaceutical~~ **said** active, **said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof,** said matrix having a substantially uniform distribution of said ~~pharmaceutical~~ active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising** conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent **from said flowable**

polymer matrix [from said flowable polymer matrix] to ~~**rapidly**~~ form a visco-elastic film**,** having said ~~**pharmaceutical**~~ active **substantially** uniformly distributed throughout ~~**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying,**~~ within about the first [10]4 minutes [or fewer]**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said ~~**pharmaceutical**~~ active by locking-in or substantially preventing migration of said ~~**pharmaceutical**~~ active within said visco-elastic film**,** wherein **during said drying said flowable** ~~**the**~~ polymer matrix temperature is 100°C or less**, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%**;

(d) forming [a] ~~**the**~~ **said** resulting ~~**pharmaceutical**~~ film from said visco-elastic film, wherein said resulting ~~**pharmaceutical**~~ film has a water content of 10% or less and said substantially uniform distribution of ~~**pharmaceutical**~~ active by said locking-in or substantially preventing migration of said ~~**pharmaceutical**~~ active is maintained; [and]

(e) [administering said resulting film to a body surface] ~~**forming a plurality of individual dosage unit samples of substantially the same size from said resulting pharmaceutical film;**~~ **performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and**

(f) ~~**performing analytical chemical tests for content uniformityon said plurality of individual dosage unit samples from said resulting pharmaceutical film, said tests indicating said substantially uniform distribution of the pharmaceutical active, in that the amount of the pharmaceutical active in the individual dosage unit samples varies by no**~~

~~more than 10%; and~~ **administering said resulting film to a body surface~~, and~~**

~~(g) administering said resulting pharmaceutical film to a body surface~~ .

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer

selected from the group consisting ofmethylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting ofwater, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (~~Original~~ Cancelled) ~~The process of claim 161, wherein said active is selected from the group consisting of bioactive active, pharmaceutical actives, drugs, medicaments and combinations thereof.~~

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti -convulsants, anti -depressants, anti -diabetic agents, anti -diarrhea preparations, antidotes, anti -histamines, anti -hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and nonsystemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, antithrombotic drugs, hypnotics, anti -emetics, anti -nauseants, [anti -convulsants,]neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, antispasmodics, uterine relaxants, anti-obesity drugs, erythropoietic

drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Cancelled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (~~Original~~ **Amended**) The process of claim 161, wherein said active is an anti-diarrhea **preparation**.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H2-antagonist.

196. (Original) The process of claim 195, wherein said H2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step ofproviding a second film layer.

234. (~~Amended~~ **Original**) The process of claim 233, wherein said second film layer is coated onto said resulting ~~pharmaceutical~~ film.

235. (~~Amended~~ **Original**) The process of claim 233, wherein said second film layer is spread onto said resulting ~~pharmaceutical~~ film.

236. (~~Amended~~ **Original**) The process of claim 233, wherein said second film layer is cast

onto said resulting ~~**pharmaceutical**~~ film.

237. (~~**Amended**~~ **Original**) The process of claim 233, wherein said second film layer is extruded onto said resulting ~~**pharmaceutical**~~ film.

238. (~~**Amended**~~ **Original**) The process of claim 233, wherein said second film layer is sprayed onto said resulting ~~**pharmaceutical**~~ film.

239. (~~**Amended**~~ **Original**) The process of claim 233, wherein said second film layer is laminated onto said resulting ~~**pharmaceutical**~~ film.

240. (~~**Amended**~~ **Original**) The process of claim 233, further comprising laminating said resulting film to another ~~**pharmaceutical**~~ film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim ~~**233**~~**241**, wherein said active in said second film is different than said active in said resulting ~~**pharmaceutical**~~ film.

243. (~~**Amended**~~ **Original**) The process of claim 1, ~~**wherein**~~ said active is an anti-nauseant.

244. (Amended) The process of claim 1, ~~**wherein**~~ said active is an erectile dysfunction **drug** ~~**therapy**~~.

245. (~~**Amended**~~ **Original**) The process of claim 1, ~~**wherein**~~ said active is a vasoconstrictor.

246. (~~**Amended**~~ **Original**) The process of claim 1, ~~**wherein**~~ said active is a stimulant.

247. (~~**Amended**~~ **Original**) The process of claim 1, ~~**wherein**~~ said active is a migraine

treatment.

248. (~~Amended~~ **Original**) The process of claim 1, ~~wherein~~ said active is granisetron hydrochloride.

249. (~~Amended~~ **Original**) The process of claim 1, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual through the buccal cavity of said individual.

250. (~~Amended~~ **Original**) The process of claim 1, wherein said resulting ~~pharmaceutical~~ film provides administration of said active through gingival application ~~to an~~ [of said] **of said** individual.

251. (~~Amended~~ **Original**) The process of claim 1, wherein said resulting ~~pharmaceutical~~ film provides administration of said active through sublingual application ~~to an~~ [of said] **of said** individual.

252. (~~Amended~~ **Original**) The process of claim 1, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (~~Amended~~ **Original**) The process of claim 1, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual by administration within the body ofthe individual during surgery.

254. (~~Amended~~ **Cancelled**) ~~The process of claim 1, wherein said resulting pharmaceutical film has a variation of the amount of the pharmaceutical active~~ [content]~~of less than~~ [10%]~~5%~~ ~~per~~ [film unit]~~individual dosage unit.~~

255. (Cancelled)

256. (~~Amended~~ **Original**) The method of claim 1, wherein said resulting ~~**pharmaceutical**~~ film contains less than about 6% by weight solvent.

257. (~~Original~~ **Cancelled**) ~~**The method of claim 1, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.**~~

258. (~~Amended~~ **Original**) The method of claim 1, wherein said resulting ~~**pharmaceutical**~~ film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Original) The method of claim 1, wherein said matrix comprises a dispersion.

261. (~~Amended~~ **Original**) The process of claim 82, ~~**wherein**~~ said active is an anti-nauseant.

262. (Amended) The process of claim 82, ~~**wherein**~~ said active is an erectile dysfunction **drug** ~~**therapy**~~.

263. (~~Amended~~ **Original**) The process of claim 82, ~~**wherein**~~ said active is a vasoconstrictor.

264. (~~Amended~~ **Original**) The process of claim 82, ~~**wherein**~~ said active is a stimulant.

265. (~~Amended~~ **Original**) The process of claim 82, ~~**wherein**~~ said active is a migraine treatment.

266. (~~Amended~~ **Original**) The process of claim 82, ~~**wherein**~~ said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (~~Amended~~ **Original**) The process of claim 82, wherein said resulting film provides administration of said active through gingival application ~~to an~~ [of said] **of said** individual.

269. (~~Amended~~ **Original**) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application ~~to an~~ [of said] **of said** individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (~~Amended~~ Cancelled) ~~The process of claim 82, wherein in step (c) the active varies less than 5% and in step (f) said resulting film has a variation of the amount of active~~ [content]~~of less than 5%~~[10%] ~~per~~ [film unit]~~individual dosage unit.~~

273. (Cancelled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (~~Original~~ Cancelled) ~~The method of claim 82, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.~~

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (~~Amended~~ **Original**) The process of claim 161, ~~wherein~~ said active is an anti-nauseant.

280. (Amended) The process of claim 161, ~~wherein~~ said active is an erectile dysfunction **drug** ~~therapy~~.

281. (~~Amended~~ **Original**) The process of claim 161, ~~wherein~~ said active is a vasoconstrictor.

282. (~~Amended~~ **Original**) The process of claim 161, ~~wherein~~ said active is a stimulant.

283. (~~Amended~~ **Original**) The process of claim 161, ~~wherein~~ said active is a migraine treatment.

284. (~~Amended~~ **Original**) The process of claim 161, ~~wherein~~ said active is granisetron hydrochloride.

285. (~~Amended~~ **Original**) The process of claim 161, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual through the buccal cavity of said individual.

286. (~~Amended~~ **Original**) The process of claim 161, wherein said resulting ~~pharmaceutical~~ film provides administration of said active through gingival application ~~to an~~ [of said] **of said** individual.

287. (~~Amended~~ **Original**) The process of claim 161, wherein said resulting ~~pharmaceutical~~

film provides administration of said active through sublingual application ~~to an~~ [of said] **of said** individual.

288. (~~Amended~~ **Original**) The process of claim 161, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (~~Amended~~ **Original**) The process of claim 161, wherein said resulting ~~pharmaceutical~~ film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (~~Amended~~ **Cancelled**) ~~The process of claim 161, wherein said resulting pharmaceutical film has a variation of in the amount of pharmaceutical active~~ [content]~~of less than~~ [10%]~~5% per~~ [film unit] ~~individual dosage unit.~~

291. (Cancelled)

292. (~~Amended~~ **Original**) The method of claim 161, wherein said resulting ~~pharmaceutical~~ film contains less than about 6% by weight solvent.

293. (~~Original~~ **Cancelled**) ~~The method ofclaim 161, wherein said at least one edible polymer, said active, and said at least one polar solvent are each ingestible materials.~~

294. (~~Amended~~ **Original**) The method of claim 161, wherein said resulting ~~pharmaceutical~~ film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) ~~The process of claim 1, wherein the forming of a plurality of individual dosage unit samples and performing analytical chemical tests comprises:~~

~~(a) cutting the substantially equally sized individual dosage unit samples from the different locations of the resulting film;~~

~~(b) dissolving at least a portion of said dosage unit samples: and~~

~~(c) testing for the amount of the pharmaceutical active present in each dosage unit sample.~~

301. (New) ~~The process of claim 1, wherein regulatory approval is provided by the U.S. Food and Drug Administration.~~

300 ~~302~~. (New) The process of claim 1, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 5%.

301 ~~303~~. (New) The process of claim 1, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 2%.

302 ~~304~~. (New) The process of claim 1, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 1 %.

303 ~~305~~. (New) The process of claim 1, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 0.5%.

~~306. (New) The process of claim 82, wherein the forming of a plurality of individual dosage unit samples and performing analytical chemical tests comprises:~~

~~(a) cutting the substantially equally sized individual dosage unit samples from the different locations ofthe resulting film;~~

~~(b) dissolving at least a portion of said dosage unit samples; and~~

~~(c) testing for the amount of the active present in each dosage unit sample.~~

~~307. (New) The process of claim 82, wherein regulatory approval is provided by the U.S. Food and Drug Administration.~~

304 ~~308~~. (New) The process of claim 82, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 5%.

305 ~~309~~. (New) The process of claim 82, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 2%.

306 ~~310~~. (New) The process of claim 82, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 1 %.

307 ~~311~~. (New) The process of claim 82, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 0.5%.

~~312. (New) The process of claim 161. wherein the forming of a plurality of individual dosage unit samples and performing analytical chemical tests comprises:~~

~~(a) cutting the substantially equally sized individual dosage unit samples from the different locations of the resulting film;~~

~~(b) dissolving at least a portion of said dosage unit samples; and~~

~~(c) testing for the amount of the pharmaceutical active present in each dosage unit sample.~~

~~313 (New) The process of claim 161. wherein regulatory approval is provided by the U.S. Food and Drug Administration.~~

308 ~~314~~. (New) The process of claim 161, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 5%.

309 ~~315~~. (New) The process of claim 161, wherein **said tests further indicate that** the amount of **~~pharmaceutical~~** active in **~~of~~ said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 2%.

310 ~~316~~. (New) The process of claim 161, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 1 %.

311 ~~317~~. (New) The process of claim 161, wherein **said tests further indicate that** the amount of ~~**pharmaceutical**~~ active in ~~**of**~~ **said** individual dosage units **sampled from said resulting film ~~has a variance of~~ varies by** less than 0.5%.

312 ~~318~~. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

313 ~~319~~. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

314 ~~320~~. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

315 ~~321~~. (New) A process for manufacturing resulting ~~**pharmaceutical**~~ films suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said films having a substantially uniform distribution of **components comprising a substantially uniform distribution of a desired amount of said ~~an~~** active **in individual dosage units of said resulting films**, comprising the steps of:

(a) forming a **flowable polymer matrix** ~~**masterbach pre-mix**~~ comprising a ~~**polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof**~~ **water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active**;

(b) ~~**adding an active selected from the group consisting of bioactive actives, pharmaceutical actives, drugs, medicaments and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;**~~

~~(c)~~ casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

~~(d)~~ **(c) controlling drying through a process comprising** conveying said ~~**flowable**~~ polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to ~~**rapidly**~~ form a visco-elastic film**,** having said active **substantially** uniformly distributed throughout ~~**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying,**~~ within about the first 4 minutes **by rapidly increasing the viscosity of said polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film**,** wherein **during said drying said flowable** ~~**the**~~ polymer matrix temperature is 100°C or less;

~~(e)~~ **(d)** forming **said** ~~**the**~~ resulting ~~**pharmaceutical**~~ film from said visco-elastic film, wherein said resulting ~~**pharmaceutical**~~ film has a water content of 10% or less and said substantially uniform distribution of **said** active by said locking-in or substantially preventing migration of said active is maintained**, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%**;

~~(f) forming a plurality of individual dosage units of substantially the same size from said resulting pharmaceutical film; and~~

~~(g)~~ **(e)** performing analytical chemical tests for ~~content~~ uniformity ~~on said plurality~~ of **content of said active in said substantially equal sized** individual dosage units ~~from~~ **of** said **sampled** resulting ~~pharmaceutical~~ film, said tests indicating ~~said substantially uniform distribution of the active, in~~ that **uniformity of content in** the amount of the active ~~in individual dosage units~~ varies by no more than 10% **and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and**

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316 ~~(322)~~. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said film ~~capable of being administered to a body surface~~ having a substantially uniform distribution of ~~an active~~ **components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film**, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and ~~an~~ **said** active**, said active** selected from the group consisting of bioactive actives, pharmaceutical actives~~, drugs, medicaments~~ and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising** conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to ~~**rapidly**~~ form a visco-elastic film**,** having said active substantially uniformly distributed throughout ~~**by rapidly increasing the viscosity of said flowable polymer matric upon initiation of drying**~~, within about the first 4 minutes **by rapidly increasing the viscosity of said polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film**,** wherein **during said drying said flowable** ~~**the**~~ polymer matrix temperature is 100°C or less;

(d) forming **said** ~~**the**~~ resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained**, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and**
~~**(e) forming a plurality of individual dosage units of substantially the same size from said resulting film;**~~

~~(f)~~ **(e)** performing analytical chemical tests for ~~**content**~~ uniformity ~~**on said plurality**~~ of **content of said active in said substantially equal sized** individual dosage units ~~**from**~~ **of** said **sampled** resulting film, said tests indicating ~~**said substantially uniform distribution**~~ **that uniformity of content in the amount** of ~~**the**~~ **said** active ~~**in individual dosage units**~~ varies by no more than 10% **and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration**~~**; and**~~

~~(g) administering said resulting film to a body surface~~.

317 ~~323~~. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said film having a substantially uniform distribution of **components comprising a substantially uniform distribution of said** ~~a desired amount of an~~ active in individual ~~doses~~ **dosage units** of **said** ~~the~~ resulting ~~pharmaceutical~~ film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and **said** ~~a pharmaceutical~~ active**, said active** selected from the group consisting of bioactive actives, pharmaceutical actives~~, drugs, medicaments~~ and combinations thereof**, said matrix having a substantially uniform distribution of said active**;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising** conveying said **flowable** polymer matrix through a drying apparatus **using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate** ~~evaporating~~ at least a portion of said solvent to ~~rapidly~~ form a visco-elastic film, having said ~~pharmaceutical~~ active **substantially** uniformly distributed throughout ~~by rapidly increasing the viscosity of said polymer matrix upon initiation of drying~~, within about the first 4 minutes **by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to maintain said **substantially** uniform distribution of said ~~pharmaceutical~~ active by lockingin or substantially preventing migration of said ~~pharmaceutical~~ active within said visco-elastic film**, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and**

wherein **during said drying said flowable ~~the~~** polymer matrix temperature is 100°C or less;

(d) forming **said ~~the~~** resulting **~~pharmaceutical~~** film from said visco-elastic film**~~, wherein said resulting pharmaceutical film has~~ by further controlling drying by continuing evaporation to** a water content **of said resulting film** of 10% or less and **wherein** said **substantially** uniform distribution of **~~pharmaceutical~~** active by said locking-in or substantially preventing migration of said **~~pharmaceutical~~** active is maintained, such that uniformity of content in the amount of **said ~~the~~** active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies **by** no more than 10% **~~from the desired amount of the active~~**; and

(e) performing analytical chemical tests for **~~content~~** uniformity **of content** of said **~~pharmaceutical~~** active in substantially equal sized individual dosage units of said sampled resulting **~~pharmaceutical~~** film, said tests indicating that uniformity of content in the amount of **said ~~the~~** active varies by no more than 10% **~~from the desired amount of the active~~ and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration**.

318 ~~324~~. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval**, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units,** said film having a substantially uniform distribution of **~~an active~~ components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film**, comprising the steps of:

(a) forming a flowable polymer matrix comprising **~~a polymer selected from the group consisting of~~** a water-soluble polymer, **~~a water swellable polymer and combinations thereof,~~** a solvent and said active**, said active** selected from the group consisting of bioactive actives, pharmaceutical actives**~~, drugs, medicaments~~** and combinations thereof, said matrix having a

substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) **controlling drying through a process comprising** conveying said flowable polymer matrix through a drying apparatus **at a temperature of about 60°C and using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate** ~~**and evaporating**~~ at least a portion of said solvent to ~~**rapidly**~~ form a visco-elastic film, having said active **substantially** uniformly distributed throughout ~~**by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying,**~~ within about the first 4 minutes **by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying** to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said viscoelastic film**, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and** wherein **during said drying said flowable** ~~**the**~~ polymer matrix temperature is 100°C or less~~**, wherein content uniformity of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%**~~;

(d) forming **said** ~~**the**~~ resulting film from said visco-elastic film~~**, wherein said resulting film has**~~ **by further controlling by continuing evaporation to** a water content of **said resulting film of** 10% or less and **wherein** said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained**, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%**; and

(e) ~~**forming a plurality of individual dosage unit samples of substantially the same size from**~~

~~said resulting film, wherein the amount of the active in the individual dosage unit samples varies by no more than 10%~~ performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

~~325. (New) The process of claim 321, wherein said water-soluble polymer comprises polyethylene oxide.~~

~~326. (New) The process of claim 321, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.~~

~~327. (New) The process of claim 326, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, polyClactic acid)/polyCglycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.~~

~~328. (New) The process of claim 326, wherein said polymer further comprises a polymer selected from the group consisting of methyl methacrylate copolymer, polyacrylic acid polymer, polyCglycolic acid) CPGA), poly(lactic acid) (PLA)' polyClactic~~

~~acid)/poly(glycolic acidVpolyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.~~

~~329. (New) The process of claim 326, wherein said polymer further comprises a polymer selected from the grOUP consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~330 . (New) The process of claim 326, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyyinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acidVpoly(glycolic acidVpolyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLAt poly(lactic acidVpoly(glycolic acidVpolyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageen an, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~331. (New) The process of claim 321. wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.~~

~~332. (New) The process of claim 331, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.~~

~~333. (New) The process of claim 321, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti¬lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti¬uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.~~

334. (New) The process of claim 321, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.

335. (New) The process of claim 321, wherein said active is a bioactive active.

336. (New) The process of claim 321, wherein said active is an opiate or opiate-derivative.

337. (New) The process of claim 321, wherein said active is an anti-emetic.

338. (New) The process of claim 321, wherein said active is an amino acid preparation.

339. (New) The process of claim 321, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

340. (New) The process of claim 321, wherein said active is a protein.

341. (New) The process of claim 321, wherein said active is insulin.

342. (New) The process of claim 321, wherein said active is an anti-diabetic.

343. (New) The process of claim 321, wherein said active is an antihistamine.

344. (New) The process of claim 321, wherein said active is an anti-tussive.

345. (New) The process of claim 321, wherein said active is a non-steroidal anti-inflammatory.

~~346. (New) The process of claim 321, wherein said active is an anti-asthmatics.~~

~~347. (New) The process of claim 321, wherein said active is an anti-diarrhea.~~

~~348. (New) The process of claim 321, wherein said active is an alkaloid.~~

~~349. (New) The process of claim 321, wherein said active is an anti-psychotic.~~

~~350. (New) The process of claim 321, wherein said active is an anti-spasmodic.~~

~~351. (New) The process of claim 321, wherein said active is a biological response modifier.~~

~~352. (New) The process of claim 321, wherein said active is an anti-obesity drug.~~

~~353. (New) The process of claim 321, wherein said active is an H_2-antagonist.~~

~~354. (New) The process of claim 321, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.~~

~~355. (New) The process of claim 321, wherein said active is a smoking cessation aid.~~

~~356. (New) The process of claim 321, wherein said active is an anti-parkinsonian agent.~~

~~357. (New) The process of claim 321, wherein said active is an anti-depressant.~~

~~358. (New) The process of claim 321, wherein said active is an anti-migraine.~~

~~359. (New) The process of claim 321, wherein said active is an anti-Alzheimer's agents.~~

~~360. (New) The process of claim 321, wherein said active is a dopamine receptor agonist.~~

~~361. (New) The process of claim 321, wherein said active is a cerebral dilator.~~

~~362. (New) The process of claim 321, wherein said active is a psychotherapeutic agent.~~

~~363. (New) The process of claim 321, wherein said active is an antibiotic.~~

~~364. (New) The process of claim 321, wherein said active is an anesthetic.~~

~~365. (New) The process of claim 321, wherein said active is a contraceptive.~~

~~366. (New) The process of claim 321, wherein said active is an anti-thrombotic drug.~~

~~367. (New) The process of claim 324, wherein said active is an analgesic.~~

~~368. (New) The process of claim 324, wherein said active is a hormone.~~

~~369. (New) The process of claim 324, wherein said active is a decongestant.~~

~~370. (New) The process of claim 324, wherein said active is a loratadine.~~

~~371. (New) The process of claim 324, wherein said active is dextromethorphan.~~

~~372. (New) The process of claim 324, wherein said active is chlorpheniramine maleate.~~

373. (New) The process of claim 324, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamIne, a decongestant, a cough suppressant and combinations thereof.

374. (New) The process of claim 324, wherein said active is an appetite stimulant.

375. (New) The process of claim 324, wherein said active is a gastrointestinal agent.

376. (New) The process of claim 324, wherein said active is a hypnotic.

377. (New) The process of claim 321, wherein said active is diphenhydramine.

378. (New) The process of claim 321, wherein said active is nabilone.

379. (New) The process of claim 321, wherein said active is albuterol sulfate.

380. (New) The process of claim 321, wherein said active is an anti-tumor drug.

381. (New) The process of claim 321, wherein said active is a glycoprotein.

382. (New) The process of claim 321, wherein said active is an analgesic.

383. (New) The process of claim 321, wherein said active is a hormone.

384. (New) The process of claim 321, wherein said active is a decongestant.

385. (New) The process of claim 321, wherein said active is a loratadine.

386. (New) The process of claim 321, wherein said active is dextromethomhan.

387. (New) The process of claim 321, wherein said active is chlorpheniramine maleate.

388. (New) The process of claim 321, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

389. (New) The process of claim 321, wherein said active is an appetite stimulant.

390. (New) The process of claim 321, wherein said active is a gastrointestinal agent.

391. (New) The process of claim 321, wherein said active is a hypnotic.

392. (New) The process of claim 321, wherein said active is taste-masked.

393. (New) The process of claim 321, wherein said active is taste-masked using a flavor.

394. (New) The process of claim 321, wherein said active is coated with a controlled release composition.

395. (New) The process of claim 394, wherein said controlled release composition provides an immediate release.

396. (New) The process of claim 394, wherein said controlled release composition provides a delayed release.

397. (New) The process of claim 394, wherein said controlled release composition provides a sustained release.

398. (New) The process of claim 394, wherein said controlled release composition provides a sequential release.

399. (New) The process of claim 321, wherein said active is a particulate.

400. (New) The process of claim 321, further comprising adding a degassing agent to said flowable polymer matrix.

401. (New) The process of claim 321, further comprising a step of providing a second film layer.

402. (New) The process of claim 401, wherein said second film layer is coated onto said resulting pharmaceutical film.

403. (New) The process of claim 401, wherein said second film layer is spread onto said resulting pharmaceutical film.

404. (New) The process of claim 401, wherein said second film layer is cast onto said resulting pharmaceutical film.

405. (New) The process of claim 401, wherein said second film layer is extruded onto said resulting pharmaceutical film.

406. (New) The process of claim 401, wherein said second film layer is sprayed onto said resulting pharmaceutical film.

407. (New) The process of claim 401, wherein said second film layer is laminated onto said resulting pharmaceutical film.

~~408. (New) The process of claim 401, further comprising laminating said resulting pharmaceutical film to another film.~~

~~409. (New) The process of claim 401, wherein said second film layer comprises an active.~~

~~410. (New) The process of claim 401, wherein said active in said second film layer is different than said active in said resulting pharmaceutical film.~~

~~411. (New) The process of claim 322, wherein said water-soluble polymer comprises polyethylene oxide.~~

~~412. (New) The process of claim 322, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullu1an, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyviny1 copolymers, hydroxypropy1methy1 cellulose, hydroxyethy1 cellulose, hydroxypropy1 cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, po1yacrylic acid, methy1methacry1ate copolymer, carboxyviny1 copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.~~

~~413. (New) The process of claim 412, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellu10se, hydroxypropy1 ethyl cellulose, cellulose acetate phthalate, hydroxypropy1 methyl cellulose phthalate, po1yviny1acetatephtha1ates, phtha1ated gelatin, crosslinked gelatin, po1y(1actic acid)/po1y(glyco1ic acid)/po1ythy1eneg1yco1 copolymers, po1ycapro1actone and combinations thereof.~~

~~414. (New) The process of claim 412, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid~~

~~polymer, polyCglycolic acid) CPGA), poly(lactic acid) CPLAt poly(lactic acid)/polyCglycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, polyCorthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.~~

~~415. (New) The process of claim 412, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~416. (New) The process of claim 412, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, polyClactic acid)/polyCglycolic acid)/polyethyleneglycol~~

~~copolymers, p~lycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, polyCglycolic acid) (PGA), polyClactic acid) CPLA), polY(lactic acid)/polyCglycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, polyCa-esters), polyanhydrides, polyacetates, polycaprolactones, polyCorthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~417. (New) The process of claim 322, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.~~

418. (New) The process of claim 417, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

419. (New) The process of claim 322, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti¬lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti¬uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, synipatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity

~~drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.~~

~~420. (New) The process of claim 322, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.~~

~~421. (New) The process of claim 322, wherein said active is a bioactive active.~~

~~422. (New) The process of claim 322, wherein said active is an opiate or opiate-derivative.~~

~~423. (New) The process of claim 322, wherein said active is an anti-emetic.~~

~~424. (New) The process of claim 322, wherein said active is an amino acid preparation.~~

~~425. (New) The process of claim 322, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.~~

~~426. (New) The process of claim 322, wherein said active is a protein.~~

~~427. (New) The process of claim 322, wherein said active is insulin.~~

~~428. (New) The process of claim 322, wherein said active is an anti-diabetic.~~

~~429. (New) The process of claim 322, wherein said active is an antihistamine.~~

~~430. (New) The process of claim 322, wherein said active is an anti-tussive.~~

~~431. (New) The process of claim 322, wherein said active is a non-steroidal anti-inflammatory.~~

~~432. (New) The process of claim 322, wherein said active is an anti-asthmatics.~~

~~433. (New) The process of claim 322, wherein said active is an anti-diarrhea.~~

~~434. (New) The process of claim 322, wherein said active is an alkaloid.~~

~~435. (New) The process of claim 322, wherein said active is an anti-psychotic.~~

~~436. (New) The process of claim 322, wherein said active is an anti-spasmodic.~~

~~437. (New) The process of claim 322, wherein said active is a biological response modifier.~~

~~438. (New) The process of claim 322, wherein said active is an anti-obesity drug.~~

~~439. (New) The process of claim 322, wherein said active is an Hrantagonist.~~

~~440. (New) The process of claim 322, wherein said Hk-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.~~
~~441. (New) The process of claim 322, wherein said active is a smoking cessation aid.~~

~~442. (New) The process of claim 322, wherein said active is an anti-parkinsonian agent.~~

~~443. (New) The process of claim 322, wherein said active is an anti-depressant.~~

~~444. (New) The process of claim 322, wherein said active is an anti-migraine.~~

~~445. (New) The process of claim 322, wherein said active is an anti-Alzheimer's agents.~~

~~446. (New) The process of claim 322, wherein said active is a dopamine receptor agonist.~~

~~447. (New) The process of claim 322, wherein said active is a cerebral dilator.~~

~~448. (New) The process of claim 322, wherein said active is a psychotherapeutic agent.~~

~~449. (New) The process of claim 322, wherein said active is an antibiotic.~~

~~450. (New) The process of claim 322, wherein said active is an anesthetic.~~

~~451. (New) The process of claim 322, wherein said active is a contraceptive.~~

~~452. (New) The process of claim 322, wherein said active is an anti-thrombotic drug.~~

~~453. (New) The process of claim 322, wherein said active is diphenhydramine.~~

~~454. (New) The process of claim 322, wherein said active is nabilone.~~

~~455. (New) The process of claim 322, wherein said active is albuterol sulfate.~~

~~456. (New) The process of claim 322, wherein said active is an anti-tumor drug.~~

~~457. (New) The process of claim 322, wherein said active is a glycoprotein.~~

~~458. (New) The process of claim 322, wherein said active is an analgesic.~~

~~459. (New) The process of claim 322, wherein said active is a hormone.~~

~~460. (New) The process of claim 322, wherein said active is a decongestant.~~

~~461. (New) The process of claim 322, wherein said active is a loratadine.~~

~~462. (New) The process of claim 322, wherein said active is dextromethorphan.~~

~~463. (New) The process of claim 322, wherein said active is chlorpheniramine maleate.~~

~~464. (New) The process of claim 322, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.~~

~~465. (New) The process of claim 322, wherein said active is an appetite stimulant.~~

~~466. (New) The process of claim 322, wherein said active is a gastrointestinal agent.~~

~~467. (New) The process of claim 322, wherein said active is a hypnotic.~~

~~468. (New) The process of claim 322, wherein said active is taste-masked.~~

~~469. (New) The process of claim 322, wherein said active is taste-masked using a flavor.~~

~~470. (New) The process of claim 322, wherein said active is coated with a controlled release composition.~~

471. (New) The process of claim 470, wherein said controlled release composition provides an immediate release.

472. (New) The process of claim 470, wherein said controlled release composition provides a delayed release.

473. (New) The process of claim 470, wherein said controlled release composition provides a sustained release.

474. (New) The process of claim 470, wherein said controlled release composition provides a sequential release.

475. (New) The process of claim 322, wherein said active is a particulate.

476. (New) The process of claim 322, further comprising adding a degassing agent to said flowable polymer matrix.

477. (New) The process of claim 322, further comprising a step of providing a second film layer.

478. (New) The process of claim 477, wherein said second film layer is coated onto said resulting film.

479. (New) The process of claim 477, wherein said second film layer is spread onto said resulting film.

480. (New) The process of claim 477, wherein said second film layer is cast onto said resulting film.

~~481. (New) The process of claim 477, wherein said second film layer is extruded onto said resulting film.~~

~~482. (New) The process of claim 477, wherein said second film layer is sprayed onto said resulting film.~~

~~483. (New) The process of claim 477, wherein said second film layer is laminated onto said resulting film.~~

~~484. (New) The process of claim 477, further comprising laminating said resulting film to another film.~~

~~485. (New) The process of claim 477, wherein said second film layer comprises an active.~~

~~486. (New) The process of claim 477, wherein said active in said second film layer is different than said active in said resulting film.~~

~~487. (New) The process of claim 323, wherein said water-soluble polymer comprises polyethylene oxide.~~

~~488. (New) The process of claim 323, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.~~

489. (New) The process of claim 488, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, polyClactic acid)/polyCglycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

490. (New) The process of claim 488, wherein said polymer further comprises a polymer selected from the group consisting of methyl methacrylate copolymer, polyacrylic acid polymer, polyCglycolic acid) CPGA), poly(lactic acid) CPLA)' polyClactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

491. (New) The process of claim 488, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, caragccnan, locust bean gum, dextran, gellan gum and combinations thereof.

492. (New) The process of claim 488, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, polyClactic acid)/polyCglycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), polyClactic acid) (PLA). polyClactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamin~ acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides,

~~poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~493. (New) The process of claim 323, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.~~

~~494. (New) The process of claim 493, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.~~

~~495. (New) The process of claim 323, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti¬lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti¬uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite~~

~~suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.~~

~~496. (New) The process of claim 323, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.~~

~~497. (New) The process of claim 323, wherein said active is a bioactive active.~~

~~498. (New) The process of claim 323, wherein said active is an opiate or opiate-derivative.~~

~~499. (New) The process of claim 323, wherein said active is an anti-emetic.~~

~~500. (New) The process of claim 323, wherein said active is an amino acid preparation.~~

~~501. (New) The process of claim 323, wherein said active is selected from the grOUP consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.~~

~~502. (New) The process of claim 323, wherein said active is a protein.~~

~~503. (New) The process of claim 323, wherein said active is insulin.~~

504. (New) The process of claim 323. wherein said active is an anti-diabetic.

505. (New) The process of claim 323. wherein said active is an antihistamine.

506. (New) The process of claim 323. wherein said active is an anti-tussive.

507. (New) The process of claim 323. wherein said active is a non-steroidal anti-inflammatory.

508. (New) The process of claim 323. wherein said active is an anti-asthmatics.

509. (New) The process of claim 323. wherein said active is an anti-diarrhea.

510. (New) The process of claim 323. wherein said active is an alkaloid.

511. (New) The process of claim 323. wherein said active is an anti-psychotic.

512. (New) The process of claim 323. wherein said active is an anti-spasmodic.

513. (New) The process of claim 323. wherein said active is a biological response modifier.

514. (New) The process of claim 323. wherein said active is an anti-obesity drug.

515. (New) The process of claim 323. wherein said active is an H:6-antagonist.

516. (New) The process of claim 323. wherein said Hz.-antagonist is selected from the group consisting of cimetidine. ranitidine hydrochloride. famotidine. nizatidine. ebrotidine. mifentidine. roxatidine. pisatidine. aceroxatidine and combinations thereof.

~~517. (New) The process of claim 323. wherein said active is a smoking cessation aid.~~

~~518. (New) The process of claim 323. wherein said active is an anti-parkinsonian agent.~~

~~519. (New) The process of claim 323. wherein said active is an anti-depressant.~~

~~520. (New) The process of claim 323. wherein said active is an anti-migraine.~~

~~521. (New) The process of claim 323. wherein said active is an anti-Alzheimer's agents.~~

~~522. (New) The process of claim 323. wherein said active is a dopamine receptor agonist.~~

~~523. (New) The process of claim 323. wherein said active is a cerebral dilator.~~

~~524. (New) The process of claim 323. wherein said active is a psychotherapeutic agent.~~

~~525. (New) The process of claim 323. wherein said active is an antibiotic.~~

~~526. (New) The process of claim 323. wherein said active is an anesthetic.~~

~~527. (New) The process of claim 323. wherein said active is a contraceptive.~~

~~528. (New) The process of claim 323. wherein said active is an anti-thrombotic drug.~~

~~529. (New) The process of claim 323. wherein said active is diphenhydramine.~~

~~530. (New) The process of claim 323. wherein said active is nabilone.~~

531. (New) The process of claim 323, wherein said active is albuterol sulfate.

532. (New) The process of claim 323, wherein said active is an anti-tumor drug.

533. (New) The process of claim 323, wherein said active is a glycoprotein.

534. (New) The process of claim 323, wherein said active is an analgesic.

535. (New) The process of claim 323, wherein said active is a hormone.

536. (New) The process of claim 323, wherein said active is a decongestant.

537. (New) The process of claim 323, wherein said active is a loratadine.

538. (New) The process of claim 323, wherein said active is dextromethorphan.

539. (New) The process of claim 323, wherein said active is chlorpheniramine maleate.

540. (New) The process of claim 323, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

541. (New) The process of claim 323, wherein said active is an appetite stimulant.

542. (New) The process of claim 323, wherein said active is a gastrointestinal agent.

543. (New) The process of claim 323, wherein said active is a hypnotic.

544. (New) The process of claim 323. wherein said active is taste-masked.

545. (New) The process of claim 323. wherein said active is taste-masked using a flavor.

546. (New) The process of claim 323. wherein said active is coated with a controlled release composition.

547. (New) The process of claim 546. wherein said controlled release composition provides an immediate release.

548. (New) The process of claim 546. wherein said controlled release composition provides a delayed release.

549. (New) The process of claim 546. wherein said controlled release composition provides a sustained release.

550. (New) The process of claim 546. wherein said controlled release composition provides a sequential release.

551. (New) The process of claim 323. wherein said active is a particulate.

552. (New) The process of claim 323. further comprising adding a degassing agent to said flowable polymer matrix.

553. (New) The process of claim 323. further comprising a step of providing a second film layer.

554. (New) The process of claim 553, wherein said second film layer is coated onto said resulting pharmaceutical film.

555. (New) The process of claim 553, wherein said second film layer is spread onto said resulting pharmaceutical film.

556. (New) The process of claim 553, wherein said second film layer is cast onto said resulting pharmaceutical film.

557. (New) The process of claim 553, wherein said second film layer is extruded onto said resulting pharmaceutical film.

558. (New) The process of claim 553, wherein said second film layer is sprayed onto said resulting pharmaceutical film.

559. (New) The process of claim 553, wherein said second film layer is laminated onto said resulting pharmaceutical film.

560. (New) The process of claim 553, further comprising laminating said resulting pharmaceutical film to another film.

561. (New) The process of claim 553, wherein said second film layer comprises an active.

562. (New) The process of claim 553, wherein said active in said second film layer is different than said active in said resulting pharmaceutical film.

563. (New) The process of claim 324, wherein said water-soluble polymer comprises polyethylene oxide.

564. (New) The process of claim 324, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers,

hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

565. (New) The process of claim 564, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(1actic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

566. (New) The process of claim 564, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (POA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers,polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

567. (New) The process of claim 564, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

568. (New) The process of claim 564, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates,

~~phthalated gelatin, crosslinked gelatin, poly(1actic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(1actic acid) (PLA)' poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(a-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.~~

~~569. (New) The process of claim 324, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.~~

~~570. (New) The process of claim 569, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.~~

~~571. (New) The process of claim 324, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti¬lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti¬uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones,~~

hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, neuromuscular drugs, hyper-and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

572. (New) The process of claim 324, wherein said active is selected from the group consisting of antigens, allergens, spores, microorganisms, seeds, enzymes, vitamins and combinations thereof.

573. (New) The process of claim 324, wherein said active is a bioactive active.

574. (New) The process of claim 324, wherein said active is an opiate or opiate-derivative.

575. (New) The process of claim 324, wherein said active is an anti-emetic.

576. (New) The process of claim 324, wherein said active is an amino acid preparation.

577. (New) The process of claim 324, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

578. (New) The process of claim 324, wherein said active is a protein.

579. (New) The process of claim 324, wherein said active is insulin.

580. (New) The process of claim 324, wherein said active is an anti-diabetic.

581. (New) The process of claim 324, wherein said active is an antihistamine.

582. (New) The process of claim 324, wherein said active is an anti-tussive.

583. (New) The process of claim 324, wherein said active is a non-steroidal anti-inflammatory.

584. (New) The process of claim 324, wherein said active is an anti-asthmatics.

585. (New) The process of claim 324, wherein said active is an anti-diarrhea.

586. (New) The process of claim 324, wherein said active is an alkaloid.

587. (New) The process of claim 324, wherein said active is an anti-psychotic.

588. (New) The process of claim 324, wherein said active is an anti-spasmodic.

589. (New) The process of claim 324, wherein said active is a biological response modifier.

~~590. (New) The process of claim 324. wherein said active is an anti-obesity drug.~~

~~591. (New) The process of claim 324. wherein said active is an H6-antagonist.~~

~~592. (New) The process of claim 324, wherein said H_2-antagonist is selected from the group consisting of cimetidine. ranitidine hydrochloride. famotidine. nizatidine. ebrotidine. mifentidine, roxatidine, pisatidine. aceroxatidine and combinations thereof.~~

~~593. (New) The process of claim 324, wherein said active is a smoking cessation aid.~~

~~594. (New) The process of claim 324. wherein said active is an anti-parkinsonian agent.~~

~~595. (New) The process of claim 324. wherein said active is an anti-depressant.~~

~~596. (New) The process of claim 324, wherein said active is an anti-migraine.~~

~~597. (New) The process of claim 324. wherein said active is an anti-Alzheimer's agents.~~

~~598. (New) The process of claim 324. wherein said active is a dopamine receptor agonist.~~

~~599. (New) The process of claim 324. wherein said active is a cerebral dilator.~~

~~600. (New) The process of claim 324, wherein said active is a psychotherapeutic agent.~~

~~601. (New) The process of claim 324. wherein said active is an antibiotic.~~

~~602. (New) The process of claim 324. wherein said active is an anesthetic.~~

~~603. (New) The process of claim 324, wherein said active is a contraceptive.~~

~~604. (New) The process of claim 324, wherein said active is an anti-thrombotic drug.~~

~~605. (New) The process of claim 324. wherein said active is diphenhydramine.~~

~~606. (New) The process of claim 324. wherein said active is nabilone.~~

~~607. (New) The process of claim 324. wherein said active is albuterol sulfate.~~

~~608. (New) The process of claim 324. wherein said active is an anti-tumor drug.~~

~~609. (New) The process of claim 324, wherein said active is a glycoprotein.~~

~~610. (New) The process of claim 324, wherein said active is taste-masked.~~

~~611. (New) The process of claim 324. wherein said active is taste-masked using a flavor.~~

~~612. (New) The process of claim 324. wherein said active is coated with a controlled release composition.~~

~~613. (New) The process of claim 612. wherein said controlled release composition provides an immediate release.~~

~~614. (New) The process of claim 612. wherein said controlled release composition provides a delayed release.~~

~~615. (New) The process of claim 612, wherein said controlled release composition provides a sustained release.~~

~~616. (New) The process of claim 612, wherein said controlled release composition provides a sequential release.~~

~~617. (New) The process of claim 324, wherein said active is a particulate.~~

~~618. (New) The process of claim 324, further comprising adding a degassing agent to said flowable polymer matrix.~~

~~619. (New) The process of claim 324, further comprising a step of providing a second film layer.~~

~~620. (New) The process of claim 619, wherein said second film layer is coated onto said resulting film.~~

~~621. (New) The process of claim 619, wherein said second film layer is spread onto said resulting film.~~

~~622. (New) The process of claim 619, wherein said second film layer is cast onto said resulting film.~~

~~623. (New) The process of claim 619, wherein said second film layer is extruded onto said resulting film.~~

~~624. (New) The process of claim 619. wherein said second film layer is sprayed onto said resulting film.~~

~~625. (New) The process of claim 619, wherein said second film layer is laminated onto said resulting film.~~

~~626. (New) The process of claim 619, further comprising laminating said resulting film to another film.~~

~~627. (New) The process of claim 619, wherein said second film layer comprises an active.~~

~~628. (New) The process of claim 619, wherein said active in said second film layer is different than said active in said resulting film.~~

Remarks[2]

I. Description of the Patent and the Applicant's Reply

The above-identified U.S. Patent No. 7,897,080 (" '080 Patent") is presently under reexamination. Claims 1-299 were issued in the '080 Patent. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 16, 95 and 177, have been canceled herein as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Claims ~~91, 255, 273 and 291~~12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293 have also been canceled purely for clarity. Claims 300 through ~~628~~318 are new.

While the Examiner's rejection of all the claims is respectfully traversed in all respects, claims 1,82 and 161 of the '080 Patent have been amended in an effort to ~~expedite~~advance the prosecution of the present reexamination. Claims 1,82 and 161 are hereby amended in accordance with 37 C.F.R. §1.530(d) (2) and (f). In accordance with 35 U.S.C. § 314(a), the amendments to claims 1,82 and 161, new independent claims ~~321~~315-~~324~~318, and new dependent claims 300-~~320 and claims 325628,~~ 314 do not enlarge the scope of the claims of the '080 Patent. Explanation of the support for these claims appears below. Entry of this amendment and reconsideration is respectfully

[2] This exhibit shows the differences between the NEW remarks filed in the March 13, 2013 Supplemental Reply and the original remarks filed in the January 29, 2013 Reply, with deletions struck through and additions underlined.

requested.

II. Status of Claims and Support for Claim Changes Pursuant to 37 C.F.R. §1.530(e)

The status of the claims as of the date of this amendment is as follows: Claims 1-299 were issued in the '080 Patent and are subject to reexamination. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 300 through ~~628~~318 are new and are subject to examination. Please cancel claims 16, 95 and 177, as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Please cancel ~~claims 91, 255, 273 and 291~~Claims 12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293, for clarity, including some limitations which now appear in the independent claims from which some depend.

In compliance with 37 C.F.R. § 1.530(j), the amendments to claims 1,82 and 161 do not enlarge their scope or the scope of the original claims or introduce new matter, nor do the amendments adding new claims 300 through ~~628~~318 enlarge the scope of the original claims or introduce new matter.

Support for the amendments to claims 1, 82 and 161 and new claims 300 through ~~628~~318 may be found throughout the '080 Patent, including, the Abstract, Specification, Figures and Claims, for example, at col. 13, ll. 23-36, col. 16, l. 62 through col. 17, l. 3, col. 28, l. 66 through col. 29, 1. 6; col. 29, ll. 20-35 and 38; col. 32, ll. 34-~~39~~41; col. 2, ll. 27-46; col. ~~28-40~~15,11. 28-43, and the Abstract; quoted in detail below; ~~and col. 2, 1. 57,~~ col. 3, ll. 58-60 ("the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval"); col. 19, 1. 30 through col. 21, l. ~~30~~31 (actives including pharmaceutical actives, bioactive actives, and combinations thereof); col. 6, ~~11.49~~ll. 49-52 ("These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process."); Figures 6, 7, 8, 35 and 36 and col. 14, ll. 20-25 ("drying" and "drying apparatus"); col. ~~13, 11.~~11, ll. 17-19 ("Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition"); col. 11,ll.

21-23 ("yield values ... force"); col. 12,11. 20-36, col. 13,11. 37-38 ("After mechanical mixing, the film may be placed on a conveyor"); col. 29, 11. 11-13 ("As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus"); col. ~~10,11.47-48 ("The film ... is finally formed on the substrate"); col. 26~~33, 1. ~~33~~10 through col. ~~27~~34, 1. ~~10 ("the coating is then deposited onto the substrate"~~24 (example M); col. 44, 11. 9-13 ("the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the 'locking-in' of uniformity of content throughout the film"); col. ~~58, claim 28 ("wherein the visco-elastic film is formed within about 4 minutes"); col.~~ 4, 1. 8; col. ~~6,11.46~~6, 11. 46-52; col. ~~13,11.36~~13,11. 36-43; col. 26, ~~11.9~~11. 9-27; col. 28, 11. 24-58; col. 29, ~~11.8~~11. 8-10; col. ~~18,11.53-58; col. 29, 1. 63 through col. 30, 1.2; support~~20, 11. 65-66 ("Erectile dysfunction ... drugs"); col. 19, 1. 55 ("anti-diarrhea preparations"); col. 6, 11. 52-60 ("Examples of controlled drying processes include ... hot air impingement across the bottom substrate and bottom heating plates ... controlled radiation drying ... such as infrared and radio frequency radiation ...."); col. 7, lines 5 through 16 ("This may be achieved by applying heat to the bottom surface of the film ... or alternatively by the introduction of controlled microwaves to evaporate the water. . .. air currents directed at the bottom of the film should desirably be controlled"); col. 27, 11. 53-55 ("The temperature at which the films are dried is about 100°C. or less"); col. 41, 11. 49-50 ("films were dried in an oven at approximately 60° C."). Support for new claims may also be found throughout the '~~337~~080 Patent, including, the Figures ~~and Claims, for example at col. 19,11. 10-25, col. 19,1. 30 through col. 22, ,~~ Tables and Claims, for example at col. 19,11. 10-25, col. 19,1. 30 through col. 22, 1. 28, col. 25, 11. 53-60, ~~1. 28, col. 25, 11.53-65, col. 28, 11. 53-58, col. 18,11.54-59,~~ col. 22, 11. 24-28; col. 28, 11. 1-2; col. 14,11. 63-65; Tables 17 and 18; Figures 6-8, 33, 34 and 35. Many of the claim elements of the new independent claims can be found in original independent claims 1,82, and 161 of the '080 patent.

> "Temperatures that approach 100° C. will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of

70° C. for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature. "Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component."

'080 Patent. col. 12, 11. 20-36.

"For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80° C. for 10 minutes produces a temperature differential of about 5° C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5° C. less than the outside exposure temperature. In many cases, however, drying times of less than 10 minutes are sufficient, such as 4 to 6 minutes. Drying for 4 minutes may be accompanied by a temperature differential of about 30° C., and drying for 6 minutes may be accompanied by a differential of about 25° C. Due to such large temperature differentials, the films may be dried at efficient, high temperatures without causing heat sensitive actives to degrade."

'080 Patent. col. 13, 11. 23-36.

"The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process."

'080 Patent, col. 16, 1. 62 through col. 17, 1. 3 (emphasis supplied).

"It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and overall appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."

'080 Patent, col. 28, 1. 66 through col. 29, 1. 6 (emphasis supplied).

"The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s) ... . After the end pieces, or sampling sections, are removed from the film portions), they may be tested for uniformity in the content of components between samples. "

'080 Patent, col. 29, 11. 20 through 35 (emphasis supplied).

"An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."

'080 Patent, col. 32, 11. ~~36~~34-41 (emphasis supplied).

"The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages ofactive, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment.

> Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present."
>
> '080 Patent, col. 2, 11. 27-46 (emphasis supplied).
>
> "Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1 % by weight, or less than 0.5% by weight. "
>
> '080 Patent, col. 15,11. 28-43 (emphasis supplied).

III. Declarations Submitted With This Reply

Along with this Reply, the Patentee is submitting the Declarations of Dr. B. Arlie Bogue (Exhibit A) ("Bogue Declaration") and Dr. ~~Gerald Fuller~~David T. Lin (Exhibit B) ~~both~~("Lin Declaration") under 37 C.F.R. § 1.132. The ~~Declarations~~ Bogue Declaration provides technical results regarding Patentee's commercial pharmaceutical films manufactured in accordance with the '080 Patent and it ~~provide no legal arguments, but rather provides technical opinions and factual statements, and thus~~ should not ~~count~~be counted toward the page limit of 37 C.F.R. § 1.943. The Lin Declaration provides Dr.

Lin's background information, information relating to FDA uniformity of content dosage requirements, and has six (6) numbered paragraphs of statements (¶ ¶ 17-22) relating to a prior art disclosure at pages 5-6, which might at most be counted as two (2) pages toward the page limit of 37 C.F.R. §1.943.

IV. Background of the '080 Patent

The '080 Patent is a continuation of U.S. application Ser. No. *10/856,176,* filed May 28, 2004 now U.S. Pat. No. 7,666,337 (" '337 Patent"), which claims the benefit ofU.S. Provisional Application No. *60/473,902,* filed May 28, 2003 and is a continuation-in-part ofU.S. application Ser. No. *101768,809,* filed Jan. 30, 2004 now U.S. Pat. No. 7,357,891 (" '891 Patent"), which claims benefit to U.S. Provisional Application No. *60/443,741* filed Jan. 30, 2003 and is a continuation-in-part of:

(a) *PCT/US02/32575* filed Oct. 11,2002, which claims priority to: (1) U.S. application Ser. No. *10/074,272,* filed Feb. 14,2002 which claims benefit to U.S. Provisional Application No. *60/328,868,* filed Oct. 12,2001 and (2) U.S. Provisional Application No. *60/386,937,* filed Jun. 7,2002;

(b) *PCT/US02/32594,* filed Oct. 11,2002, which claims priority to: (1) U.S. Provisional Application No. *60/414,276,* filed Sep. 27,2002, (2) U.S. application Ser. No. *10/074,272,* filed Feb. 14,2002, which claims benefit to U.S. Provisional Application No. *60/328,868,* filed Oct. 12,2001 and (3) U.S. Provisional Application No. *60/386,937,* filed Jun. 7, 2002; and

(c) *PCT/US02/32542,* filed Oct. 11,2002, which claims priority to: (1) U.S. Provisional Application No. *60/371,940,* filed Apr. 11,2002, (2) U.S. application Ser. No. *10/074,272,* filed Feb. 14,2002, which claims benefit to U.S. Provisional Application No. *60/328,868,* filed Oct. 12,2001 and (3) U.S. Provisional Application No. *60/386,937,* filed Jun. 7, 2002.

~~The '080 Patent has not been and is not currently involved in litigation.~~

There are pending applications claiming the benefit ofthe priority of all and/or some of the above.

The '891 Patent is involved in a U.S. litigation wherein Patentee has alleged that the Third Party Requester, BioDelivery Sciences International, Inc. ("BDSI") has infringed its '891 Patent. The litigation is Civil Action No. 10-cv-5695 in the U.S. District Court in the District of New Jersey. In the litigation, Patentee also alleged that the Third Party Requester infringed two other of Patentee's patents, U.S. 7,425,292 (" '292 Patent") and U.S. 7,824,588 (" '588 Patent").

Third Party Requester requested reexamination of the '891 Patent *(90/012,098),* the '292 Patent *(90/012,097)* and the '588 Patent *(95/001,753)* as well. Both the '292 and the '891 Patent successfully exited reexamination. The Examiner on January 23,2013 issued a Right of Appeal Notice ("RAN") for the '588 Patent reexamination. ~~Finally,~~In response, Patentee filed a Notice of Appeal, a Petition Under 37 C.F.R. § 1.183 Requesting Waiver of the Prohibition of an Extension of Time for Filing an Appeal Brief and for an Extension of Time for Filing an Appeal Brief, and a Petition Under 37 C.F.R. § 1.182 Requesting Continued Reexamination.

Third Party Requester requested reexamination ~~ofthe '080 Patent and~~of another of Patentee's related patents namely U.S. Pat. No. 7,666,337 (Control No. *95/002,171),* reexamination was ordered, an Office Action issued ~~and,~~ Patentee ~~is preparing a response thereto~~Replied, and Third Party Requester submitted its Comments.

Finally, Third Party Requester requested the reexamination herein of the '080 Patent.

The '080 Patent has not been and is not currently involved in litigation.

'080 Patent Office Action Statements

In connection with the Order Granting Request for Inter Partes Reexamination of the '080 Patent, Control No. *95/002,170* ("Order Granting IPR Request '080 Patent"),

noted above, certain comments were made by the Examiner with respect to Claim 25 ofthe '337 Patent. The statements were made when the Examiner addressed Third Party Requester's request to find that claim 82 of the '080 Patent should be rejected under 35 U.S.C. § 101 double patenting over claim 25 of the '337 Patent. Patentee supports the Examiner's finding that the Third Party Requester had failed to demonstrate a reasonable likelihood of success~~, in that respect, with at~~ of arriving at the subject matter of at least one claim ofthe '080 Patent. However, Patentee respectfully disagrees with the Examiner's statements interpreting "uniform" and "substantially uniform" therein. In particular, Patentee disagrees that "the active is uniformly distributed (i.e. no variance of active)" in the matrix. Certainly a uniform distribution does not require a state of "no variance". See pages 21 and 22 of the Order Granting IPR Request '080 Patent~~:~~. "Uniform" and "substantially uniform" are indeed different, but "uniform" from a practical standpoint must of necessity allow for some variance, albeit less than "substantially uniform". ~~The concept of "no variance" of anything has little practical value in the real physical world and in the '337 Patent, where the phrase does not appear. The '337 Patent makes no claim to some form of absolute 100% uniformity, it discloses, *inter alia,* uniformity ofactive and substantial uniformity of active both with no more than 10% variance. As used in the '337 Patent, while a "uniform distribution of active" has little variance in active, and in particular, less variance in active than a "substantially uniform distribution ofactive", Patentee does not claim its processes involve obtaining absolute uniformity of composition or content uniformity of no variance. The variance in uniformity may be very small but that is not the same as saying that a uniform distribution has no variance in the distribution. As the Examiner can appreciate, manufacturing processes never result in "no variance" in the quantitative compositional makeup ofproducts made therefrom. In short, "uniform" and "substantially uniform" are indeed different, but "uniform" from a practical standpoint,. Must of necessity allow for some variance, albeit less than "substantially uniform".~~

V. The Patented Invention

The present invention is directed to novel and non-obvious processes for manufacturing pharmaceutical and bioactive active containing films, suitable for commercialization and U.S. Food and Drug Administration ("FDA") approval. As noted in the Bogue Declaration, ¶ 4, one manufactured lot of such resulting film can contain 2,000,000 individual dosage units. The claimed processes accomplish this feat while providing the necessary narrow ranges in the amount of active in individual dosage units. As claimed, the '080 Patent, at least, requires a uniformity of content in amount of active (i) in individual dosage units sampled from a resulting film of 10% or less (independent claims 1,82,161, and 316-318, see Appendix A, Bogue Declaration), and (ii) in individual dosage units sampled from two or more resulting films of 10% or less as a percent difference from a desired amount (independent claim 315, see Appendix B, Bogue Declaration).

One conceptual approach to understanding (i) and (ii) is as follows. A baker has a good recipe or process for making bread. The recipe includes the ingredients and the controlled baking conditions. On Monday the baker bakes a loaf of bread strictly following the recipe. On Friday the baker bakes a loaf of bread again strictly following the recipe. The loaves are cut into individual slices. When tasted, all the slices from Monday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Monday's loaf. In the same fashion, when tasted, all the slices from Friday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Friday's loaf. However, when a slice from Monday's loaf is compared to a slice from Friday's loaf, the difference in taste is more pronounced than between individual slices from the same loaf. Since the baker follows the same recipe for all his/her bread the baker expects that all slices from all loaves should taste alike or almost alike. However, the difference in taste between slices from Monday and slices from Friday is greater than the difference between slices in the same loaf. Indeed, the taste difference is now about 10% from what the baker believes all his/her bread should be expected to taste like--that is, 10% from the high quality standard ("desired amount" and/or "target amount") for all the bread baked.

In a similar fashion, the "recipe" of Patentee's claimed processes keep differences between individual dosage units from one manufactured lot very small--e.g. smaller than 10% in amount of pharmaceutical active. See, independent claims 1,82,161 and 316-318. The "recipe" of Patentee's claimed processes also keeps differences between individual dosage units between different manufactured lots small as well, just not necessarily as small--e.g. smaller than a 10% difference from the standard, i.e. desired amount. See, independent claim 315.

~~The present invention is directed to a novel and non-obvious method of manufacturing an ingestible therapeutic active delivery system and uses thereof. The patented invention, as explicitly claimed, covers a process for manufacturing a resulting film suitable for commercialization and regulatory approval said film having a~~Thus, in the case of a resulting film from one manufacturing lot, the substantially uniform distribution ~~of a pharmaceutical active components, wherein substantially uniform distribution ofthe pharmaceutical~~of the active is indicated through analytical chemical tests ~~for active~~which indicate that uniformity of content ~~of~~in the amount of the active in substantially equal sized individual dosage units sampled from the resulting film varies by no more than 10%. ~~Hence the commercially~~See Appendix A from Bogue Declaration copied below and Bogue Declaration, ¶ 9, where this is shown to be true for 73 separately manufactured ~~'337 Patent~~lots of film ~~is both a~~, all manufactured by Patentee in accordance with the claimed invention.

APPENDIX A (Bogue Declaration)

(THE GRAPH WAS REMOVED FOR THE SAKE OF BREVITY)

In the case of resulting films from different manufacturing lots the substantially

uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active varies by no more than 10% from a desired amount. See Appendix B from Bogue Declaration copied below and Bogue Declaration, ¶ 10, where this is shown to be true across 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention. 100.0% indicating the desired amount.

APPENDIX B (Bogue Declaration)

(THE GRAPH WAS REMOVED FOR THE SAKE OF BREVITY)

Hence, the manufacturing process of the '080 Patent as claimed is a commercially viable ~~product as well as a product which can and does meet, for example,~~processes which yields commercial viable products meeting FDA regulations, including active assaying requirements. This should be compared to the laboratory produced films described in the prior art relied on by the Examiner. In the cited prior art, terms such as uniformity, substantial uniformity, and homogeneity~~,~~ are all accepted without real support. They cannot be relied upon. What is missing is the support for the statements~~,~~ -- that is, having had the amount of active tested by analytical chemical testing, including assaying. *See* Lin Declaration, ¶17-22 (statements about insufficient disclosure in cited prior art reference). Patentee uses the '~~337~~080 Patent invention to manufacture commercially acceptable ~~pharmaceutical~~ products for which Patentee must establish ~~the content~~ uniformity of content in the amount of active in its products by such analytical chemical testing as required by regulatory agencies, such as the FDA. Dr. Bogue's Declaration describes such testing on Patentee's products produced in accordance with the invention and the results which are consistent with the '~~337~~080 Patent's claims for ~~active~~uniformity of content ~~of substantially equal sized~~ in the amount of active (i) in

individual dosage units sampled from ~~the~~a resulting film ~~varies by no more than~~of 10% or less, and (ii) in individual dosage units sampled from two or more resulting films of 10% or less as a percent difference from a desired amount. Bogue Declaration, ¶¶ 4~~, r, r 5-13~~11.

PATENTEE'S CLAIMS

Patentee's instant claims ~~recited~~recite additional ~~detail~~details about its processes for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval. Some of the details include: forming a flowable polymer matrix~~;~~ comprising a polymer, a solvent and an active, said matrix having a substantially uniform distribution of said ~~pharmaceutical~~ active; casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps ~~and~~; controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to ~~rapidly~~ form a visco-elastic film, having said ~~pharmaceutical~~ active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying ~~within about the first 4 minutes~~ to maintain said substantially uniform distribution of said ~~pharmaceutical~~ active by locking-in or substantially preventing migration of said ~~pharmaceutical~~ active within said visco-elastic film~~,~~ wherein the polymer matrix temperature is 100°C or less; forming ~~the~~said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of ~~pharmaceutical~~said active by said locking-in or substantially preventing migration of said ~~pharmaceutical~~ active is maintained, ~~wherein~~ performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film from one lot, said tests indicating that uniformity of content in the amount ofthe active varies by no more than 10% and said resulting film is suitable for ~~commercialization~~commercial and regulatory approval~~; sampling the resulting film at~~

~~different locations of the resulting film in order to perform the analytical chemical tests for content uniformity ofsaid pharmaceutical active and thus establish for commercialization and regulatory purposes the substantially uniform distribution of the pharmaceutical active throughout the film product at a desired/required degree of uniformity, i.e., vary by~~, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and, in the case of more than one resulting film lot, repeating the process for forming one film lot such that uniformity of content in the amount of said active across all said resulting film lots varies no more than 10% from the desired amount ofthe active as indicated by said analytical chemical tests.

Additional claim limitations can be found in some of Patentee's narrower independent claims, for example claims 317-318. These claims generally add to the above, *inter alia,* conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60°C and using air currents, which have forces below the yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising continuing evaporation to a water content of said resulting film of 10% or less. ~~Ofparticular relevance to the Office Action, the patented invention relates to film products and film-containing products, wherein controlling the viscosity of the polymer matrix and controlling the drying process, among other things, ensures that the active components maintain their uniform distribution throughout the film product so that the desired uniformity is found in the resulting product as indicated and/or verified by testing, such as the steps of cutting samples from the resulting film product, dissolving at least portions of the samples and then testing each sample for the actual amount ofactives present using analytical equipment.~~

~~As used throughout the '080 Patent, the resulting visco-elastic product is defined as a product that has maintained the desired uniformity ofcontent of the active after being~~

~~subjected to a coating/deposition step (i.e., casting) and drying. For example, the '080 Patent, at col. 8, lines 64-66, discloses that the stability is important "in the wet film stage until sufficient drying has occurred to lock in the particles and matrix into a sufficiently solid form such that uniformity is maintained." The '080 Patent, at col. 13, lines 53-54 clearly discloses that: "The resulting dried film 1 is a visco-elastic solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film." Thus, as~~As defined in the ~~application as filed and present in the issued claims, a viscoelastic solid~~'080 Patent, a visco-elastic film is one that has been controllably dried to lock its components into a substantially uniform distribution throughout the film while avoiding problems associated with conventional drying methods. By providing a visco-elastic film product having this compositional uniformity or uniformity of content, the user can be assured that the product includes the proper amount of components, such as an active contained therein. ~~Thus, a visco-elastic product is one in which the active contained therein is present in an amount that is substantially uniform in the visco-elastic product.~~ Further, ~~when~~ the process ~~is~~can be used to make commercially viable large-scale film products, such as large rolls of film from which smaller ~~films~~individual dosage units are cut, the user can feel confident that no matter where the large roll of film is cut, the resulting pieces (e.g., individual unit dosages) will have a substantially uniform composition. As noted above, Patentee successfully manufactures pharmaceutical films containing 2,000,000 individual dosage units meeting FDA requirements using the claimed processes. Bogie Declaration, ¶ 4. As claimed, the uniformity of content as a percent difference will be no more than 10% and in some cases less. The need for providing a process for obtaining the desired uniformity of content of the desired amount of active in the resulting products is critically important, particularly for regulated products, such as the claimed pharmaceuticals.

Prior to the present invention, it was known to prepare ~~film products~~films. However, in many cases the end product was merely assumed to be homogeneous, either because the initial components were blended together or because after the blending step the physically observable properties of the resulting film product, for example, its

appearance or weight, were satisfactory. However, these physical properties do not indicate ~~that~~or establish that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units varies by no more than 10%~~. The only way to actually test for the amount of the active present in individual dosage unit samples, is to use analytical chemical testing and actually test for the presence of the desired amount of active.~~ for a particular film. By contrast, for example, in one instance, "the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix." '080 Patent, col. 18, 11. 37-40.

Nor do physical properties indicate or establish that that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units from one film to another film varies by no more than 10% from a desired amount. This range of uniformity is disclosed in connection with, for example, the uniformity of content disclosed in the '080 Patent when referencing the FDA and other regulatory requirements. "Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present." '080 Patent, col 2, 11. 43-45. In these cases, the FDA and/or other regulatory agency sets the amount of active that must be present in an individual dosage unit (or dosage form), *i.e.,* the desired amount, and provides for the necessary uniformity of content, in this case the active may vary by 10% from the desired amount. A" desired amount" is an essential concept, as the FDA indicates the required dosage for each drug, and each drug has its own specified dosage amount. Essential to any pharmaceutical and related product is a viable means of actually testing for the amount of the active present in individual dosage unit samples, and that is to use analytical chemical testing and actually test for the presence of the desired amount of active and thereby determine whether the prescribed uniformity of content of active is present. *See* Lin Declaration, ¶¶9-16.

Importantly, the process of forming a proper film product with the claimed levels of uniformity of content in, for example, the amount of active does not end at the mixing stage. Patentee has discovered that the various steps post-mixing ~~also play an~~play a very

important role in ensuring that the resulting product ~~composition~~complies with the stringent requirements for uniformity of content. For example, one key step in the formation of a film product is the drying step, particularly when heat and/or radiation is used to dry the film. Patentee has discovered that controlled drying methods ~~may be used to prepare a compositionally uniform film product~~is essential in meeting these claimed requirements. Controlled drying includes methods that ~~do not include~~avoid, for example, the formation of bubbles, or uncontrolled air currents that may cause movement of particles within the visco-elastic film forming matrix. Controlled drying, as required by the invention as claimed, may be effectuated through evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100°C or less.

It is important to understand that compositional uniformity or uniformity ofcontent is not the same as ~~uniform thickness, nor is it the same as~~ having a surface that appears free of defects.

Importantly, having a glossy surface does not equate to a uniform film, ~~since~~because the bottom side of a film product formed on a substrate will take the surface features of the substrate. If the substrate is smooth, the resulting bottom surface will also be smooth and possibly glossy. A product that has a surface that appears free of defects may have experienced significant non-uniformity below the surface, for example due to aggregation and agglomeration of components~~, movement due to the Soret effect, etc~~. It is important to note that just because the surface of a resulting product looks glossy or free of defects does not inherently mean that the actives within the film product ~~are uniform so as~~exhibit the level of uniformity of content necessary to satisfy regulatory requirements and/or deliver the desired amount to the patient. ~~See Fuller Declaration, ~ 11-13.~~

The '080 Patent discloses in a section entitled "Testing Films for Uniformity" (col. 28, 1. 65 through col. 29, 1. 53) that "[i]t may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process". '080 Patent, col. 28, 1. 66 through col. 29, 1. 1. In particular:

> "It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and over all appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."
>
> '080 Patent, col. 28, 1. 66 through col. 29, 1. 6 (emphasis supplied).

Thus disclosed are two general types of testing, one for physical uniformity, and one for chemical uniformity. The disclosure goes on to provide different ways to test for each.

> "After the end pieces, or sampling sections, are removed from the film portiones), they may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art. If the testing results show non-uniformity between film samples, the manufacturing process may be altered. This can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions, mixing conditions, compositional components and/or film viscosity may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others."
>
> '080 Patent, col. 29, 11. 33-38 (emphasis supplied).

In this way the '080 Patent provides multiple tests for non-uniformity, which are extremely useful in guiding the commercial manufacture of films. For example,

manufacturing runs of films which appear to exhibit "non-uniformity" may be adjusted early in the run with less waste of materials, thus saving time and expense associated with the possibility of a non-uniform film. Physical tests, such as observational tests, are insufficient to determine the ~~degree of uniformity. However, especially in the case ofindividual doses of actives, for example, pharmaceutical actives, the actual uniformity of content in the amount of active is essential and must be quantified through analytical chemical testing. For example,~~level of uniformity of content disclosed and claimed by the '080 Patent--they do not determine the actual amount of active in samples.

The '080 Patent discloses testing to determine the appropriate degree ~~ofcontent uniformity of the~~of uniformity of content of the resulting film ~~for commercial scale and regulatory compliance may involve~~involving sampling substantially equal sized individual dosage units of the resulting film, dissolving ~~at least a portion ofthe~~the active in the sampled resulting film, and testing for the amount of active present in the sampled resulting film. Thus, the '080 Patent discloses that uniformity of the active is demonstrated through testing.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain ~~.~~substantially the same amount of active."
>
> '080 Patent, col. 32, 11. 36-41 (emphasis supplied).

In this respect the Examiner, in his Scope of Claims section has mistakenly included physical uniformity type tests, used to quickly and/or easily suggest non-uniformity, with chemical uniformity type tests involving analytic equipment, that is, the actual testing of the uniformity of content for the amount of active. In the Scope of Claims section of the Office Action (pp. 3-7), the Examiner refers to two different portions of the '080 Patent's "EXAMPLES" section as follows:

> "An alternative means for evaluating uniformity is to cut the

> films into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39)."
>
> Office Action, p. 7.

~~Unfortunately~~Significantly, the two sentences are not related to each other, other than that both deal with examples and with cutting the film into dosage forms. The first is from a physical test, the second, relating to actives, is from an analytical chemical test for uniformity of content of active.

First is the physical test which refers to uniformity in mass.

> "Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:
>
> [Table omitted.]
>
> "The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass."
>
> '080 Patent, col. 31, 1. 46 through col. 32, 1. 34 (emphasis supplied).

In accordance with this test, if the masses are unequal that would be an indication of mass nonuniformity.

Immediately after the above quoted disclosure, the '080 Patent discloses

essentially that to demonstrate uniformity of content for active, the amount of active in each substantially similarly sized sample must be determined.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."
>
> '080 Patent, col. 32, 11. 35-40 (emphasis supplied).

The Examiner also relies on the paragraph at '080 Patent, col. 31, 11. 38-45 for support that physical type tests, in this case observational tests, are sufficient to establish uniformity of content of active.

> "The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film."
>
> '080 Patent, col. 31, 11. 38-45

However, it is one thing to have films which appear to be substantially free of aggregation and rely on that to say there is substantially no disparity among the amount of active in any portion of the film, and it is a totally different thing to demonstrate ~~by testing for the active that its distribution among film samples of the same size establishes a~~the presence of the required level of uniformity of content ~~within a desired range~~in the amount of active by analytical chemical testing and determining the actual amount of active in samples.

This paragraph, again, from the '080 Patent's section on "EXAMPLES", sets the

stage for disclosing both the physical and chemical type tests referred to above at '080 Patent, col. 31, 1. 46 through col. ~~32,1~~32, 1. 40, which follows this paragraph (see citation). Moreover, this paragraph itself follows the manufacture of the film of Examples A-I and starts with what would be ~~a~~an expected quick and inexpensive procedure of looking at the film right after making ~~the film taking a look at~~ it~~,~~ to see if it appears non-uniform~~. That is, look at the film and see if it looks like everything is~~ or uniform~~ and, if it does, then test the film to make sure it is~~. Such an observational test is at a macro level and does not indicate the degree of uniformity. Even if the film appears uniform, analytical chemical tests must then be conducted to verify uniformity of content at the prescribed level. What followed next were the two other tests discussed above.

Importantly, the first test is obviously a physical type test needed to rely on assumptions to reach its conclusion of substantially no disparity among the amount of active found in any portion of the film. Namely, by "viewing the films it was apparent that they were substantially free of aggregation. .. . Therefore, there was substantially no disparity among the amount of active found in any portion of the film." Based on physical observations a conclusion was drawn. The second, another physical test, concluded "individual dosages forms from the same film of substantially equal dimensions will contain the same mass;" again, referring to mass not uniformity of content of active. Again, no simple declarative statement~~,~~ that the amount of active in each sample was substantially the same~~. [If we modify the independent claim to include test for the active, we should refer to that here~~ or that the actual amount of active was determined.~~]~~

It was only the third test, the analytical chemical type test that could directly establish that "films of substantially similar size cut from different locations on the same film contain substantially the same amount of active". This is to be expected as only the chemical based tests could provide the necessary assurance for the statement that substantially the same amount of active was present in each dose. Thus, ~~it is wrong to~~one cannot solely rely on physical tests in prior art disclosures to "establish" that the prior art films actually possessed the ~~uniformity ofactive required~~levels of uniformity of content

as claimed by the '080 Patent ~~as determined by actual~~. However, analytical chemical testing ~~for the active. In fact, such physical tests would not result in the type of quantitative assay which would yield the percent (%) variance as recited in the claims.~~ is used in the '080 Patent to establish the actual amount of active in samples. In one example, in the '080 Patent analytical chemical testing was used to test for the amount of one component, a red dye, and in so doing established that the uniformity of content of the component fell well within the 10% level, particularly, it was 4%. See, '080 Patent, col. 33, l. 10 through col. 34, l. 24 (example M). ~~The resulting product of the present invention is a useful, active-containing, visco-elastic film product that has a substantially uniform distribution ofactive components after formation, such that uniformity of content of the resulting film varies no more than 10% with respect to the desired amount of the active present in substantially equally sized individual dosage units sampled from different locations ofthe resulting film. Importantly, in accordance with the invention the patented processes can be used in the manufacture of commercial products.~~

VI. Arriving at the Invention

The inventors of the ~~'337~~'080 Patent are the first to not only identify the problems associated with manufacturing commercially and pharmaceutically viable active containing film individual dosage units or forms, but also to solve those problems, especially as same relate to obtaining required levels of uniformity of content. Although many prior publications discussed the use of film as a dosage form for drugs, none of the publications identified nor solved the problems and complications associated with their manufacture. These early publications focused on the compositional and qualitative aspects of the films only and merely treated the manufacturing, if mentioned at all, as being simple, such as exposing the cast wet film to a conventional hot air circulating oven. However, especially in a commercial manufacturing setting, drying an active-containing cast wet film (even if the wet film is homogenous), in a conventional hot air circulating oven does not necessarily produce a film that is commercially viable, or

deliver a film with the prescribed degree of uniformity of content in said setting. The '~~337~~080 Patent does. *See*

Bogue Declaration, ¶[~~5~~4-~~13~~11.

A. Recognition of the Problem

The inventors ~~have~~ discovered that it is not commercially viable to manufacture therapeutic-active-containing films using conventional drying methods. Even when a wet film matrix is properly formed so as to have a substantially uniform distribution of active within it, there are numerous factors which can destroy that uniformity of content during later processing such as casting and drying. The present specification describes many of these problems, which include
(i) self-aggregation and agglomeration of active; (ii) skinning of the surface (a barrier through which remaining solvent must penetrate) before the thickness of the film is sufficiently dried, resulting in ripping and re-forming of the surface; (iii) forming of ripples on the surface; (iv) formation of air bubbles, which result in voids or air spaces within the film product; (v) maintaining the active in a substantially stable and uniformly dispersed state; ~~or~~ (vi) movement of active particles due to uncontrolled air currents during drying; (vii) using air currents which create forces which overcome the yield value of the polymer matrix, or which would disturb or break the surface of the polymer matrix, or which overcome the inherent viscosity of the polymer matrix. See, for example, col. ~~3,~~ ~~I~~3,1. 33 through col. 4, ~~I~~1. 6, and col. 11, ll. 14-25, the '080 Patent.

B. Solving the Problem

The inventors not only were the first to identify all the problems described above, but the first to solve them. Failure to solve one or more of these problems results in a film product that lacks the desired degree of uniformity of content of active per unit dose of film and therefore when equal dosage sizes are cut from the bulk film product, the desired amount of active per dosage lacks the desired and/or required degree of uniformity of

content of active. The inventive methods and processes of the '080 Patent maintain the desired uniformity of content of active by, *inter alia,* controlling polymer matrix viscosity and controlling the drying processes so as to avoid the aforementioned problems. Thereby, forming a visco-elastic film that locks-in the substantially uniform distribution of actives) during the drying steps. As described in the specification and claims, the present invention ~~substantially~~ maintains the ~~uniformity~~claimed levels of uniformity of content of active from the formation of the initial matrix through the final drying process, such that the pharmaceutical active varies by no more than 10% within a film lot, and by no more than 10% when sampled from different film lots.

The Examiner has cited several references, which will be discussed in further detail below. For ease of understanding, the Patentee will briefly discuss the primary cited references herein. During the discussion, it is important to keep in mind that statements from these sources regarding uniformity of content of components, especially actives, are not based on analytical chemical testing for the amount of active present in equally sized samples, but are at best assumptions, generally based on physically observable properties of the film in its intact state. The below discussion is supported by the Bogue Declaration and the Fuller Declaration.

VIII. The Claim Rejections.

The Examiner's rejection of the claims begins on page 7 of the Office Action.

A. Claims 1-299 were improperly rejected.

Claims 1-299 were rejected as allegedly anticipated under 35 U.S.C. §102(b), or, in the alternative under 35 U.S.C. § 103(a), as obvious over, each of the following references: Chen (WO *00/42992)* ("Chen"), Staab (U.S. 5,393,528) ("Staab"), Le Person *(Chemical Engineering and Processing,* Vol. 37, pp. 257-263 (1998)) ("Le Person") and Horstmann (U.S. 5,629,003) ("Horstmann") or some combination thereof as set forth in the Office Action. These rejections relied on the Examiner's findings that material claim elements of the '080 Patent's only independent claims in reexamination, Claims 1, 82 and

161, were inherent in the cited references. Two limitations were of paramount importance, namely the limitations of "substantially uniform distribution of components" and of "locking-in or substantially preventing migration of" active ~~component~~.

Patentee maintains that the foregoing claim limitations are sufficient in themselves to establish patentability. Nevertheless, to advance prosecution, Patentee has explicitly added to all the independent claims herein presented specified levels of uniformity of content in the amount of active. Either a 10% limitation on the amount by which an active can vary between individual dosage units sampled from a particular film, and/or a 10% limitation by which the amount of active can vary from a desired amount among individual dosage units sampled from more than one film, which specified levels of uniformity of content in the amount of active are not disclosed expressly nor are they inherent in the art of record. Patentee has also explicitly required manufacturing resulting pharmaceutical and/or bioactive active-containing films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units. Additional aspects not present in the art of record include, *inter alia,* viscosity ranges, controlled drying, conveying, applying air currents which have forces below the yield value of the polymer matrix during drying, forming a visco-elastic film in about 4 minutes, keeping the polymer matrix temperature below 100°C, wherein resulting film has a water content of 10% or less. And the foregoing was just a partial listing of new claim elements. Hence, independent claims 1,82 and 161, as amended, and all the new independent claims, claims ~~321~~315-~~324~~318, are not ~~explictly, implicitly or inherently~~ disclosed ~~or suggested~~and/or made obvious, explictly or inherently, in the cited prior art. ~~In particular, the prior art ofrecod does not disclose, forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a uniform distribution ofsaid pharmaceutical active, casting said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps and conveying said polymer matrix through a drying apparatus and evaporating at least a portion ofsaid solvent to rapidly form a visco-elastic film having~~

~~said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity ofsaid polymer matrix upon initiation ofdrying within about the first 4 minutes to maintain said uniform distribution ofsaid pharmaceutical active by locking in or substantially preventing migration ofsaid pharmaceutical active within said visco-elastic film wherein the polymer matrix temperature is 100°C or less, forming the resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said uniform distribution ofpharmaceutical active by said locking in or substantially preventing migration ofsaid pharmaceutical active is maintained, wherein said resulting film is suitable for commercialization and regulatory approval, sampling the resulting film at different locations ofthe resulting film, in order to perform the analytical chemical tests for content uniformity ofsaid pharmaceutical active, and thus establish for commercialization and regulatory purposes the substantially uniform distribution of the pharmaceutical active throughout the film product, and/or where the required degree ofuniformity is such that the amount ofactive does not vary by more than 10%.~~

The Examiner ~~basically~~ relies on the Declaration ofEdward D. Cohen, Ph.D. under 37 C.F.R. § 1.132, dated September 6,2012 ("Cohen Declaration) ~~for his~~to support the assumption that it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active. Office Action, pp. 14 and 43. However, Dr. Cohen's assumption is dead wrong on its face or does not apply to the '080 Patent. Importantly, Dr. Cohen does not discuss the degree of uniformity of content. He refers generally to "substantial uniformity of content of active" and "uniform content of active" per unit dosage. Cohen Declaration, ¶¶ 8-10. Dr. Cohen's statement about uniform content of active, without providing the degree of uniformity of content cannot be applied to the '080 Patent's invention. Especially now that the claims of the '080 Patent expressly ~~claims~~require a degree of uniformity of content, namely, that uniformity of content of the resulting ~~film~~film(s) varies (i) no more than 10% with respect to the amount of active within a film (claims 1,82,161,316-318) and/or (ii) no more than 10% from a desired amount ~~ofthe active present~~with respect to the amount of active; said active sampled from

different films in substantially equally sized individual dosage units sampled from different locations of the ~~resulting film~~relevant film(s) (claim 315). ~~Moreover, the Declaration of Dr. Fuller on the other hand provides, at paragraphs 6-10, a basis and opinion for a conclusion much different from that provided by Dr. Cohen.~~

~~"6. It is my opinion that the film process as described by Chen at commercial scale would not inherently result in a film having a uniform distribution ofactive in the film. In particular, it is also my opinion that the film process of Chen would not inherently result in a film having a uniformity ofcontent of active in substantially equal sized individual dosage units sampled from Chen's resultant film, where the active in the dosage units varies no more than 10%. The process described by Chen does not describe how to dry in a manner that would avoid redistribution and inhomogeneity of a dissolved solute or suspended actives due to well known thermodiffusive effects. The effects, also referred to as the Soret effect, can drive inhomogeneities during the drying ofa previously homogeneous mixture. In other words, even ifa solution containing a solute or suspended actives is spatially homogeneous in that constituent, the act of drying the solution to create a solid film can cause redistribution ofthe solute or suspended actives through the creation oftemperature variations. This is the result oftemperature gradients within the polymer film matrix causing the solute or suspended actives in the film to migrate and accumulate in different locations even ifthe solute or suspended actives were initially uniformly distributed. The Soret effect, which was described in 1800's, is a classical phenomenon, and is well-known to the chemical process industry. (see Appendix II)~~

~~"8. Dr. Cohen's assumption that Chen's process wi11lead to films that are spatially homogeneous in composition is flawed because it does not recognize that thermodiffusive effects can result in spatial redistribution of constituents even if they were initially homogeneous prior to the application of heating during the process of film formation. Because Chen does not describe the film drying process, it cannot be assumed that any resulting temperature gradients within the polymer film matrix during the drying process will not lead to thermodiffusion and spatial inhomogeneity.~~

~~9. Chen does not discuss the development of viscoelasticity in the film during the drying process. Chen discloses the use of hydro colloids and it is wellestablished that these materials can increase viscosity but will not necessarily enhance viscoelasticity. It is well known that viscosity is only one property within the general description of viscoelasticity. Even though these materials, such as Carbopol®, can lead to shear thinning materials, they are often inelastic and purely viscous. Chen does not recognize the mechanism of viscoelasticity of a film undergoing drying needs to be effectuated to retain the spatial uniformity of the constituents ofthat film. The development of viscoelasticity has the ability of arresting processes such as the Soret effect that can induce inhomogeneities. The Monosol process that creates a viscoelastic film within the first four (4) minutes ofdrying has the important benefit of locking in a spatially homogeneous distribution ofcomponents by inhibiting the effects of thermodiffusion to obtain active uniformity that does not vary more than 10% in the amount of active present in substantially equal sized individual dosage units.~~

~~"10. Dr. Cohen is incorrect in his assumption that simply increasing the viscosity of a hydrocolloid material through film drying will retain spatial uniformity of the constituents ofa film. In the absence of conditions which rapidly build viscoelasticity, components can diffuse spatially in a viscous media in response to thermodiffusive effects. The development of a rapid viscoelastic network formation is able to spatially constrain the diffusion of components and inhibit thermodiffusivity and retain spatial uniformity to the desired degree."~~

Moreover, as set forth in the Bogue Declaration, ¶¶~~10~~4-~~14~~11, 730 samples of individual dosage units, ten each from 73 ~~separate manufacturing~~separately manufactured lots of resulting films produced in accordance with Patentee's invention, were tested for active content. The results were that the active content of each individual dosage unit remained well within the control limits of 90% to 110% of the desired amount.

> "The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of

content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A. Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C .."

~~"It can be seen from Appendix A that the active content ofeach individual dosage unit remains well within the control limits of90% to 110%. The target or desired amount is 8.00 mg ofactive per individual dosage unit. The range of analytical chemical testing results among those 730 individual dosage units was 93.50% (7.48 mg) to 105.80% (8.47 mg) ofthe target or desired amount ofactive. This uniformity ofcontent level is consistent with that described in the '337 Patent."~~

Bogue Declaration, ¶ ~~12~~11.

As noted, the FDA requires that the amount ~~ofactive~~of active vary from dose to dose by no more than a prescribed percentage from the desired amount of active, essentially prescribing a degree of uniformity of content ~~uniformity~~in the amount of active which must be met. *See* Lin declaration, ¶9-16. Dr. Cohen provides no support for any prescribed degree of uniformity, and certainly not for the prescribed degree of uniformity of content in the amount of active explicitly recited by Patentee's claims under examination to meet commercial and/or regulatory requirements, or the degree of uniformity present in resulting films manufactured in accordance with Patentee's invention, as clearly demonstrated by the Bogue Declaration.

As held by the Court of Appeals for the Federal Circuit ("Federal Circuit") inherency requires much more than probabilities, possibilities, or for that matter assumptions~~, such as, that by starting with so called "uniform" mix ofmaterials, stirring them, then casting and drying inherently results in the processes claimed in the '080 Patent~~. In *Crown Operations Intern., Ltd. V. Solutia Inc.,* 289 F.3d 1367 (Fed.Cir. 2002) *("Crown"),* the patents at issue related to layered films used to create safety and solar control glass. The multi-layer film added properties to the glass assembly, such as impact resistance. An inner layer had solar control properties to reflect, absorb (and thus convert to heat), or transmit defined percentages of certain wavelengths oflight. *Crown,* at 1370. The district court had held the only relevant independent claim ofone ofthe patents, the '511 patent, not invalid on the grounds of anticipation and obviousness. It claimed a composite solar/safety film, comprised ofa solar control film "wherein said solar control film contributes no more than about 2% visible reflectance". *Crown,* at 1372.

> "Crown [the declaratory judgment plaintiff] argued that U.S. Patent No. 4,017,661 to Gillery (the "Gillery patent") anticipates the '511 patent. The district court held otherwise, because, while the Gillery patent discloses the first three limitations of claim ~~1~~1 ofthe'511 patent, it does not disclose the two percent visible reflectance limitation. The court found that neither the Gillery patent claims nor its description expressly disclose a two percent limit on reflectance contribution from the solar control film layer. Crown argued that the two percent limitation was inherently present in the Gillery patent's teachings because the Gillery patent disclosed an assembly with PVB layers, substrate layer, and substrate metalcoating - arguably of the same composition and thickness of the films disclosed by the '511 patent. Thus, Crown argued, because the structure, thickness and materials ofthe assembly were the same or within the same range(s), the Gillery patent must inherently disclose a two percent limitation. The district court rejected this argument because it found that none of the embodiments disclosed by the Gillery patent meet the two percent visible light reflectance limit."
>
> *Crown,* at 1372.

The Federal Circuit, in upholding the decision of the District Court as well as the

validity of the '511 patent, discussed the application ofinherency to validity that is most relevant here.

> "Regarding alleged anticipation by the Gillery patent, on its face the Gillery patent does not disclose or discuss a two percent limitation for the reflectance contribution of the solar control film. Crown maintains that the'511 patent merely claims a preexisting property inherent in the structure disclosed in the prior art. Crown urges us to accept the proposition that if a prior art reference discloses the same structure as claimed by a patent, the resulting property, in this case, two percent solar control film reflectance, should be assumed. We decline to adopt this approach because this proposition is not in accordance with our cases on inherency. If the two percent reflectance limitation is inherently disclosed by the Gillery patent, it must be necessarily present and a person of ordinary skill in the art would recognize its presence. In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed.Cir.1999); Continental Can, 948 F.2d at 1268, 20 USPQ2d at 1749. Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." Id. at 1269,20 USPQ2d at 1749 (quoting In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)) (emphasis supplied)."

The alleged inherency of the art cited by the Examiner and discussed below has not been established other than by statements of probabilities and/or possibilities and/or just statements that things are uniform without providing any degree of uniformity that must be present. For example, the assumption that by starting with so-called "uniform" mix of materials, stirring them, then casting and drying as alleged to be disclosed in the prior art is insufficient to establish inherency. Again, inherency requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. Importantly, the mere possibility that some of the films produced as disclosed by the art cited might result in some type of "uniform" film is not sufficient.

1. Chen's alleged inherency.

> "The claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" of the active in independent claims 1,82 and 161, and the variation of active content of 10% or less in dependent claims 254-255,272-273 and 290-291, are inherent in Chen's exemplified films and process. Inherency is based on the following: As discussed above, Chen uses the same materials and method as here claimed. Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection."
>
> Office Action, p. 13.

The criteria used by Chen as cited by the Examiner for evaluation of "substantial uniform distribution" are physical observations. Such "observations" cannot be used, either inherently or otherwise, to establish the uniformity ofcontent in the actual amount of active in equally sized samples in Chen's examples. Absent, statements or data based on analytical chemical testing, not weighing or visual inspection, for the amount ofactive present in the film, Chen does not and cannot inherently disclose Patentee's resulting film having ~~uniformity ofcontent, with respect to the amount ofthe active present in substantially equally sized individual dosage units sampled from different locations ofthe resulting film, which varies by no more than 10% from the desired amount ofthe active~~the claimed levels of uniformity of content. Moreover, even if Chen disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra,* at 1378.

Moreover, Third Party Requester has not provided any proof that Chen's process examples when followed exactly, with all the components exactly as listed, and all other conditions of Chen exactly met, will provide a process suitable for commercial manufacture, a process which produces products which are regulatory approvable by the FDA, and which exhibit the levels of uniformity of content in actual amount of active

claimed by Patentee's processes. Indeed, FIG. 5 of Chen describes a release profile of almost 120% of active from a film, which certainly exceeds the levels of uniformity of content in the amount of active that Patentee claims. This single active content result voids all claims to Chen's alleged inherency regarding same.

> "Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film."
>
> Lin Declaration, ¶ 22.

The Examiner states that the films made in accordance with the claims as issued are inherent in Chen. This conclusion is based on the belief that Chen uses the "same materials and method" as the Patentee, but even if true, much more is required. Patentee respectfully submits that this conclusion is incorrect, and particularly incorrect ~~with the amended claims. The examiner~~in light of the claims as amended. The Examiner erroneously states that Chen "uses the same criteria" as the '080 Patent that issued in evaluating substantial uniform distribution, i.e. weights of dosages and visual inspection." Although, a number of ways to test films in the patent are disclosed, in order to test content uniformity ~~ofan~~of an FDA regulated film product, it is necessary to assay using analytical chemical tests for drug or therapeutic active content of unit film doses. *See,* Lin declaration, ¶ 9-16. This is necessary to ensure the amount of active is within acceptable guidelines. Visual observation and physical measurements such as weight is insufficient

to determine the active amount in equally sized dosage units~~. Almost all~~ at the level of uniformity of content required.

All of Patentees' ~~amended~~ claims now require analytical chemical testing and~~/or~~ that the films have ~~uniformity~~levels of uniformity in the amount of active which varies by no more than 10% ~~variance~~from film to film and/or no more than 10% from a desired amount across several films. The Examiner's assumption that visual inspection and weight measurements ~~provide this information~~establish these levels of uniformity of content in and by themselves is therefore incorrect~~.~~, in so far at least as is required by the FDA, for example. Moreover, "Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products." Lin Declaration, ¶21.

~~Fuller Declaration, especially at " 6-14, provides further reasoning regarding this incorrect assumption and lack of inherency. According to Dr. Fuller, "the film process as described by Chen would not inherently result in a film having a uniform distribution of active in the film ... [or] a uniformity ofcontent of active in substantially equal sized individual dosage units sampled from Chen's resultant film, where the active in the dosage units varies no more than 10%." Fuller Declaration, , 6. Moreover, Chen disclosure exhibits a lack ofunderstanding and more importantly any teaching "to describe the drying operation that would cause it to avoid redistribution and inhomogeneity ofa dissolved solute or suspended actives due to well known thermodiffusive effects. The effects, also referred to as the Soret effect can drive inhomogeneities during the drying ofa previously homogeneous mixture. In other words, even if a solution containing an active ingredient is spatially homogeneous in that constituent, the act of drying the solution to create a solid film can cause redistribution of the solute through the creation of temperature variations." Fuller Declaration, ~ 7. "Chen does not recognize that the mechanism ofviscoelasticity of a film undergoing drying to retain the spatial uniformity of the constituents of that film. The development of~~

~~viscoelasticity has the ability of arresting processes such as the Soret effect that can induce inhomogeneities. The Monosol process that creates a viscoelastic film within the first four minutes of drying has the important benefit of locking in a spatially homogeneous distribution of components by inhibiting the effects of thermodiffusion." Fuller Declaration, ~ 9.~~

Finally, ~~Dr. Fuller's Declaration addresses the~~there is a misplaced reliance on the physical terms "glossy" and "transparent" in the Office Action, which the Examiner use to establish the presence of "uniformity" in Chen's films. However, ~~as Dr. Fuller declares,~~ the ~~"~~term ~~'~~"glossy~~'~~" is purely a visual characteristic ("surface luster or brightness") and is not interchangeable with nor equivalent to the uniformity of content of components of a film, nor the content uniformity of an active in the film. *See,* www.merriam-webster.comldictionary/glossy. It is also not interchangeable with ~~a specific variation ofactive~~specified levels of uniformity of content in ~~unit dosage samples taken~~amount ofactive in individual dosage units sampled from a film~~...~~ or sampled from different films. The term ~~'~~transparent~~'...~~ is also a purely visual appearance characteristic ~~that is neither~~("transmitting light without appreciable scattering ... "). *See,* www.merriam-webster.coml dictionary/transparent. It is not indicative ~~nor suggestive of the~~of the uniformity of content ~~of the~~of the film~~. In particular, this term does not necessarily provide any indication or suggestion of a specific variance of active per unit dose of film sampled therefrom." Fuller Declaration, ~~~ 12-13. As such the Chen's films~~. As such, Chen can neither ~~inherently~~ anticipate, explicitly or inherently, nor make obvious the '~~337~~080 Patent claims, see discussion below.

2. Staab's alleged inherency.

> "Staab also discloses that "[t]he device of the invention thus is composed of a biologically-compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium

chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Accordingly, Staab's films inherently have the instantly claimed substantially uniform distribution of components and active. Also, in view of the fact that each film contains 19 mg of benzalkonium chloride and in view of said homogeneous blending, the variation of active in the dosage units is 0% (sic 10%), as per claims 254, 255, 272, 273, 290 and 291."

Office Action, p. 29.

"In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. Accordingly, Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, after drying for about 10 minutes, a viscoelastic film having less water that before drying is formed."

Office Action, p. 30.

"While Staab does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process."

Office Action, p. 31.

Again, as with Chen, absent statements based on testing ~~and/or a determination of the actual~~to determine the actual uniformity of content in the amount of active present in the film, so as to meet FDA approval, Staab does not and cannot inherently disclose Patentee's resulting film having ~~uniformity~~the claimed levels of uniformity of content, with respect to the amount of the active present in substantially equally sized individual

dosage units sampled from different locations of the resulting film~~, which varies no more than 10% from the desired amount ofthe active~~ and/or of different resulting films. Staab does not and cannot inherently form a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content within ~~this~~the recited ~~10% variance~~levels of uniformity of content.

Moreover, even if Staab disclosed, which it does not, the use of the same materials and methods as the '~~337~~080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra,* at 1378. Moreover, Staab just states that there is 19 mg of benzalkonium chloride present in each sample weighing 190 mg. However, ~~however~~ Staab does not disclose testing to determine the amount of benzalkonium chloride present in the final film product or even how each and every sample turned out to be 19 mg. Staab, ~~coL 11, L~~col. 11,1. 35 ~~through coL 12, L~~col. 12, 1. 3. Staab's resulting structure is a foam rather than ~~a substantially solid~~the recited visco-elastic ~~structure~~film formed within 4 minutes and Staab also would not inherently have the recited degree of uniformity of amount of active in substantially equal sized dosage units. Moreover, Staab starts with a composition having 10% by weight of benzalkonium chloride (50% aqueous)~~. Yet~~ yet allegedly obtains a resulting film with 19 mg benzalkonium chloride in a 190 mg film, to once again obtain a 10% benzalkonium chloride resulting composition. A perfect yield must always be considered suspect. Inherency should never be based on a suspect disclosure. As such, Staab can neither anticipate, explicitly nor inherently, nor make obvious the '080 Patent claims, see discussion below.

3. Le Person's alleged inherency.

> "Le Person discloses that after 5 min of the drying, 'the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates.' (See p. 262, coL 2, third full paragraph.) Le Person also teaches that '[b]etween the 5th and 10th min of drying the heavy solvent migrates ... active substance, slowed

down in its migration, stays in the bottom of the layer.' (See the last four lines at page 262, coL 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that, inherently, a substantial uniform distribution of the active is locked-in and migration is substantially prevented within the film, as here claimed. The active material homogenizes and a quasi-equilibrium is obtained for the components of the Page 38 active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13), and thus, there is a variation of active content of less than 10%, as per claims 272, 273, 290 and 291.

Office Action, pp. 37-38.

"While Le Person does not discuss viscoelasticity or that the films in its process have a 'substantially uniform distribution of components' or disclose 'locking-in or substantially preventing migration' of the active, Le Person, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 82,89-91,161,171-173,272-274 and 290-292, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."

Office Action, p. 38.

Le Person is entirely devoid of any details with respect to its process and materials. For example, nowhere does Le Person discuss what type of acrylic polymer he uses~~,~~ nor the molecular weight of the polymer. Thus, Le Person allows for materials which may have such a low molecular weight that forming a visco-elastic film may not be possible. Moreover, Le Person lacks sufficient enabling disclosure to be an effective reference as applied in view of the amended claims. Such deficiencies cannot be used in support of an inherency argument.

Again, absent statements and data based on testing for the amount of active present in the film with results establishing a substantial uniformity ~~ofcontent, which~~

~~active varies by no more than 10%~~of content at the claimed levels and suitable for FDA approval, Le Person does not and cannot inherently disclose Patentee's resulting film~~, having uniformity of content, with respect to the amount ofthe active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, varying by no more than 10% from the desired amount ofthe active. .~~. Moreover, Le Person does not and cannot inherently form a viscoelastic film in about 4 minutes which locks-in the claimed uniformity of content ~~within this recited 10% variance~~in the amount of active.

~~Moreover, Le~~ Le Person discloses ~~.~~very little about the acrylic polymer, such as the molecular weight. If the molecular weight was low enough it may not become a viscoelastic material. Patentee asks, how could Le Person anticipate and/or make obvious the '080 Patent which is directed to the commercial manufacture of a regulatory approvable resulting film ~~with a~~meeting required specified ~~content uniformity of~~levels of uniformity of content in the amount of the active, where Le Person's goal, as noted in its abstract, was devoted to determining "cases ~~of mal distribution of the~~of maldistribution of the active substance," in connection with different drying methods, and not to providing a process for manufacturing films with ~~active~~ uniformity of ~~the~~content of the desired amount of an active. Importantly, Patentee has added several additional process steps not in the prior art. These new process steps present in the amended independent claim, as well as the new independent claims, further distance Patentee's patent from the prior art~~, by negating any anticipation and obviousness assertions.~~. As such, Le Person can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

4. Horstmann's alleged inherency.

> "The claimed substantially uniform distribution of components and active, and locking-in or substantially preventing migration of active, and the variance of active content of 10% or less in dependent claims 254, 272 and 290 are also inherent in Horstmann's Examples 1,3 and 4. In particular, Horstmann's

> films before drying are described as being uniform and homogeneous (see col. .3, line 11-19,29-34 and 37-41; col. 5, lines 1 and 50), and as noted above, Horstmann uses the same components and process steps as here claimed. The '080 patent notes that Horstmann addressed the problem of self-aggregation and nonuniformity by increasing the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film (see col. 2, line 60 through col. 3, line 1).
>
> Office Action, p. 43.
>
> "While Horstmann does not discuss viscoelasticity, water content of its dried films or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the, active, Horstmann, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1,5,7-10,12-1423,63,64,82,84,86-89,91-93,102,142,143,161, 166, 168-171, 173-175, 184,224,225,249,254,267,272,285 and 290, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, pp. 43-44.

Horstmann forms a gel, rather than a solid film as in the present invention. Thus the gel rheological properties of Horstmann are very different than a solid visco-elastic film having a water content of 10% or less. Moreover, Horstmann specifically teaches protecting the gels from drying up by placing the cut out gel shapes in a water vapor impermeable sealing material. See Horstmann, col. 5, 11. 11-13. This is a direct teaching away from drying to a water content of 10% or less. ~~Moreover,~~ Horstmann at col. 2, 11. 25-29, suggests drying may not be necessary.

Again, absent statements based on testing for the amount of active present in the film with results establishing a ~~substantial uniformity of content, with no more than 10% variation from a desired amount ofthe active~~the claimed levels of uniformity of content in the amount of active, suitable for FDA approval, Horstmann does not and cannot

inherently disclose Patentee's resulting film ~~having said uniformity of content which varies no more than 10% with respect to the desired amount ofthe active present in substantially equally sized individual dosage units sampled from different locations ofthe resulting film.~~claiming the specified levels of uniformity of content in the amount of active.

Additionally, as the Examiner admits, Horstmann discloses only that its film is alleged to be uniform at a point prior to drying. Horstmann, col. 3, 11.37-41. Horstmann says nothing about the uniformity of the product during or after drying. Again, *Crown* holds that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* A disclosure of some unspecified degree of uniformity of a film prior to drying in Horstmann does not establish that the product after drying is uniform, let alone the degree of uniformity as claimed by the '080 Patent. As noted throughout the '080 Patent, controlled drying is required for ensuring~~, among other things, [that uniformity of content ofthe resulting film varies no more than 10% with respect to the desired amount ofthe active present in substantially equally sized individual dosage units sampled from different locations ofthe resulting film].~~ the claimed levels of uniformity of content. As such, Horstmann can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

Importantly, Patentee has added several additional process steps also not in the prior art. See above. These new process steps present in the amended independent claims, as well as the new independent claims, further distance Patentee's patent from the prior art, by negating any anticipation and obviousness assertions. Even without the additional process steps, even if it were possible that a resulting film with the proper ~~uniformity~~levels of uniformity of content in the amount of active might possibly result from some manipulations of the disclosures given in any of Chen, Staab, Le Person and/or Horstmann, it is incorrect to rely on these references in an attempt to show they inherently disclosed Patentee's resulting film. See *Crown,* at 1377-1378, *supra.*

As the absence of inherency in and of itself removes Chen, Staab, Le Person and

Horstmann as viable prior art for rejecting Patentee's claims under ~~either~~ 35 U.S.C. § 102, the Examiner should withdraw his rejections of Patentee's claims ~~claims~~ 1,82 and 161 based on same. For the same reasons new independent claims ~~321~~315-~~324~~318 are allowable. Moreover, these references for the same reasons discussed above, as well as the reason discussed below, do not support any finding of obviousness, and thus the rejections of claims 1,82, and 161 ~~rejections~~ based on 35

U.S.C. § 103 should be withdrawn as well. For the same reasons new independent claims ~~321324~~315-318 are not obvious in light of the prior art. Finally, Patentee's claims 2 through 81, 83 through 160, ~~163~~162 through 299 and 300 through ~~320 and 325 through 628~~314 as they depend from independent claims ~~1,82, 161, and 321-324~~1,82,161 should all be allowed as well, with any rejections withdrawn.

B. Third Party Requester's Wherein Argument is Wrong

Patentee finds it necessary to address Third Party Requester's attempt to vitiate the '080 Patent's claim language beginning with "wherein". Third Party Requester cites to the Federal Circuit for the premise that "a whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Minton* v. *Nat'l Ass'n o/Securities Dealers, Inc.,* 336 F.3d 1373, 1381 (Fed.Cir.2003). Third Party Requester's Request for Inter Partes Reexamination ("The Request"), p. 16.

However, the Federal Circuit has also strongly held that "when the 'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer* v. *Microsoft Corp.,* 405 F. 3d 1326, 1329 (Fed. Cir. 2005). Essentially, Requester proposes that with elimination of the "whereby" clauses, the claims 1, 82 and 161 (before the amendments herein) would not require "wherein said resulting film has a water content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained." The Request, p. 20.

~~Patentee's fundamental invention concerns among other things making a film having a substantially uniform distribution~~

~~ofcomponents or, as now claimed a uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film is such that uniformity of content of the resulting film varies no more than 10% with respect to the amount ofthe active present in substantially equally sized individual dosage units sampled from different locations of the resulting film.~~

As noted above, "when the whereby clause states a condition that is material to patentability, it cannot be ignored to change the substance of the invention." *Hoffer* v. *Microsoft Corp.,* 405 F.3d 1326 (Fed. Cir. 2005); *see also Fantasy Sports Properties, Inc.* v. *Sportsline.com, Inc.,* 287 F.3d 1108, 1111-16 (Fed. Cir. 2002); *Griffin* v. *Bertina,* 285 F.3d 1029, 1034 (Fed. Cir. 2002). In *Griffin,* for example, the court found that "wherein" clauses were claim limitations "because they relate back to and clarify what is required by the count. Each 'wherein' clause ... expresses the inventive discovery [and] ... elaborates the meaning of the preamble." *Griffin,* 285 F. 3d at 1033-34. Further, "the allegedly inherent properties of the 'wherein clauses' provide the necessary purpose to the steps." *Id.* See also, MPEP, § 2111.04.

The ~~original~~ '080 Patent independent claims' wherein clause limitations cannot be disregarded. The '080 Patent claims processes for manufacturing ~~pharmaceutical films with a substantial uniform distribution ofcomponents~~resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the u.s. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films. The ability to make such films with the required ~~amount~~level of uniformity in ~~distribution~~content of active is the essence of Patentee's invention. Thus ~~any~~, such wherein ~~clause~~clauses which ~~expresses~~express the inventive discovery and elaborates the meaning of the preamble~~, for example, that the uniformity of content of the resulting film varies by no more than 10% with respect to the amount ofthe active present in substantially equally sized individual dosage units sampled from different locations of the~~

~~resulting film, or that such uniformity must be determined by analytical chemical testing in compliance with regulations,~~ cannot be ignored for purposes of patentability.

Finally, Third Party Requester has made many allegations about the '080 Patent and its specifications and claims, and the prior art in The Request. Patent owner believes ~~the amendment to claim 25~~that the amendments to claims 1, 82 and 161 herein clarifying the scope of same~~, obviates~~ and thereby advancing the prosecution of same, obviate the need to address Third Party Requester's allegations or the Examiner's statements made without the benefit of the amendments~~, nevertheless~~. Nevertheless, to the extent that any are not explicitly addressed herein, Patentee hereby asserts they are wrong and unsupported in either fact or law.

C. Claims ~~1,4,5,8-18,20-32,34,36-40,44-47,51,53,54,59~~1,4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84,87-97, 99-111,113,115-119,123-126,130,132,133,138,141-150,161-166,169-179, 181-193,195,197-201,205-208,212,214,215,220,223-232,243,244,246, 247,249-262,264,265,267-280,282,283 and 285-299 were rejected under 35
U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen. Claims ~~2,3,6,7~~2, 3, 6, 7, 19,33,35,41-43,48-50,52,55-58,60,61,85,86,98, 112, 114, 120~~-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196,202~~122,127-129,131,134-137,139,140,167,168,180,194,196,202-204, 209~~-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281~~211,213,216-219,221,222,245,248,263,266,281 and 284 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Chen, WO *00/42992* ("Chen") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Chen. Patentee incorporates its previous discussions in sections A. and B. above. Chen is a primary reference relied upon by the Examiner in the Office Action. Patentee respectfully traverses the ~~rejection~~above rejections on the basis, among others, that Chen does not disclose ~~the~~as claimed~~: particular drying methods; resulting visco-elastic product~~ in the '080 patent: the recited controlled drying; the recited

viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of ~~pharmaceutical~~ active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of a lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Chen also fails to disclose, explicitly or inherently, the additional elements found in Claim 317. Claim 317 generally adds, *inter alia,* conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60°C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30°C between polymer matrix inside temperature and outside exposure temperature.

Chen discloses two methods of forming a film product, a solvent casting method and an extrusion method. The extrusion method does not rely upon putting a hydrocolloid in a solvent, nor does the extrusion method use a drying oven and is apparently preferred by Chen over the solvent method. Chen, page 15, lines 9-21. In the solvent casting method, Chen states that a hydrocolloid is dissolved or dispersed in water, and mixed to form a homogeneous solution. The active agent and other ingredients may be added and dispersed or dissolved uniformly in the hydrocolloid solution. The coating solution with a

solid content of 5-50% and a viscosity of 500-15000cps is degassed and coated onto a polyester film and "dried under aeration" at a temperature between 40-100°C to avoid destabilizing the agents. Chen, p. 15,11. 19-29. The dry film formed by this process is described to be a "glossy, stand alone, self supporting, non-tacky and flexible film". Chen, p. 15, 11, 30-31. These very general statements are all that are given by Chen as to the formation and drying of Chen's film product. These statements cannot support either anticipation ~~nor~~or obviousness rejections. ~~See, e.g., Fuller Declaration, ~~ 6-13.~~

Chen's drying process is so general and devoid of detail so as to provide no guidance other than that to dry, one places a film in a conventional hot air circulating oven at temperatures ~~of from~~of from 40-100°C and leaves it for a period of time. ~~As shown in Patentee's photographs (Figures 9-16), drying in a hot air oven does not produce uniform films through the locking in of the active in a substantially uniform distribution throughout the visco-elastic film. Again, it is important to note that while physical testing and observations such as Patentee's photographs (Figures 9-16) may be generally relied on to show non-uniformity, direct establishment of the uniformity ofcontent for the amount ofactive is by testing for the active needed to demonstrate that the amount of active is substantially uniform throughout the film. Importantly, Chen's "tests" for uniformity, except perhaps for water content, are for physical uniformity, that is, appearance (glossy, transparent), weight, density, thickness and not the relevant testing of the active itself to demonstrate the desired uniformity ofcontent ofthe desired amount ofactive per unit dosage as required by the claims in reexamination. Fuller Declaration, ~ 11-13.~~

Chen does not disclose any other drying methods beyond drying "under aeration", nor does Chen disclose any controlled drying processes whatsoever. Chen showed no recognition of the complexities involved in the commercial manufacturing of films, as Chen's focus relates solely to the ingredients and mechanical properties, not the process. Without any recognition of the problems, and without any appreciation of the difficulties in preventing the settling, migration and/or aggregation or agglomeration of active(s) in the cast flowable mass, Chen neither sought nor found the solution to creating

commercial scale films having ~~substantial~~ uniformity ~~ofactive(s) per unit dose or per unit of film~~of content of pharmaceutical and bioactive actives per individual dosage unit and meet FDA requirements regarding same. Chen lacks substantial disclosure in view ~~of the '337~~of the '080 Patent. Among its deficiencies, Chen lacks any disclosure as to specific processing means (beyond generally drying in a generic oven) or the formation of a visco-elastic film state. Chen only discloses the apparent homogeneity of a blended matrix, and this is prior to the addition of actives. There is no disclosure or suggestion as to how to create a substantially uniform distribution of the pharmaceutical or biological ~~active~~ active in the blended matrix and then cast that matrix to maintain uniformity, and then ~~convey~~control drying through among other processes conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 to maintain said uniform distribution of said pharmaceutical or biological active by locking-in or substantially preventing migration of said· pharmaceutical active within said visco-elastic film and then test it to establish the substantially uniform distribution of pharmaceutical or biological active content, in compliance with FDA regulations.

~~Thus, among~~Among other things, the '~~337~~080 Patent claims are directed to locking-in ~~the~~an active such as a pharmaceutical or biological active, by controlling drying to form a viscoelastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes. The Examiner has stated in the Reexamination, Reasons for Patentability/Confirmation *("RFP/C"),* in connection with both the '292 Patent and the '891 Patent reexaminations that "Chen does not discuss what happens within the first 4 minutes of drying." Moreover, in the '891 Patent *RFP/C* the Examiner goes on to state that: "Chen does not discuss uniformity of pharmaceutical or biological active components in its doses. Table 4 of Chen gives the grams per unit dosage film and density for Example 1 with standard deviation based on three or four measurements, but does not give compositional uniformity." Additionally, Chen's

Example 1 contains only food flavorings and a sweetener.

Chen does not disclose that the resulting products are compositionally uniform, but only that they are "glossy". ~~Glossy~~As stated above, glossy does not imply or establish compositionally ~~uniform. Fuller Declaration, ~~ 11-13~~uniformity. **In** fact, Chen's Figure 5 (Examples 5-8) clearly shows a lack of compositional uniformity of active. ~~While~~Although statistics are not defined in the text, the error bars represent either high or low values, standard deviation or some measure of variation. Given that the compositions of Examples 5-8 are the same, except for the amount of active, it is reasonable to ~~assume~~conclude that the active is not uniformly present in the individual films due to the wide variation of release of active from the same film compositions. For example, with regard to the release of nicotine in the same film compositions, the release reaches in excess of ~~100%. It is reasonable to conclude that a major reason for these release differences is that~~118%. Certainly there is neither disclosure of, nor inherency in, the that the level uniformity of content in the amount of active ~~in each film tested varies by more than the claimed 10%, despite the identical film-forming compositions.~~as sampled in individual dosage units of the same film be 10% or less. "The release profile data presented in Figure 5 show a high degree of variability at each data point. This indicates that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film." Lin Declaration, ¶ 22.

~~Patentee's claims are directed to the formation of a suitable visco-elastic product, prepared through the methods of the invention. As used throughout the application, the formation of a suitable commercial and regulatory compliant product is the desired goal, and a suitable product is one that is substantially uniform in active content to the extent required by said commercial and regulatory concerns. For example, those regulations and directions provided by the FDA for pharmaceuticals and biologic actives. As used throughout the application, the resulting visco-elastic product is defined as a product that has maintained the desired compositional uniformity after being subjected to a~~

~~coating/deposition step and drying. For example, the '080 Patent at col. 8, 11. 64-66 states that the stability is important "in the wet film stage until sufficient drying has occurred to lock in the particles and matrix into a sufficiently solid form such that uniformity is maintained." The '080 Patent at col. 13,11. 53-59 even more clearly states that: "The resulting dried film 1 is a viscoelastic solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film."~~

~~Thus, as~~As defined in the specification for the '~~337~~080 Patent as filed, a visco-elastic solid is one that has been sufficiently dried to lock its active components into a substantially uniform distribution throughout the film. The '~~337~~080 Patent claims require that this be done within about the first 4 minutes or less. The Examiner has previously ~~stated~~acknowledged that Chen does not disclose that the resulting film product has any compositional uniformity of pharmaceutical or biological active at that point in time. See '891 Patent *RFP/C.* ~~The Examiner cannot point to any portion of~~Neither Chen~~, or~~ nor the other references~~, that teaches~~ teach this step.

As explained throughout the '080 Patent and as summarized above, the present invention is based upon the discovery that certain process parameters, such as, viscosity and controlled drying methods to avoid non-uniformity of content in the amount of active must be employed to provide a commercially and FDA viable film product. Chen does not disclose or suggest such a resulting product. *See* Lin Declaration, ¶¶ 17-22. Chen discloses that various components (absent the active) are combined and that the mixture is blended to form a "uniform" solution. (Chen, p. 20, 11. 19-20). ~~While~~although even the formation of a uniform solution in a blender is beneficial, it is not the end of the process by any means~~. Chen's initial blend (without the active) may be mixed to be homogeneous, but there is absolutely no disclosure whatsoever of forming a homogeneous mixture containing an active and casting and drying to maintain such uniformity in the resulting film~~. Further, as explained above, conventional drying methods do not inherently provide uniform films and, in fact, would not be expected to provide resulting films having ~~compositional~~ the claimed uniformity of content in the amount of active. ~~uniformity or uniformity of content of active. See Fuller Declaration,~~

~~ 6-10.

In addition, use ofnon-controlled drying methods such as described in the '080 Patent specification can lead to compositional non-uniformity, as explained above, due to the number of problems associated with conventional drying, see col. 3,11. 13-57 ofthe '080 Patent. In fact, as explained in the '080 Patent, depending upon the drying methods used, various "hot spots" can form due to uneven air flow and temperatures, which destroy the compositional uniformity of the resulting product. See the '080 Patent, col. 13,11.6-16, as well as, Figs. 9-16. Chen's drying methods, such as the use ofuncontrolled hot air circulating ovens, do not inherently provide compositionally uniform films. In fact, the Patentee has demonstrated quite the contrary occurs.

See also, Fuller Declaration, ~~ 6-10.

Patentee's claimed process isprocesses are not present in Chen, either literallyexpressly or inherently, and it Chen cannot anticipate the claims as pending. Moreover, one of ordinaryof ordinary skill in the art, considering the teachings of the cited Chen reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Chen does not render obvious the pending claims ofthis rejection.

D. Claims 2, 3,16,32,55,72-81,95,111,134,151-160,177,193,216 and 233-242 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

The Office Action rejected the above claims under 35 U.S.C. § 103(a), as being unpatentable over the combined teaching of Chen and Staab, U.S. 5,393,528 ("Staab").

Patentee incorporates its previous discussions in sections A., B. and C., above, and DE., below and traverses all said rejections thereon. As all the above claims depend from one of the independent claims, claims 1,82 and 161, they are allowable for all the reasons provided in the sections dealing with Chen, above, and Staab, below and even combined Chen and Staab do not render obvious the pending claims ofthis rejection.

E. Claims 1-5, 10, 12-16,21,24,25,32,44-46,54,55,59,63-70,72-75,78-84, 89, 91-~~95,100,103,104,111,123-125,133,134,138~~95, 100, 103, 104,111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171,173-177,182,185,186,193,205-207,215,216, 220, 224-231, 233-236, 239242,249-252,254,255,257-260,267-270,272,273,275-278,285-288,290,291 and 293-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Staab. Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170,237 and 238 were rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102 (b) by Staab, or, under 35 U.S.C. § 1 03(a), as obvious or unpatentable over Staab. Patentee incorporates its previous discussions in sections A., B., C. and D., above, Patentee respectfully traverses the rejection on the basis, among others, that Staab does not disclose ~~the~~as claimed~~: particular drying methods; resulting visco-elastic product~~ in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution ~~ofcomponents; casting a flowable polymer matrix_having a viscosity from about 400 to about 100,000 cps~~of components; or locking-in or substantially preventing migration of the pharmaceutical and/or bioactive active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution ~~ofpharmaceutical active~~of active, such that uniformity of content of the resulting film ~~vary~~varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Staab certainly does not disclose, explicitly or inherently, the additional claim elements of Claim 317. Claim 317 generally adds to the above, *inter alia,* conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60°C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said viscoelastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5°C to 30°C between polymer matrix inside temperature and outside exposure temperature.

~~Staab teaches the benefits ofusing a "gas foamed film" or films. Staab, col. 5, 11.33-35; col. 8,11.33. Staab also teaches away from the '337 Patent by teaching that air bubbles are necessary, which are contraindicated in Patentee's invention requiring the uniform distribution of active. Staab instead teaches that gas bubbles must be added to the polymer/drug mixture prior to casting. .~~

> ~~"It should be noted that heretofore, the significance ofthe addition ofgases in the formation ofthe film to alter the texture and solubility ofthe film has not been recognized. "~~
>
> ~~Staab, col. 3, 11. 15-20.~~

~~"The fine tuning of dissolution rates and delivery of agent material, by the addition of gases and by altering the grades or mixtures of polymer materials or layers, is an important aspect of the present invention.~~

~~"On addition ofthe gas, preferably nitrogen, a web is formed ofthe final formulation and the gas. The resultant structure can be described as a foam with various sized air bubbles trapped in the matrix. There is a dual benefit that has~~

~~been surprisingly observed in this connection, namely that not only can the size of the bubbles in the foam alter the dissolution rates and correct what is a serious flaw in standard polymer films, it also offers to the user a perceptible softness to the film which enables the delivery of many types of drugs to tender mucosal tissues. It has been observed that the formation of this web ofthe polymer/drug formulation and the gas must be made just prior to casting on the glass or steel plates. This offers precise control over the microbubbles and resultant control over the dissolution,~~

~~"Without this web formation, the quick release of drug was heretofore not possible.•This frothy foam mixture or web can also be added to a mold to provide a formed device such as a barrier delivery system which completely dissolves upon use in a body cavity, e.g. the vagina.~~

> ~~"The gases, for example, air or nitrogen are introduced near the point of application of the liquid polymer material to the stainless steel casting sheet. The gases are added in a closed system by mixing with whipping blades or a motor driven homogenizer to homogenize the mixture of polymer, active material and gas to form a frothy foam. The final mixture then sets up or gels as a foam. It is also possible to pour the frothy foam mixture into a mold. The mold is then deformed and the formed device such as a diaphragm, is removed." Staab, col. 8, 11. 29-64 (emphasis supplied). In direct conflict with Staab's teaching, the '080 Patent teaches the use ofanti-foamingagents to prevent gas bubble formation. "Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which rovide a substantially non-self-aggregating uniform heterogeneity throughout the area ofthe films .... Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product."~~
>
> ~~'080 Patent, col. 4, 11.5-21 (emphasis supplied).~~

~~"A number of techniques may be employed in the mixing stage~~

~~to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed ofthe mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film."~~

~~'080 Patent, col. 9,11.56-65 (emphasis supplied).~~

~~See also section of '080 Patent entitled "Anti-foaming and De-foaming Compositions" ('080 Patent, col. 22, 1. 47 through col. 23, 1. 53).~~

~~Staab addresses the fine tuning ofdissolution rates and delivery of active agent, by teaching the addition of gases as an important aspect ofhis invention (Staab, col. 8,11.30-34).~~

~~Staab is silent with respect to the claimed uniformity ofcontent, the essence of the '080 Patent. The '080 Patent in connection with achieving said unifonnity of content teaches the removal of such gases and bubbles ('080 Patent, col. 9, 11. 56-65). Moreover, Staab uses conventional drying (Staab, col. 11, 11. 64-65) rather than the particular drying methods used to ensure the unifonnity of content claimed by the '080 Patent.~~

~~Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that contains the recited level of active unifonnity. Similar to the discussion of Chen above, Staab teaches general drying methods that would be expected to subject the material to similar air forces as in Chen's air drying oven, but does not teach the fonnation of and maintenance of a film having a substantially unifonn active content. Again, as explained above, Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that includes the claimed content unifonnity. Similar to the discussion of Chen above, Staab teaches general drying methods that are likely to subject~~

~~the material to similar air forces as in a conventional air drying oven, but does not teach the fonnation ofand maintenance ofa film having a substantially unifonn active content.~~

~~The presently claimed process is not present in Staab, either literally or inherently, and it cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings ofthe cited reference as a whole, would not predictably or rationally arrive at the limitations ofthe present claims. For these reasons, Staab does not render obvious the pending claims ofthis rejection. Patentee respectfully traverses the rejection on the basis, among others, that Staab does not disclose the claimed: particular drying methods; resulting visco-elastic product; substantially unifonn distribution ofcomponents; casting a flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; or locking-in or substantially preventing migration ofthe active; or said unifonn distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidily increasing the viscosity ofthe polymer matrix upon initiation ofdrying within about 4 minutes to maintain said unifonn distribution ofpharmaceutical active, such that unifonnity of Patent No.: US 7,897,080 content of the resulting film's variation in amount ofthe active present in substantially equally sized individual dosage units sampled from different locations ofthe resulting film is in compliance with regulations governing same.~~

Moreover, Staab teaches the benefits ofusing a "gas foamed film" or films. Staab, col. 5, 11.33-35; col. 8, 11. 33. Staab ~~also~~thus teaches away from the '~~337~~080 Patent by teaching that air bubbles are necessary, which are contraindicated ~~for the patented~~ in Patentee's invention requiring a substantially uniform ~~compositional~~ distribution of active. Staab instead teaches that gas bubbles must be added to the polymer/drug mixture prior to casting~~.~~

> "It should be noted that heretofore, the significance ofthe addition of gases in the formation of the ~~mm~~film to alter the texture and solubility ofthe film has not been recognized. "

Staab, col. 3, 11. 15-20.

"The fine tuning of dissolution rates and delivery of agent material, by the addition of gases and by altering the grades or mixtures of polymer materials or layers, is an important aspect of the present invention.

* * * *

~~"On addition ofthe gas, preferably nitrogen, a web is formed ofthe final formulation and the gas. The resultant structure can be described as a foam with various sized air bubbles trapped in the matrix. There is a dual benefit that has been surprisingly observed in this connection, namely that not only can the size of the bubbles in the foam alter the dissolution rates and correct what is a serious flaw in standard polymer films, it also offers to the user a perceptible softness to the film which enables the delivery ofmany types ofdrugs to tender mucosal tissues. It has been observed that the formation ofthis web ofthe polymer/drug formulation and the gas must be made just prior to casting on the glass or steel plates. This offers precise control over the microbubbles and resultant control over the dissolution, "Without this web formation, the quick release ofdrug was heretofore not possible.•This frothy foam mixture or web can also be added to a mold to provide a formed device such as a barrier delivery system which completely dissolves upon use in a body cavity, e.g. the vagina.~~

"The gases, for example, air or nitrogen are introduced near the point of application of the liquid polymer material to the stainless steel casting sheet. The gases are added in a closed system by mixing with whipping blades or a motor driven homogenizer to homogenize the mixture of polymer, active material and gas to form a frothy foam. The final mixture then sets up or gels as a foam. It is also possible to pour the frothy foam mixture into a mold. The mold is then deformed and the formed device such as a diaphragm, is removed." Staab, col. 8, 11. 29-64 (emphasis supplied).

In direct conflict with Staab's teaching, the '~~337~~080 Patent teaches the use ofanti-foaming

agents to prevent gas bubble formation~~.~~ and thereby promote uniformity. Importantly, Patentee's processes, in many cases, avoid the formation of bubbles, without the need to use anti-foaming agents.

"~~Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films ....~~

> Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product."

'~~337~~080 Patent, col. 4, 11. 5-21 (emphasis supplied).

> "A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed.~~ Additionally, the speed ofthe mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film."~~."

'~~337~~080 Patent, col. 9, 11.56-65 (emphasis supplied).

See also section of '~~337~~080 Patent entitled "Anti-foaming and De-foaming Compositions" ('~~337~~ 080 Patent, col. 22, 1. 47 through col. 23, 1. 53).

Staab addresses the fine tuning of dissolution rates and delivery of active agent ~~material~~, by teaching the addition of gases as an important aspect of his invention (Staab, col. 8,11.30-34). Staab is silent with respect to the ~~claimed uniformity~~recited levels of uniformity of content~~, the essence of the '337 Patent~~. The '~~337~~080 Patent in connection with achieving ~~said~~ uniformity of content in the amount of active teaches avoiding bubble

formation and the removal of such gases and bubbles ('~~337~~080 Patent, col. 9, 11. 56-65). Moreover, Staab uses conventional drying (Staab, col. 11,11.64-65) rather than the particular drying methods used to ensure the uniformity of content claimed by the '~~337~~080 Patent.

~~Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that contains the recited level ofactive uniformity. Similar to the discussion of Chen above, Staab teaches general drying methods that would be expected to subject the material to similar air forces as in Chen's air drying oven, but does not teach the formation of and maintenance ofa film having a substantially uniform active content. Again, as explained above, Staab provides absolutely no teaching or suggestion as to how to arrive at a final product that includes the claimed content uniformity. Similar to the discussion of Chen above, Staab teaches general drying methods that are likely to subject the material to similar air forces as in a conventional air drying oven, but does not teach the formation of and maintenance of a film having a substantially uniform active content.~~

The presently claimed process is not ~~present~~disclosed in Staab, either ~~literally~~expressly or inherently, and ~~it cannot~~Staab does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Staab does not render obvious the pending claims ~~of this rejection~~of the above rejections.

F. Claims 82, 89-~~91, 161, 171~~91,161,171-173,272-274 and 290-292 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Le Person.

Claims 92 and 174 were rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Le Person, Chemical Engineering and Processing, Vol. 37, pp. 257-263 (1998) ("Le Person") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Le Person. Patentee incorporates its previous discussions in sections A., B., C., D. and E., above,

Patentee respectfully traverses the rejection on the basis, among others, that Le Person does not disclose ~~the~~as claimed~~: particular drying methods to provide a substantially uniform distribution ofcomponents; resulting visco-elastic product~~ in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution ~~of components; casting a flowable polymer matrix_having a viscosity from about 400 to about 100,000 cps~~of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of ~~pharmaceutical~~ active, such that uniformity of content of the resulting ~~films vary~~film varies by no more than 10% in ~~the~~ amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of ~~the~~ resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same. ~~Le Person discloses that~~

Le Person certainly does not disclose, either explicitly or inherently, the additional claim elements found in Claim 317. Claim 317 generally adds to the above, *inter alia,* conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60°C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized

individual dosage units, sampled from different locations of said viscoelastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30°C between polymer matrix inside temperature and outside exposure temperature.

Le Person does disclose that the drying step used plays a role in the final product, but fails to disclose or suggest how to achieve a uniform final product. In fact, Le Person discloses methods that result in a non-uniform product prior to and at 10 minutes. According to Le Person, the resulting product dried in 9 minutes would not have claimed uniformity of content of active.

Le Person's goal was to determine "cases of maldistribution of the active substance," in connection with different drying methods, said mal distribution having consequences on storage and delivery of a drug and proposes the use of Laser Scanning Confocal Microscopy on the active substance and the heavy solvent to determine same. (Le Person, Abstract). Le Person acknowledges that in the formation of a film product, "drying is the essential unit operation necessary to form the final product." (Le Person, p. 257). ~~In Le Person's experiment, a coating mixture includes a polymer, three light solvents, a heavy solvent, and a pharmaceutical active substance. Le Person stated that the drying process used must evacuate the light solvent and preserve the heavy solvent.~~ Le Person's experimental set-up was composed of two parts, "the drying cell and the wind tunnel. . . . [wherein] the wind tunnel is a conventional drying rig ...." Le Person, p. 258, col. 2 & Fig. 1. Le Person's disclosure of the use of a wind tunnel further negates any argument that Le Place inherently anticipates or makes obvious Patentee's invention.

~~Le Person conducted experiments on drying conditions. At the 5 minute mark, Le Person noted that intense moisture removal through the exposed surface ofthe layer to radiation during the first three minutes of drying produced a stress on the polymer and caused "displacement of the active phase towards the bottom ofthe layer." (Le Person, p. 261). Le Person noted that, initially, the constituents of the active phase are apparantly homogeneously distributed, but during a drying process, the active substance separated and sunk to the bottom. (Le Person, p. 262). Le Person noted that, between 5 and 10~~

~~minutes ofdrying, the heavy solvent migrates towards the top surface and the active substance stays in the bottom layer. (Le Person, p. 262). After 15 minutes, Le Person notes that the active substance crystallizes, due to the lack of solvent contained therein. (Le Person, p. 263). Eventually, the active substance homogenizes, and only after 15 minutes a quasi equilibrium is obtained for the active phase, taking into account the evaporation ofheavy solvent. (Le Person, p. 263). Thus, Le Person acknowledged that the drying step ofa film formation is critical, and noted the non-homogeneity ofthe film product it produced during drying.~~

It is important to note that Le Person simply recognized the overall, general difficulty in obtaining films with a substantially uniform distribution of active. ~~However~~Le Person did not try to solve this problem, only to determine means to identify it. Thus, Le Person did not recognize the specific reasons therefor, nor did Le Person recognize the solutions needed to overcome this difficulty. Le Person's goal was to find ways to best determine whether or not there was homogeneity of film product. ~~Le Person uses water with a heavy solvent (see abstract and Table 1), and does not complete its drying, and in particular removal of the heavy solvent, until after 15 minutes (see Le Person, pp. 261-263). After 10 minutes, Le Person's heavy solvent has migrated to the exposed surface; and after 15 minutes, a quasi-equilibrium is obtained for the components of the active phase, taking into account the evaporation ofthe heavy solvent (see Le Person, p. 263).~~

However, the point of Le Person is that, in the time period (i.e., less than 10 minutes), there is non-uniformity of the product. Le Person even states that "intense moisture removal through the exposed surface of the layer to the radiation, during the first 3 min of drying (Le Person, Fig. 7) produces a stress on the polymer skeleton ... and as a result the acrylic polymer becomes more and more dense in the upper part of the layer (exposed surface)." (Le Person, p. 261). As a result, this "intense" shrinkage results in displacement of the active phase. As such, Le Person's disclosure ~~,~~is not directed towards achievement of a film having a substantially uniform ~~film~~distribution of an

active through drying, and in fact, if anything, teaches away from achieving ~~such content~~ uniformity of content in the amount of an active.

The presently claimed ~~process is~~processes are not present in Le Person, either ~~literally~~expressly or inherently, and ~~it cannot~~Le Person does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Le Person does not render obvious the pending claims ~~of this rejection~~.

G. Claims 1,5,7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166,168-171,173-175,184,224,225,249,254,267,272,285 and 290 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hortsmann.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Horstman, et al. U.S. 5,629,003 ("Horstmann") or, in the alternative under 35 U.S.C.

§ 103(a), as obvious over Horstmann. Patentee incorporates its previous discussions in sections A., B., C., D., E. and F., above, Patentee respectfully traverses the rejection on the basis, among others, that Horstmann does not disclose ~~the~~as claimed~~: particular drying methods to provide a substantially uniform distribution of components; resulting visco-elastic product~~in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components~~; casting a flowable polymer matrix having a viscosity from about 400 to about 100,000 cps~~; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of ~~pharmaceutical~~ active, such that uniformity of

content of the resulting ~~films vary~~film varies by no more than 10% in ~~the~~ amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, by no more than 10% from the desired amount across different resulting films, and is in compliance with FDA regulations governing same.

Horstmann certainly does not disclose, either explicitly or inherently, the additional claim elements of Claim 317. Claim 317 generally adds to the above, *inter alia,* conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60°C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said viscoelastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30°C between polymer matrix inside temperature and outside exposure temperature.

Moreover, the '080 Patent's description of the differences between Horstmann and Patentee's invention claimed in the '080 Patent is relevant to the Examiner's current rejections as well. For example:

> "In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann ... incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers."

'080 Patent, col. 2, 1. 63 to col. 3,1. 9.

Horstmann's use of conventional drying methods and need for gel formers teaches away from obtaining a resulting film with the desired ~~uniformity~~levels of uniformity of content ~~ofactive ofno more than 10% variation~~in the amount of active. Horstmann does not disclose the degree of uniformity of content, merely, for example, in Example 2, referring to film sections containing "approximately" 3 mg of active and a weight of "approximately" 80 mg. Horstmann, col. 5, 11. 15-36. Horstmann does not disclose that these amounts are based on any testing, or for that matter what they are based upon, or that they comply with FDA requirements relating to drug products.

The presently claimed process is not present in Horstmann, either ~~literally~~expressly or inherently, and ~~it~~Horstmann cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Horstmann does not render obvious the pending claims~~ of this rejection~~.

IX. Conclusion

No reference, either alone or in combination with other references, teaches the processes claimed by the '080 Patent. Entry of the amendments herein is respectfully requested. Patentee traverses all rejections of its claims. For at least the reasons set forth above, independent claims 1, 82, 161, and ~~321~~315-~~324~~318 are allowable. Claims 2 -81,83 -160, 162 -~~320, and 325-628~~314 are allowable at least based on their dependencies, whether direct or indirect, from independent Claims 1, 82, ~~161,321 and 322~~161 . Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections to same~~. Fees for addition of 4 new independent claims and 324 new dependent claims are due with this submission, and the Commissioner is authorized to charge this fee to Deposit Account No. 08-2461. Should any additional fees be due, the Commissioner is authorized to charge any additional fees, such as fees for extensions of time or additional claims, to Deposit Account No. 08-2461~~. Should the Examiner have any questions regarding this response, the undersigned would be pleased to address them.

Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Danielle L. Herritt
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
PETITION IN REEXAM PROCEEDING	1824	1	1940	1940
Petition fee- 37 CFR 1.17(f) (Group I)	1462	1	400	400
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2340**

Electronic Acknowledgement Receipt

EFS ID:	15337222
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Danielle L. Herritt
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	22-MAR-2013
Filing Date:	10-SEP-2012
Time Stamp:	22:44:33
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2340
RAM confirmation Number	6177
Deposit Account	504876
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		117744_0023_Petition_to_Expedite.PDF	12606 4ab6e559f42569b5a68aa49ea6bf40c43b78549b	yes	3

Multipart Description/PDF files in .zip description

Document Description	Start	End
Receipt of Petition in a Reexam	1	2
Reexam Certificate of Service	3	3

Warnings:

Information:

2		117744_00023_Petition_to_Deny_Entry_of_Supp_Resp.PDF	35522 1edc91f633aa74c00eb9edd1dfbd45a8f88ff4f5	yes	8

Multipart Description/PDF files in .zip description

Document Description	Start	End
Receipt of Petition in a Reexam	1	7
Reexam Certificate of Service	8	8

Warnings:

Information:

3	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Exhibit_A.PDF	12648302 8d8dea68dbe9138f1f7495717e4341166119e11c	no	205

Warnings:

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4	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Exhibit_B.PDF	6235292 b01d153dde8db3d40aaace72394663b6d681a580	no	117

Warnings:

Information:

5	Reexam - Affidavit/Decl/Exhibit Filed by 3rd Party	Exhibit_C.PDF	663537 0ab69cceab75f118a5a6617717a6f74019d0ec64	no	146

Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	31786 7b9c4d0d113a565d33ce49a60dd4345454df316e	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	19627045	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

Mail Stop Inter Partes Reexam
Central Reexamination Unit
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P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on March 13, 2013
Signed: Michael I. Chakansky /Michael I Chakansky/

REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111

Madame:

In compliance with the Notice Re Defective Paper in *Inter Partes* Reexamination, mail date February 26, 2013, Patent owner MonoSol Rx, LLC ("Patentee" and/or "MonoSol") hereby presents its re-drafted response to the Office Action in the above-identified *Inter Partes* Reexamination, dated November 29, 2012 ("Office Action"), a reply to which is due March 13, 2013. Please amend U.S. Patent No. 7,897,080 ("the '080 Patent") in reexamination as set forth hereinbelow. The present amendments are being made in accordance with 37 C.F.R. §1.530(d)–(j). Patentee has previously paid fees for the addition of 4 new independent claims and 324 new dependent in connection with this reexamination. Accordingly, no claim fees are believed to be due with this submission. If, however, there are any fees due in connection with this submission, authorization to charge such fees, including any claim fees, and authorization to credit any overpayments, to Deposit Account No. 08-2461 are hereby provided.

Amendment to the Claims begins on page 2 of this paper.

Remarks begin on page 42 of this paper.

Amendment to the Claims

1. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a masterbatch pre-mix comprising a solvent and a polymer selected from the group consisting of water-soluble polymers, water-swellable polymers and combinations thereof;

(b) adding [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, to a pre-determined amount of said masterbatch pre-mix to form a flowable polymer matrix, said matrix having a substantially uniform distribution of said active;

(c) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(d) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less; [and]

(e) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; and

(f) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

2. (Original) The process of claim 1, wherein said pre-determined amount of master batch pre-mix is controllably fed via a first metering pump and a control valve to a first mixer and a second mixer.

3. (Original) The process of claim 2, wherein said first mixer and said second mixer are arranged in parallel, series or a combination thereof.

4. (Original) The process of claim 1, wherein said water-soluble polymer comprises polyethylene oxide.

5. (Original) The process of claim 1, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

6. (Original) The process of claim 5, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl

cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

7. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

8. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

9. (Original) The process of claim 5, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(d-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

10. (Original) The process of claim 1, wherein said solvent is selected from the group

consisting of water, polar organic solvent, and combinations thereof.

11. (Original) The process of claim 10, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

12. (Cancelled)

13. (Amended) The process of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-

spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

14. (Amended) The process of claim 1, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

15. (Original) The process of claim 1, wherein said active is a bioactive active.

16. (Cancelled)

17. (Original) The process of claim 1, wherein said active is an opiate or opiate-derivative.

18. (Original) The process of claim 1, wherein said active is an anti-emetic.

19. (Original) The process of claim 1, wherein said active is an amino acid preparation.

20. (Original) The process of claim 1, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

21. (Original) The process of claim 1, wherein said active is a protein.

22. (Original) The process of claim 1, wherein said active is insulin.

23. (Original) The process of claim 1, wherein said active is an anti-diabetic.

24. (Original) The process of claim 1, wherein said active is an antihistamine.

25. (Original) The process of claim 1, wherein said active is an anti-tussive.

26. (Original) The process of claim 1, wherein said active is a non-steroidal anti-inflammatory.

27. (Original) The process of claim 1, wherein said active is an anti-asthmatics.

28. (Amended) The process of claim 1, wherein said active is an anti-diarrhea preparation.

29. (Original) The process of claim 1, wherein said active is an alkaloid.

30. (Original) The process of claim 1, wherein said active is an anti-psychotic.

31. (Original) The process of claim 1, wherein said active is an anti-spasmodic.

32. (Original) The process of claim 1, wherein said active is a biological response modifier.

33. (Original) The process of claim 1, wherein said active is an anti-obesity drug.

34. (Original) The process of claim 1, wherein said active is an H_2-antagonist.

35. (Original) The process of claim 34, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

36. (Original) The process of claim 1, wherein said active is a smoking cessation aid.

37. (Original) The process of claim 1, wherein said active is an anti-parkinsonian agent.

38. (Original) The process of claim 1, wherein said active is an anti-depressant.

39. (Original) The process of claim 1, wherein said active is an anti-migraine.

40. (Original) The process of claim 1, wherein said active is an anti-Alzheimer's agents.

41. (Original) The process of claim 1, wherein said active is a dopamine receptor agonist.

42. (Original) The process of claim 1, wherein said active is a cerebral dilator.

43. (Original) The process of claim 1, wherein said active is a psychotherapeutic agent.

44. (Original) The process of claim 1, wherein said active is an antibiotic.

45. (Original) The process of claim 1, wherein said active is an anesthetic.

46. (Original) The process of claim 1, wherein said active is a contraceptive.

47. (Original) The process of claim 1, wherein said active is an anti-thrombotic drug.

48. (Original) The process of claim 1, wherein said active is diphenhydramine.

49. (Original) The process of claim 1, wherein said active is nabilone.

50. (Original) The process of claim 1, wherein said active is albuterol sulfate.

51. (Original) The process of claim 1, wherein said active is an anti-tumor drug.

52. (Original) The process of claim 1, wherein said active is a glycoprotein.

53. (Original) The process of claim 1, wherein said active is an analgesic.

54. (Original) The process of claim 1, wherein said active is a hormone.

55. (Original) The process of claim 1, wherein said active is a decongestant.

56. (Original) The process of claim 1, wherein said active is a loratadine.

57. (Original) The process of claim 1, wherein said active is dextromethorphan.

58. (Original) The process of claim 1, wherein said active is chlorpheniramine maleate.

59. (Original) The process of claim 1, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

60. (Original) The process of claim 1, wherein said active is an appetite stimulant.

61. (Original) The process of claim 1, wherein said active is a gastrointestinal agent.

62. (Original) The process of claim 1, wherein said active is a hypnotic.

63. (Original) The process of claim 1, wherein said active is taste-masked.

64. (Original) The process of claim 1, wherein said active is taste-masked using a flavor.

65. (Original) The process of claim 1, wherein said active is coated with a controlled release composition.

66. (Original) The process of claim 65, wherein said controlled release composition provides an immediate release.

67. (Original) The process of claim 65, wherein said controlled release composition provides a delayed release.

68. (Original) The process of claim 65, wherein said controlled release composition provides a sustained release.

69. (Original) The process of claim 65, wherein said controlled release composition provides a sequential release.

70. (Original) The process of claim 1, wherein said active is a particulate.

71. (Original) The process of claim 1, further comprising adding a degassing agent to said masterbatch premix.

72. (Original) The process of claim 1, further comprising a step of providing a second film layer.

73. (Original) The process of claim 72, wherein said second film layer is coated onto said resulting film.

74. (Original) The process of claim 72, wherein said second film layer is spread onto said resulting film.

75. (Original) The process of claim 72, wherein said second film layer is cast onto said resulting film.

76. (Original) The process of claim 72, wherein said second film layer is extruded onto said resulting film. .

77. (Original) The process of claim 72, wherein said second film layer is sprayed onto said resulting film.

78. (Original) The process of claim 72, wherein said second film is laminated onto said resulting film.

79. (Original) The process of claim 72, further comprising laminating said resulting film to another film.

80. (Original) The process of claim 72, wherein said second film layer comprises an active.

81. (Amended) The process of claim [72]80, wherein said active in said second film is different than said active in said resulting film.

82. (Amended) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said [making a]films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a polymer selected from the group consisting of a water-soluble polymer, a water swellable polymer and combinations thereof, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives[, drugs, medicaments] and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%; [and]

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained;

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

83. (Original) The process of claim 82, wherein said water-soluble polymer comprises polyethylene oxide.

84. (Original) The process of claim 82, wherein said polymer comprises a polymer selected

from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

85. (Original) The process of claim 84, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

86. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

87. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

88. (Original) The process of claim 84, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol

copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

89. (Original) The process of claim 82, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

90. (Original) The process of claim 89, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

91. (Cancelled)

92. (Amended) The process of claim 82, wherein the active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management

agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

93. (Amended) The process of claim 82, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,]vitamins and combinations thereof.

94. (Original) The process of claim 82, wherein said active is a bioactive active.

95. (Cancelled)

96. (Original) The process of claim 82, wherein said active is an opiate or opiate-derivative.

97. (Original) The process of claim 82, wherein said active is an anti-emetic.

98. (Original) The process of claim 82, wherein said active is an amino acid preparation.

99. (Original) The process of claim 82, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

100. (Original) The process of claim 82, wherein said active is a protein.

101. (Original) The process of claim 82, wherein said active is insulin.

102. (Original) The process of claim 82, wherein said active is an anti-diabetic.

103. (Original) The process of claim 82, wherein said active is an antihistamine.

104. (Original) The process of claim 82, wherein said active is an anti-tussive.

105. (Original) The process of claim 82, wherein said active is a non-steroidal anti-inflammatory.

106. (Original) The process of claim 82, wherein said active is an anti-asthmatics.

107. (Amended) The process of claim 82, wherein said active is an anti-diarrhea preparation.

108. (Original) The process of claim 82, wherein said active is an alkaloid.

109. (Original) The process of claim 82, wherein said active is an anti-psychotic.

110. (Original) The process of claim 82, wherein said active is an anti-spasmodic.

111. (Original) The process of claim 82, wherein said active is a biological response modifier.

112. (Original) The process of claim 82, wherein said active is an anti-obesity drug.

113. (Original) The process of claim 82, wherein said active is an H_2-antagonist.

114. (Amended) The process of claim [82]113, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

115. (Original) The process of claim 82, wherein said active is a smoking cessation aid.

116. (Original) The process of claim 82, wherein said active is an anti-parkinsonian agent.

117. (Original) The process of claim 82, wherein said active is an anti-depressant.

118. (Original) The process of claim 82, wherein said active is an anti-migraine.

119. (Original) The process of claim 82, wherein said active is an anti-Alzheimer's agents.

120. (Original) The process of claim 82, wherein said active is a dopamine receptor agonist.

121. (Original) The process of claim 82, wherein said active is a cerebral dilator.

122. (Original) The process of claim 82, wherein said active is a psychotherapeutic agent.

123. (Original) The process of claim 82, wherein said active is an antibiotic.

124. (Original) The process of claim 82, wherein said active is an anesthetic.

125. (Original) The process of claim 82, wherein said active is a contraceptive.

126. (Original) The process of claim 82, wherein said active is an anti-thrombotic drug.

127. (Original) The process of claim 82, wherein said active is diphenhydramine.

128. (Original) The process of claim 82, wherein said active is nabilone.

129. (Original) The process of claim 82, wherein said active is albuterol sulfate.

130. (Original) The process of claim 82, wherein said active is an anti-tumor drug.

131. (Original) The process of claim 82, wherein said active is a glycoprotein.

132. (Original) The process of claim 82, wherein said active is an analgesic.

133. (Original) The process of claim 82, wherein said active is a hormone.

134. (Original) The process of claim 82, wherein said active is a decongestant.

135. (Original) The process of claim 82, wherein said active is a loratadine.

136. (Original) The process of claim 82, wherein said active is dextromethorphan.

137. (Original) The process of claim 82, wherein said active is chlorpheniramine maleate.

138. (Original) The process of claim 82, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

139. (Original) The process of claim 82, wherein said active is an appetite stimulant.

140. (Original) The process of claim 82, wherein said active is a gastrointestinal agent.

141. (Original) The process of claim 82, wherein said active is a hypnotic.

142. (Original) The process of claim 82, wherein said active is taste-masked.

143. (Original) The process of claim 82, wherein said active is taste-masked using a flavor.

144. (Original) The process of claim 82, wherein said active is coated with a controlled release composition.

145. (Original) The process of claim 144, wherein said controlled release composition provides an immediate release.

146. (Original) The process of claim 144, wherein said controlled release composition provides a delayed release.

147. (Original) The process of claim 144, wherein said controlled release composition provides a sustained release.

148. (Original) The process of claim 144, wherein said controlled release composition provides a sequential release.

149. (Original) The process of claim 82, wherein said active is a particulate.

150. (Original) The process of claim 82, further comprising adding a degassing agent to said flowable polymer matrix.

151. (Original) The process of claim 82, further comprising a step of providing a second film layer.

152. (Original) The process of claim 151, wherein said second film layer is coated onto said resulting film.

153. (Original) The process of claim 151, wherein said second film layer is spread onto said resulting film.

154. (Original) The process of claim 151, wherein said second film layer is cast onto said resulting film.

155. (Original) The process of claim 151, wherein said second film layer is extruded onto said resulting film.

156. (Original) The process of claim 151, wherein said second film layer is sprayed onto said resulting film.

157. (Original) The process of claim 151, wherein said second film layer is laminated onto said resulting film.

158. (Original) The process of claim 151, further comprising laminating said resulting film to another film.

159. (Original) The process of claim 151, wherein said second film comprises an active.

160. (Amended) The process of claim [151]159, wherein said active in said second film is different than said active in said resulting film.

161. (Amended) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said[making a] film capable of being administered to a body surface and having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and [an]said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus and evaporating at least a portion of said solvent from said flowable polymer matrix to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first [10]4 minutes [or fewer]by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less, and wherein uniformity of content of said active in substantially equal sized individual dosage units of said visco-elastic film is such that the amount of the active varies by no more than 10%;

(d) forming [a]said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained; [and]

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units sampled from different locations of said resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration, and

[(e)](f) administering said resulting film to a body surface.

162. (Original) The process of claim 161, wherein said body surface is a mucous membrane.

163. (Original) The process of claim 162, wherein said mucous membrane is oral, anal, vaginal or ophthalmological.

164. (Original) The process of claim 161, wherein said body surface is the surface of a wound.

165. (Original) The process of claim 161, wherein said water-soluble polymer comprises polyethylene oxide.

166. (Original) The process of claim 161, wherein said polymer comprises a polymer selected from the group consisting of cellulose, a cellulose derivative, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, carboxyvinyl copolymers, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof, alone or in combination with polyethylene oxide.

167. (Original) The process of claim 166, wherein said polymer further comprises a water insoluble polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone and combinations thereof.

168. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic

acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof.

169. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

170. (Original) The process of claim 166, wherein said polymer further comprises a polymer selected from the group consisting of ethylcellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyvinylacetatephthalates, phthalated gelatin, crosslinked gelatin, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polycaprolactone, methylmethacrylate copolymer, polyacrylic acid polymer, poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, polydioxanones, polyoxalates, poly(ά-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), sodium alginate, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, starch, gelatin, carageenan, locust bean gum, dextran, gellan gum and combinations thereof.

171. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of water, polar organic solvent, and combinations thereof.

172. (Original) The process of claim 161, wherein said solvent is selected from the group consisting of ethanol, isopropanol, acetone, and combinations thereof.

173. (Cancelled)

174. (Amended) The process of claim 161, wherein said active is selected from the group consisting of ace-inhibitors, anti-anginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, [anti-tumor drugs,]anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, [anti-convulsants,]neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, anti-obesity drugs, erythropoietic drugs, [anti-asthmatics,]cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

175. (Amended) The process of claim 161, wherein said active is selected from the group consisting of [cosmetic actives,]antigens, allergens, spores, microorganisms, seeds, [mouthwash components, flavors, fragrances,]enzymes, [preservatives, sweetening agents, colorants, spices,

]vitamins and combinations thereof.

176. (Original) The process of claim 161, wherein said active is a bioactive active.

177. (Cancelled)

178. (Original) The process of claim 161, wherein said active is an opiate or opiate-derivative.

179. (Original) The process of claim 161, wherein said active is an anti-emetic.

180. (Original) The process of claim 161 wherein said active is an amino acid preparation.

181. (Original) The process of claim 161, wherein said active is selected from the group consisting of sildenafils, tadalafils, vardenafils, apomorphines, yohimbine hydrochlorides, alprostadils and combinations thereof.

182. (Original) The process of claim 161, wherein said active is a protein.

183. (Original) The process of claim 161, wherein said active is insulin.

184. (Original) The process of claim 161, wherein said active is an anti-diabetic.

185. (Original) The process of claim 161, wherein said active is an antihistamine.

186. (Original) The process of claim 161, wherein said active is an anti-tussive.

187. (Original) The process of claim 161, wherein said active is a non-steroidal anti-inflammatory.

188. (Original) The process of claim 161, wherein said active is an anti-asthmatics.

189. (Amended) The process of claim 161, wherein said active is an anti-diarrhea preparation.

190. (Original) The process of claim 161, wherein said active is an alkaloid.

191. (Original) The process of claim 161, wherein said active is an anti-psychotic.

192. (Original) The process of claim 161, wherein said active is an anti-spasmodic.

193. (Original) The process of claim 161, wherein said active is a biological response modifier.

194. (Original) The process of claim 161, wherein said active is an anti-obesity drug.

195. (Original) The process of claim 161, wherein said active is an H_2-antagonist.

196. (Original) The process of claim 195, wherein said H_2-antagonist is selected from the group consisting of cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine, aceroxatidine and combinations thereof.

197. (Original) The process of claim 161, wherein said active is a smoking cessation aid.

198. (Original) The process of claim 161, wherein said active is an anti-parkinsonian agent.

199. (Original) The process of claim 161, wherein said active is an anti-depressant.

200. (Original) The process of claim 161, wherein said active is an anti-migraine.

201. (Original) The process of claim 161, wherein said active is an anti-Alzheimer's agents.

202. (Original) The process of claim 161, wherein said active is a dopamine receptor agonist.

203. (Original) The process of claim 161, wherein said active is a cerebral dilator.

204. (Original) The process of claim 161, wherein said active is a psychotherapeutic agent.

205. (Original) The process of claim 161, wherein said active is an antibiotic.

206. (Original) The process of claim 161, wherein said active is an anesthetic.

207. (Original) The process of claim 161, wherein said active is a contraceptive.

208. (Original) The process of claim 161, wherein said active is an anti-thrombotic drug.

209. (Original) The process of claim 161, wherein said active is diphenhydramine.

210. (Original) The process of claim 161, wherein said active is nabilone.

211. (Original) The process of claim 161, wherein said active is albuterol sulfate.

212. (Original) The process of claim 161, wherein said active is an anti-tumor drug.

213. (Original) The process of claim 161, wherein said active is a glycoprotein.

214. (Original) The process of claim 161, wherein said active is an analgesic.

215. (Original) The process of claim 161, wherein said active is a hormone.

216. (Original) The process of claim 161, wherein said active is a decongestant.

217. (Original) The process of claim 161, wherein said active is a loratadine.

218. (Original) The process of claim 161, wherein said active is dextromethorphan.

219. (Original) The process of claim 161, wherein said active is chlorpheniramine maleate.

220. (Original) The process of claim 161, wherein said active is selected from the group consisting of an analgesic, an anti-inflammatory, an antihistamine, a decongestant, a cough suppressant and combinations thereof.

221. (Original) The process of claim 161, wherein said active is an appetite stimulant.

222. (Original) The process of claim 161, wherein said active is a gastrointestinal agent.

223. (Original) The process of claim 161, wherein said active is a hypnotic.

224. (Original) The process of claim 161, wherein said active is taste-masked.

225. (Original) The process of claim 161, wherein said active is taste-masked using a flavor.

226. (Original) The process of claim 161, wherein said active is coated with a controlled release composition.

227. (Original) The process of claim 226, wherein said controlled release composition provides an immediate release.

228. (Original) The process of 226, wherein said controlled release composition provides a delayed release.

229. (Original) The process of claim 226, wherein said controlled release composition

provides a sustained release.

230. (Original) The process of claim 226, wherein said controlled release composition provides a sequential release.

231. (Original) The process of claim 161, wherein said active is a particulate.

232. (Original) The process of claim 161, further comprising adding a degassing agent to said flowable polymer matrix.

233. (Original) The process of claim 161, further comprising a step of providing a second film layer.

234. (Original) The process of claim 233, wherein said second film layer is coated onto said resulting film.

235. (Original) The process of claim 233, wherein said second film layer is spread onto said resulting film.

236. (Original) The process of claim 233, wherein said second film layer is cast onto said resulting film.

237. (Original) The process of claim 233, wherein said second film layer is extruded onto said resulting film.

238. (Original) The process of claim 233, wherein said second film layer is sprayed onto said resulting film.

239. (Original) The process of claim 233, wherein said second film layer is laminated onto said resulting film.

240. (Original) The process of claim 233, further comprising laminating said resulting film to another film.

241. (Original) The process of claim 233, wherein said second film comprises an active.

242. (Amended) The process of claim [233]241, wherein said active in said second film is different than said active in said resulting film.

243. (Original) The process of claim 1, said active is an anti-nauseant.

244. (Amended) The process of claim 1, said active is an erectile dysfunction drug.

245. (Original) The process of claim 1, said active is a vasoconstrictor.

246. (Original) The process of claim 1, said active is a stimulant.

247. (Original) The process of claim 1, said active is a migraine treatment.

248. (Original) The process of claim 1, said active is granisetron hydrochloride.

249. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

250. (Original) The process of claim 1, wherein said resulting film provides administration of said active through gingival application of said individual.

251. (Original) The process of claim 1, wherein said resulting film provides administration of said active through sublingual application of said individual.

252. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

253. (Original) The process of claim 1, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

254. (Cancelled)

255. (Cancelled)

256. (Original) The method of claim 1, wherein said resulting film contains less than about 6% by weight solvent.

257. (Cancelled)

258. (Original) The method of claim 1, wherein said resulting film is orally administrable.

259. (Original) The method of claim 1, wherein said active is in the form of a particle.

260. (Original) The method of claim 1, wherein said matrix comprises a dispersion.

261. (Original) The process of claim 82, said active is an anti-nauseant.

262. (Amended) The process of claim 82, said active is an erectile dysfunction drug.

263. (Original) The process of claim 82, said active is a vasoconstrictor.

264. (Original) The process of claim 82, said active is a stimulant.

265. (Original) The process of claim 82, said active is a migraine treatment.

266. (Original) The process of claim 82, said active is granisetron hydrochloride.

267. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

268. (Original) The process of claim 82, wherein said resulting film provides administration of said active through gingival application of said individual.

269. (Original) The process of claim 82, wherein said resulting film provides administration of said active through sublingual application of said individual.

270. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

271. (Original) The process of claim 82, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

272. (Cancelled)

273. (Cancelled)

274. (Original) The method of claim 82, wherein said resulting film contains less than about 6% by weight solvent.

275. (Cancelled)

276. (Original) The method of claim 82, wherein said resulting film is orally administrable.

277. (Original) The method of claim 82, wherein said active is in the form of a particle.

278. (Original) The method of claim 82, wherein said matrix comprises a dispersion.

279. (Original) The process of claim 161, said active is an anti-nauseant.

280. (Amended) The process of claim 161, said active is an erectile dysfunction drug.

281. (Original) The process of claim 161, said active is a vasoconstrictor.

282. (Original) The process of claim 161, said active is a stimulant.

283. (Original) The process of claim 161, said active is a migraine treatment.

284. (Original) The process of claim 161, said active is granisetron hydrochloride.

285. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through the buccal cavity of said individual.

286. (Original) The process of claim 161, wherein said resulting film provides administration of said active through gingival application of said individual.

287. (Original) The process of claim 161, wherein said resulting film provides administration of said active through sublingual application of said individual.

288. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual through a mucosal membrane of said individual.

289. (Original) The process of claim 161, wherein said resulting film provides administration of said active to an individual by administration within the body of the individual during surgery.

290. (Cancelled)

291. (Cancelled)

292. (Original) The method of claim 161, wherein said resulting film contains less than about 6% by weight solvent.

293. (Cancelled)

294. (Original) The method of claim 161, wherein said resulting film is orally administrable.

295. (Original) The method of claim 161, wherein said active is in the form of a particle.

296. (Original) The method of claim 161, wherein said matrix comprises a dispersion.

297. (Original) The method of claim 1, wherein said matrix comprises an emulsion, a colloid or a suspension.

298. (Original) The method of claim 82, wherein said matrix comprises an emulsion, a colloid or a suspension.

299. (Original) The method of claim 161, wherein said matrix comprises an emulsion, a colloid or a suspension.

300. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

301. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

302. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

303. (New) The process of claim 1, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

304. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

305. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

306. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

307. (New) The process of claim 82, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

308. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 5%.

309. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 2%.

310. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 1%.

311. (New) The process of claim 161, wherein said tests further indicate that the amount of active in said individual dosage units sampled from said resulting film varies by less than 0.5%.

312. (New) The process of claim 1, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

313. (New) The process of claim 82, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

314. (New) The process of claim 161, wherein said evaporating is conducted by applying radiant energy selected from the group consisting of hot air currents, heat, infrared radiation, radio frequency radiation and combinations thereof.

315. (New) A process for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes

by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%;

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and

(f) repeating steps (a) through (e) to form additional resulting films, such that uniformity of content in the amount of said active in said resulting film and said additional resulting films varies no more than 10% from the desired amount of said active as indicated by said analytical chemical tests.

316. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in said substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

317. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus using air currents, which have forces below a yield value of said flowable polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by no more than 10%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling drying by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said

active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

318. (New) A process for manufacturing a resulting film suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said film having a substantially uniform distribution of components comprising a substantially uniform distribution of said active in individual dosage units of said resulting film, comprising the steps of:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and said active, said active selected from the group consisting of bioactive actives, pharmaceutical actives and combinations thereof, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said flowable polymer matrix through a drying apparatus at a temperature of about 60 °C and using air currents, which have forces below a yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said flowable polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-

elastic film, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and wherein during said drying said flowable polymer matrix temperature is 100 °C or less;

(d) forming said resulting film from said visco-elastic film by further controlling by continuing evaporation to a water content of said resulting film of 10% or less and wherein said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said resulting film, varies by less than 5%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film, said tests indicating that uniformity of content in the amount of said active varies by less than 5% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

REMARKS

I. Description of the Patent and the Applicant's Reply

The above-identified U.S. Patent No. 7,897,080 (" '080 Patent") is presently under reexamination. Claims 1-299 were issued in the '080 Patent. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 16, 95 and 177, have been canceled herein as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Claims 12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293 have also been canceled purely for clarity. Claims 300 through 318 are new.

While the Examiner's rejection of all the claims is respectfully traversed in all respects, claims 1, 82 and 161 of the '080 Patent have been amended in an effort to advance the prosecution of the present reexamination. Claims 1, 82 and 161 are hereby amended in accordance with 37 C.F.R. §1.530(d) (2) and (f). In accordance with 35 U.S.C. § 314(a), the amendments to claims 1, 82 and 161, new independent claims 315-318, and new dependent claims 300-314 do not enlarge the scope of the claims of the '080 Patent. Explanation of the support for these claims appears below. Entry of this amendment and reconsideration is respectfully requested.

II. Status of Claims and Support for Claim Changes Pursuant to 37 C.F.R. §1.530(e)

The status of the claims as of the date of this amendment is as follows: Claims 1-299 were issued in the '080 Patent and are subject to reexamination. Claims 1-299, subject to reexamination, were rejected in the Office Action. Claims 300 through 318 are new and are subject to examination. Please cancel claims 16, 95 and 177, as they are identical to claims 32, 111 and 193, respectively. See Office Action, p. 7. Please cancel Claims 12, 91, 173, 254, 255, 257, 272, 273, 275, 290, 291, and 293, for clarity, including some limitations which now appear in the independent claims from which some depend.

In compliance with 37 C.F.R. § 1.530(j), the amendments to claims 1, 82 and 161 do not enlarge their scope or the scope of the original claims or introduce new matter, nor do the

amendments adding new claims 300 through 318 enlarge the scope of the original claims or introduce new matter.

Support for the amendments to claims 1, 82 and 161 and new claims 300 through 318 may be found throughout the '080 Patent, including, the Abstract, Specification, Figures and Claims, for example, at col. 13, ll. 23-36, col. 16, l. 62 through col. 17, l. 3, col. 28, l. 66 through col. 29, l. 6; col. 29, ll. 20-35 and 38; col. 32, ll. 34-41; col. 2, ll. 27-46; col. 15, ll. 28-43, and the Abstract; quoted in detail below; col. 3, ll. 58-60 ("the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval"); col. 19, l. 30 through col. 21, l. 31 (actives including pharmaceutical actives, bioactive actives, and combinations thereof); col. 6, ll. 49-52 ("These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process."); Figures 6, 7, 8, 35 and 36 and col. 14, ll. 20-25 ("drying" and "drying apparatus"); col. 11, ll. 17-19 ("Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition"); col. 11, ll. 21-23 ("yield values . . . force"); col. 12, ll. 20-36, col. 13, ll. 37-38 ("After mechanical mixing, the film may be placed on a conveyor"); col. 29, ll. 11-13 ("As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus"); col. 33, l. 10 through col. 34, l. 24 (example M); col. 44, 11. 9-13 ("the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the 'locking-in' of uniformity of content throughout the film"); col. 4, l. 8; col. 6, ll. 46-52; col. 13, ll. 36-43; col. 26, ll. 9-27; col. 28, ll. 24-58; col. 29, ll. 8-10; col. 20, ll. 65-66 ("Erectile dysfunction . . . drugs"); col. 19, l. 55 ("anti-diarrhea preparations"); col. 6, ll. 52-60 ("Examples of controlled drying processes include . . . hot air impingement across the bottom substrate and bottom heating plates . . . controlled radiation drying . . . such as infrared and radio frequency radiation . . . ."); col. 7, lines 5 through 16 ("This may be achieved by applying heat to the bottom surface of the film . . . or alternatively by the introduction of controlled microwaves to evaporate the water . . . . air currents directed at the bottom of the film should desirably be controlled"); col. 27, ll. 53-55 ("The temperature at which the films are dried is about 100°C. or less"); col. 41, ll. 49-50 ("films were dried in an oven at approximately 60° C."). Support for new claims may also be found throughout the '080 Patent, including, the Figures, Tables and

Claims, for example at col. 19, ll. 10-25, col. 19, l. 30 through col. 22, l. 28, col. 25, ll. 53-60, col. 22, ll. 24-28; col. 28, ll. 1-2; col. 14, ll. 63-65; Tables 17 and 18; Figures 6-8, 33, 34 and 35. Many of the claim elements of the new independent claims can be found in original independent claims 1, 82, and 161 of the '080 patent.

> "Temperatures that approach 100° C. will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of 70° C. for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature.
>
> "Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component."
>
> '080 Patent. col. 12, ll. 20-36.
>
> "For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80° C. for 10 minutes produces a temperature differential of about 5° C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5° C. less than the outside exposure temperature. In many cases, however, drying times of less than 10 minutes are sufficient, such as 4 to 6 minutes. Drying for 4 minutes may be accompanied by a temperature differential of about 30° C., and drying for 6 minutes may be accompanied by a differential of about 25° C. Due to such large temperature differentials, the films may be dried at efficient, high temperatures without causing heat sensitive actives to degrade."
>
> '080 Patent. col. 13, ll. 23-36.
>
> "The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process."

'080 Patent, col. 16, l. 62 through col. 17, l. 3 (emphasis supplied).

"It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and overall appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."

'080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

"The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s). . . . After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples."

'080 Patent, col. 29, ll. 20 through 35 (emphasis supplied).

"An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."

'080 Patent, col. 32, ll. 34-41 (emphasis supplied).

"The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage

units based on films, this virtually mandates that uniformity in the film be present."

'080 Patent, col. 2, ll. 27-46 (emphasis supplied).

"Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. "

'080 Patent, col. 15, ll. 28-43 (emphasis supplied).

III. Declarations Submitted With This Reply

Along with this Reply, the Patentee is submitting the Declarations of Dr. B. Arlie Bogue (Exhibit A) ("Bogue Declaration") and Dr. David T. Lin (Exhibit B) ("Lin Declaration") under 37 C.F.R. §1.132. The Bogue Declaration provides technical results regarding Patentee's commercial pharmaceutical films manufactured in accordance with the '080 Patent and it should not be counted toward the page limit of 37 C.F.R. §1.943. The Lin Declaration provides Dr. Lin's background information, information relating to FDA uniformity of content dosage requirements, and has six (6) numbered paragraphs of statements (¶¶ 17-22) relating to a prior art disclosure at pages 5-6, which might at most be counted as two (2) pages toward the page limit of 37 C.F.R. §1.943.

IV. Background of the '080 Patent

The '080 Patent is a continuation of U.S. application Ser. No. 10/856,176, filed May 28, 2004 now U.S. Pat. No. 7,666,337 (" '337 Patent"), which claims the benefit of U.S. Provisional Application No. 60/473,902, filed May 28, 2003 and is a continuation-in-part of U.S. application Ser. No. 10/768,809, filed Jan. 30, 2004 now U.S. Pat. No. 7,357,891 (" '891 Patent"), which claims benefit to U.S. Provisional Application No. 60/443,741 filed Jan. 30, 2003 and is a continuation-in-part of:

(a) PCT/US02/32575 filed Oct. 11, 2002, which claims priority to: (1) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002 which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (2) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002;

(b) PCT/US02/32594, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and

(c) PCT/US02/32542, filed Oct. 11, 2002, which claims priority to: (1) U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, (2) U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims benefit to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and (3) U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002.

There are pending applications claiming the benefit of the priority of all and/or some of the above.

The '891 Patent is involved in a U.S. litigation wherein Patentee has alleged that the Third Party Requester, BioDelivery Sciences International, Inc. ("BDSI") has infringed its '891 Patent. The litigation is Civil Action No. 10-cv-5695 in the U.S. District Court in the District of New Jersey. In the litigation, Patentee also alleged that the Third Party Requester infringed two other of Patentee's patents, U.S. 7,425,292 (" '292 Patent") and U.S. 7,824,588 (" '588 Patent").

Third Party Requester requested reexamination of the '891 Patent (90/012,098), the '292 Patent (90/012,097) and the '588 Patent (95/001,753) as well. Both the '292 and the '891 Patent successfully exited reexamination. The Examiner on January 23, 2013 issued a Right of Appeal Notice ("RAN") for the '588 Patent reexamination. In response, Patentee filed a Notice of Appeal, a Petition Under 37 C.F.R. § 1.183 Requesting Waiver of the Prohibition of an Extension of Time for Filing an Appeal Brief and for an Extension of Time for Filing an Appeal Brief, and a Petition Under 37 C.F.R. § 1.182 Requesting Continued Reexamination.

Third Party Requester requested reexamination of another of Patentee's related patents namely U.S. Pat. No. 7,666,337 (Control No. 95/002,171), reexamination was ordered, an Office Action issued, Patentee Replied, and Third Party Requester submitted its Comments.

Finally, Third Party Requester requested the reexamination herein of the '080 Patent. .

The '080 Patent has not been and is not currently involved in litigation.

'080 Patent Office Action Statements

In connection with the Order Granting Request for Inter Partes Reexamination of the '080 Patent, Control No. 95/002,170 ("Order Granting IPR Request '080 Patent"), noted above, certain comments were made by the Examiner with respect to Claim 25 of the '337 Patent. The statements were made when the Examiner addressed Third Party Requester's request to find that claim 82 of the '080 Patent should be rejected under 35 U.S.C. § 101 double patenting over claim 25 of the '337 Patent. Patentee supports the Examiner's finding that the Third Party Requester had failed to demonstrate a reasonable likelihood of success of arriving at the subject matter of at least one claim of the '080 Patent. However, Patentee respectfully disagrees with the Examiner's statements interpreting "uniform" and "substantially uniform" therein. In particular, Patentee disagrees that "the active is uniformly distributed (i.e. no variance of active)" in the matrix. Certainly a uniform distribution does not require a state of "no variance". See pages 21 and 22 of the Order Granting IPR Request '080 Patent. "Uniform" and "substantially uniform" are indeed different, but "uniform" from a practical standpoint must of necessity allow for some variance, albeit less than "substantially uniform".

V. The Patented Invention

The present invention is directed to novel and non-obvious processes for manufacturing pharmaceutical and bioactive active containing films, suitable for commercialization and U.S. Food and Drug Administration ("FDA") approval. As noted in the Bogue Declaration, ¶ 4, one manufactured lot of such resulting film can contain 2,000,000 individual dosage units. The claimed processes accomplish this feat while providing the necessary narrow ranges in the amount of active in individual dosage units. As claimed, the '080 Patent, at least, requires a uniformity of content in amount of active (i) in individual dosage units sampled from a resulting film of 10% or less (independent claims 1, 82, 161, and 316-318, see Appendix A, Bogue Declaration), and (ii) in individual dosage units sampled from two or more resulting films of

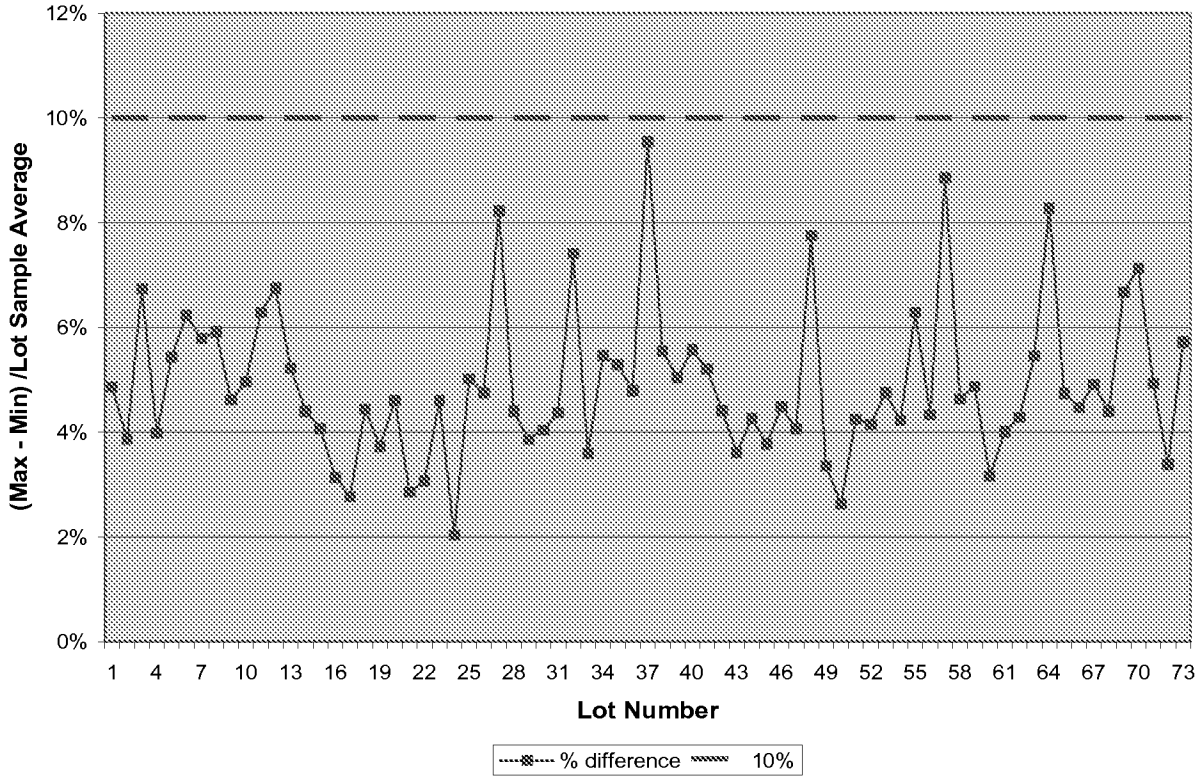
10% or less as a percent difference from a desired amount (independent claim 315, see Appendix B, Bogue Declaration).

One conceptual approach to understanding (i) and (ii) is as follows. A baker has a good recipe or process for making bread. The recipe includes the ingredients and the controlled baking conditions. On Monday the baker bakes a loaf of bread strictly following the recipe. On Friday the baker bakes a loaf of bread again strictly following the recipe. The loaves are cut into individual slices. When tasted, all the slices from Monday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Monday's loaf. In the same fashion, when tasted, all the slices from Friday's loaf taste almost the same, indeed the tastes differs by only 10% between slices from Friday's loaf. However, when a slice from Monday's loaf is compared to a slice from Friday's loaf, the difference in taste is more pronounced than between individual slices from the same loaf. Since the baker follows the same recipe for all his/her bread the baker expects that all slices from all loaves should taste alike or almost alike. However, the difference in taste between slices from Monday and slices from Friday is greater than the difference between slices in the same loaf. Indeed, the taste difference is now about 10% from what the baker believes all his/her bread should be expected to taste like-- that is, 10% from the high quality standard ("desired amount" and/or "target amount") for all the bread baked.

In a similar fashion, the "recipe" of Patentee's claimed processes keep differences between individual dosage units from one manufactured lot very small-- e.g. smaller than 10% in amount of pharmaceutical active. See, independent claims 1, 82, 161 and 316-318. The "recipe" of Patentee's claimed processes also keeps differences between individual dosage units between different manufactured lots small as well, just not necessarily as small-- e.g. smaller than a 10% difference from the standard, i.e. desired amount. See, independent claim 315.

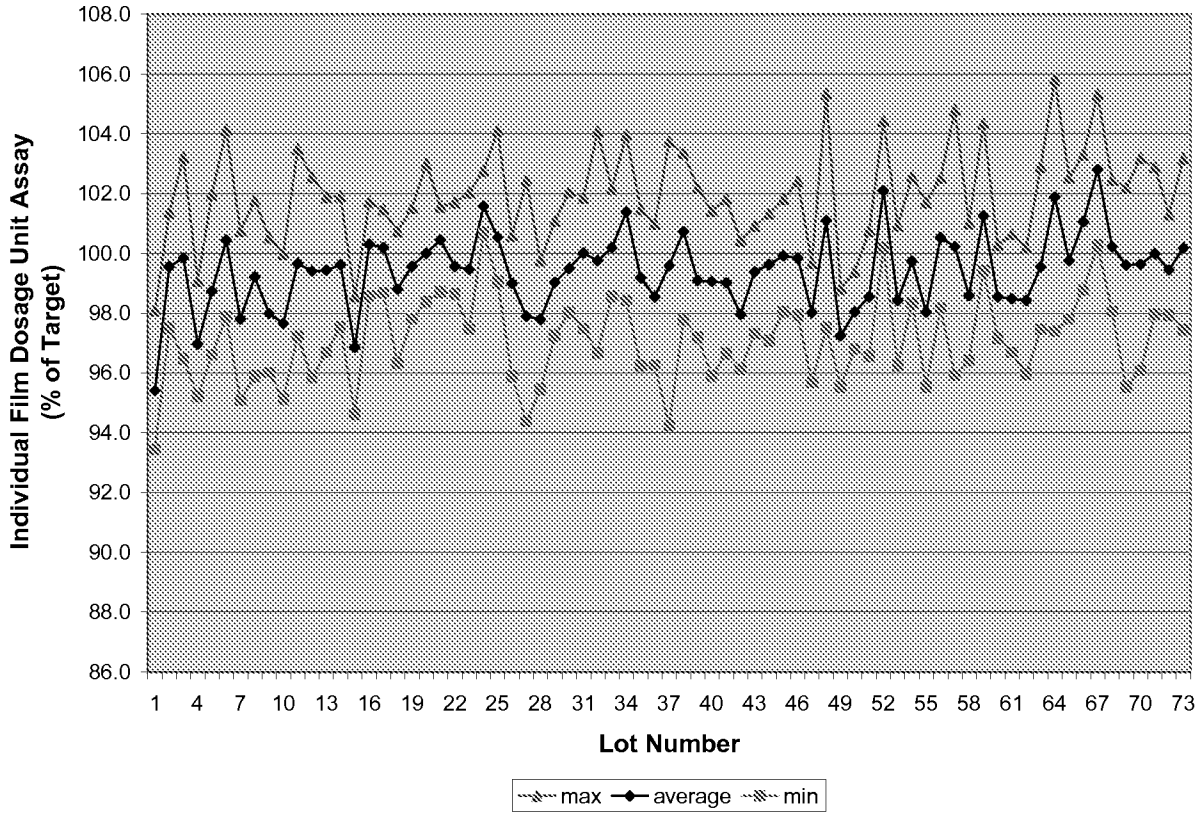
Thus, in the case of a resulting film from one manufacturing lot, the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active in substantially equal sized individual dosage units sampled from the resulting film varies by no more than 10%. See Appendix A from Bogue Declaration copied below and Bogue Declaration, ¶ 9, where this is shown to be true for 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention.

APPENDIX A (Bogue Declaration)



In the case of resulting films from different manufacturing lots the substantially uniform distribution of the active is indicated through analytical chemical tests which indicate that uniformity of content in the amount of the active varies by no more than 10% from a desired amount. See Appendix B from Bogue Declaration copied below and Bogue Declaration, ¶ 10, where this is shown to be true across 73 separately manufactured lots of film, all manufactured by Patentee in accordance with the claimed invention. 100.0% indicating the desired amount.

APPENDIX B (Bogue Declaration)



Hence, the manufacturing process of the '080 Patent as claimed is a commercially viable processes which yields commercial viable products meeting FDA regulations, including active assaying requirements.

This should be compared to the laboratory produced films described in the prior art relied on by the Examiner. In the cited prior art, terms such as uniformity, substantial uniformity, and homogeneity are all accepted without real support. They cannot be relied upon. What is missing is the support for the statements -- that is, having had the amount of active tested by analytical chemical testing, including assaying. *See* Lin Declaration, ¶¶ 17-22 (statements about insufficient disclosure in cited prior art reference). Patentee uses the '080 Patent invention to manufacture commercially acceptable products for which Patentee must establish uniformity of content in the amount of active in its products by such analytical chemical testing as required by regulatory agencies, such as the FDA. Dr. Bogue's Declaration describes such testing on

Patentee's products produced in accordance with the invention and the results which are consistent with the '080 Patent's claims for uniformity of content in the amount of active (i) in individual dosage units sampled from a resulting film of 10% or less, and (ii) in individual dosage units sampled from two or more resulting films of 10% or less as a percent difference from a desired amount. Bogue Declaration, ¶¶ 4-11.

PATENTEE'S CLAIMS

Patentee's instant claims recite additional details about its processes for manufacturing a resulting pharmaceutical film suitable for commercialization and regulatory approval. Some of the details include: forming a flowable polymer matrix comprising a polymer, a solvent and an active, said matrix having a substantially uniform distribution of said active; casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps; controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less; forming said resulting film from said visco-elastic film, wherein said resulting film has a water content of 10% or less and said substantially uniform distribution of said active by said locking-in or substantially preventing migration of said active is maintained, performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting film from one lot, said tests indicating that uniformity of content in the amount of the active varies by no more than 10% and said resulting film is suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration; and, in the case of more than one resulting film lot, repeating the process for forming one film lot such that uniformity of content in the amount of said active across all said resulting film lots varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests.

Additional claim limitations can be found in some of Patentee's narrower independent claims, for example claims 317-318. These claims generally add to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix during drying, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising continuing evaporation to a water content of said resulting film of 10% or less.

As defined in the '080 Patent, a visco-elastic film is one that has been controllably dried to lock its components into a substantially uniform distribution throughout the film while avoiding problems associated with conventional drying methods. By providing a visco-elastic film product having this compositional uniformity or uniformity of content, the user can be assured that the product includes the proper amount of components, such as an active contained therein. Further, the process can be used to make commercially viable large-scale film products, such as large rolls of film from which smaller individual dosage units are cut, the user can feel confident that no matter where the large roll of film is cut, the resulting pieces (e.g., individual unit dosages) will have a substantially uniform composition. As noted above, Patentee successfully manufactures pharmaceutical films containing 2,000,000 individual dosage units meeting FDA requirements using the claimed processes. Bogie Declaration, ¶ 4. As claimed, the uniformity of content as a percent difference will be no more than 10% and in some cases less. The need for providing a process for obtaining the desired uniformity of content of the desired amount of active in the resulting products is critically important, particularly for regulated products, such as the claimed pharmaceuticals.

Prior to the present invention, it was known to prepare films. However, in many cases the end product was merely assumed to be homogeneous, either because the initial components were blended together or because after the blending step the physically observable properties of the resulting film product, for example, its appearance or weight, were satisfactory. However,

these physical properties do not indicate or establish that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units varies by no more than 10% for a particular film. By contrast, for example, in one instance, "the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix." '080 Patent, col. 18, ll. 37-40.

Nor do physical properties indicate or establish that that the uniformity of content of the components is such that, for example, the amount of the active in individual dosage units from one film to another film varies by no more than 10% from a desired amount. This range of uniformity is disclosed in connection with, for example, the uniformity of content disclosed in the '080 Patent when referencing the FDA and other regulatory requirements. "Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present." '080 Patent, col 2, ll. 43-45. In these cases, the FDA and/or other regulatory agency sets the amount of active that must be present in an individual dosage unit (or dosage form), *i.e.,* the desired amount, and provides for the necessary uniformity of content, in this case the active may vary by 10% from the desired amount. A "desired amount" is an essential concept, as the FDA indicates the required dosage for each drug, and each drug has its own specified dosage amount. Essential to any pharmaceutical and related product is a viable means of actually testing for the amount of the active present in individual dosage unit samples, and that is to use analytical chemical testing and actually test for the presence of the desired amount of active and thereby determine whether the prescribed uniformity of content of active is present. *See* Lin Declaration, ¶¶ 9-16.

Importantly, the process of forming a proper film product with the claimed levels of uniformity of content in, for example, the amount of active does not end at the mixing stage. Patentee has discovered that the various steps post-mixing play a very important role in ensuring that the resulting product complies with the stringent requirements for uniformity of content. For example, one key step in the formation of a film product is the drying step, particularly when heat and/or radiation is used to dry the film. Patentee has discovered that controlled drying methods is essential in meeting these claimed requirements. Controlled drying includes methods that avoid, for example, the formation of bubbles, or uncontrolled air currents that may cause

movement of particles within the visco-elastic film forming matrix. Controlled drying, as required by the invention as claimed, may be effectuated through evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less.

It is important to understand that compositional uniformity or uniformity of content is not the same as having a surface that appears free of defects. Importantly, having a glossy surface does not equate to a uniform film, because the bottom side of a film product formed on a substrate will take the surface features of the substrate. If the substrate is smooth, the resulting bottom surface will also be smooth and possibly glossy. A product that has a surface that appears free of defects may have experienced significant non-uniformity below the surface, for example due to aggregation and agglomeration of components. It is important to note that just because the surface of a resulting product looks glossy or free of defects does not inherently mean that the actives within the film product exhibit the level of uniformity of content necessary to satisfy regulatory requirements and/or deliver the desired amount to the patient.

The '080 Patent discloses in a section entitled "Testing Films for Uniformity" (col. 28, l. 65 through col. 29, l. 53) that "[i]t may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process". '080 Patent, col. 28, l. 66 through col. 29, l. 1. In particular:

> "It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and over all appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons."
>
> '080 Patent, col. 28, l. 66 through col. 29, l. 6 (emphasis supplied).

Thus disclosed are two general types of testing, one for physical uniformity, and one for chemical uniformity. The disclosure goes on to provide different ways to test for each.

> "After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art. If the testing results show non-uniformity between film samples, the manufacturing process may be altered. This can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions, mixing conditions, compositional components and/or film viscosity may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others."
>
> '080 Patent, col. 29, ll. 33-38 (emphasis supplied).

In this way the '080 Patent provides multiple tests for non-uniformity, which are extremely useful in guiding the commercial manufacture of films. For example, manufacturing runs of films which appear to exhibit "non-uniformity" may be adjusted early in the run with less waste of materials, thus saving time and expense associated with the possibility of a non-uniform film. Physical tests, such as observational tests, are insufficient to determine the level of uniformity of content disclosed and claimed by the '080 Patent-- they do not determine the actual amount of active in samples.

The '080 Patent discloses testing to determine the appropriate degree of uniformity of content of the resulting film involving sampling substantially equal sized individual dosage units of the resulting film, dissolving the active in the sampled resulting film, and testing for the amount of active present in the sampled resulting film. Thus, the '080 Patent discloses that uniformity of the active is demonstrated through testing.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active."
>
> '080 Patent, col. 32, ll. 36-41 (emphasis supplied).

In this respect the Examiner, in his Scope of Claims section has mistakenly included physical uniformity type tests, used to quickly and/or easily suggest non-uniformity, with chemical uniformity type tests involving analytic equipment, that is, the actual testing of the uniformity of content for the amount of active. In the Scope of Claims section of the Office Action (pp. 3-7), the Examiner refers to two different portions of the '080 Patent's "EXAMPLES" section as follows:

> "An alternative means for evaluating uniformity is to cut the films into individual doses and measure the weight of the doses (col. 31, line 46 through col. 32, line 45). The '080 patent notes that "films of substantially similar size cut from different locations of the same film contain substantially the same amount of active." (col. 32, lines 37-39)."
>
> Office Action, p. 7.

Significantly, the two sentences are not related to each other, other than that both deal with examples and with cutting the film into dosage forms. The first is from a physical test, the second, relating to actives, is from an analytical chemical test for uniformity of content of active.

First is the physical test which refers to uniformity in mass.

> "Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:
>
> [Table omitted.]
>
> "The individual dosages were consistently 0.04 gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. **Therefore,** when the components of different densities are combined in a uniform manner in a film, as in the present invention, **individual dosages forms from the same film of substantially equal dimensions, will contain the same mass**."
>
> '080 Patent, col. 31, l. 46 through col. 32, l. 34 (emphasis supplied).

In accordance with this test, if the masses are unequal that would be an indication of mass non-uniformity.

Immediately after the above quoted disclosure, the '080 Patent discloses essentially that to demonstrate uniformity of content for active, the amount of active in each substantially similarly sized sample must be determined.

> "An alternative method of determining the uniformity of the active is to cut the film into individual doses. **The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active**."
>
> '080 Patent, col. 32, ll. 35-40 (emphasis supplied).

The Examiner also relies on the paragraph at '080 Patent, col. 31, ll. 38-45 for support that physical type tests, in this case observational tests, are sufficient to establish uniformity of content of active.

> "The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film."
>
> '080 Patent, col. 31, ll. 38-45

However, it is one thing to have films which appear to be substantially free of aggregation and rely on that to say there is substantially no disparity among the amount of active in any portion of the film, and it is a totally different thing to demonstrate the presence of the required level of uniformity of content in the amount of active by analytical chemical testing and determining the actual amount of active in samples.

This paragraph, again, from the '080 Patent's section on "EXAMPLES", sets the stage for disclosing both the physical and chemical type tests referred to above at '080 Patent, col. 31, l. 46 through col. 32, l. 40, which follows this paragraph (see citation). Moreover, this paragraph

itself follows the manufacture of the film of Examples A-I and starts with what would be an expected quick and inexpensive procedure of looking at the film right after making it to see if it appears non-uniform or uniform. Such an observational test is at a macro level and does not indicate the degree of uniformity. Even if the film appears uniform, analytical chemical tests must then be conducted to verify uniformity of content at the prescribed level. What followed next were the two other tests discussed above.

Importantly, the first test is obviously a physical type test needed to rely on assumptions to reach its conclusion of substantially no disparity among the amount of active found in any portion of the film. Namely, by "viewing the films it was apparent that they were substantially free of aggregation . . . . Therefore, there was substantially no disparity among the amount of active found in any portion of the film." Based on physical observations a conclusion was drawn. The second, another physical test, concluded "individual dosages forms from the same film of substantially equal dimensions will contain the same mass;" again, referring to mass not uniformity of content of active. Again, no simple declarative statement that the amount of active in each sample was substantially the same or that the actual amount of active was determined.

It was only the third test, the analytical chemical type test that could directly establish that "films of substantially similar size cut from different locations on the same film contain substantially the same amount of active". This is to be expected as only the chemical based tests could provide the necessary assurance for the statement that substantially the same amount of active was present in each dose. Thus, one cannot solely rely on physical tests in prior art disclosures to "establish" that the prior art films actually possessed the levels of uniformity of content as claimed by the '080 Patent. However, analytical chemical testing is used in the '080 Patent to establish the actual amount of active in samples. In one example, in the '080 Patent analytical chemical testing was used to test for the amount of one component, a red dye, and in so doing established that the uniformity of content of the component fell well within the 10% level, particularly, it was 4%. See, '080 Patent, col. 33, l. 10 through col. 34, l. 24 (example M).

VI. Arriving at the Invention

The inventors of the '080 Patent are the first to not only identify the problems associated with manufacturing commercially and pharmaceutically viable active containing film individual

dosage units or forms, but also to solve those problems, especially as same relate to obtaining required levels of uniformity of content. Although many prior publications discussed the use of film as a dosage form for drugs, none of the publications identified nor solved the problems and complications associated with their manufacture. These early publications focused on the compositional and qualitative aspects of the films only and merely treated the manufacturing, if mentioned at all, as being simple, such as exposing the cast wet film to a conventional hot air circulating oven. However, especially in a commercial manufacturing setting, drying an active-containing cast wet film (even if the wet film is homogenous), in a conventional hot air circulating oven does not necessarily produce a film that is commercially viable, or deliver a film with the prescribed degree of uniformity of content in said setting. The '080 Patent does. *See* Bogue Declaration, ¶¶ 4-11.

A. Recognition of the Problem

The inventors discovered that it is not commercially viable to manufacture therapeutic–active-containing films using conventional drying methods. Even when a wet film matrix is properly formed so as to have a substantially uniform distribution of active within it, there are numerous factors which can destroy that uniformity of content during later processing such as casting and drying. The present specification describes many of these problems, which include (i) self-aggregation and agglomeration of active; (ii) skinning of the surface (a barrier through which remaining solvent must penetrate) before the thickness of the film is sufficiently dried, resulting in ripping and re-forming of the surface; (iii) forming of ripples on the surface; (iv) formation of air bubbles, which result in voids or air spaces within the film product; (v) maintaining the active in a substantially stable and uniformly dispersed state; (vi) movement of active particles due to uncontrolled air currents during drying; (vii) using air currents which create forces which overcome the yield value of the polymer matrix, or which would disturb or break the surface of the polymer matrix, or which overcome the inherent viscosity of the polymer matrix. See, for example, col. 3, l. 33 through col. 4, l. 6, and col. 11, ll. 14-25, the '080 Patent.

B. Solving the Problem

The inventors not only were the first to identify all the problems described above, but the first to solve them. Failure to solve one or more of these problems results in a film product that lacks the desired degree of uniformity of content of active per unit dose of film and therefore when equal dosage sizes are cut from the bulk film product, the desired amount of active per dosage lacks the desired and/or required degree of uniformity of content of active. The inventive methods and processes of the '080 Patent maintain the desired uniformity of content of active by, *inter alia*, controlling polymer matrix viscosity and controlling the drying processes so as to avoid the aforementioned problems, thereby forming a visco-elastic film that locks-in the substantially uniform distribution of active(s) during the drying steps. As described in the specification and claims, the present invention maintains the claimed levels of uniformity of content of active from the formation of the initial matrix through the final drying process, such that the pharmaceutical active varies by no more than 10% within a film lot, and by no more than 10% when sampled from different film lots.

The Examiner has cited several references, which will be discussed in further detail below. For ease of understanding, the Patentee will briefly discuss the primary cited references herein. During the discussion, it is important to keep in mind that statements from these sources regarding uniformity of content of components, especially actives, are not based on analytical chemical testing for the amount of active present in equally sized samples, but are at best assumptions, generally based on physically observable properties of the film in its intact state. The below discussion is supported by the Bogue Declaration and the Fuller Declaration.

VIII. The Claim Rejections.

The Examiner's rejection of the claims begins on page 7 of the Office Action.

A. Claims 1-299 were improperly rejected.

Claims 1-299 were rejected as allegedly anticipated under 35 U.S.C. §102(b), or, in the alternative under 35 U.S.C. § 103(a), as obvious over, each of the following references: Chen (WO 00/42992) ("Chen"), Staab (U.S. 5,393,528) ("Staab"), Le Person (*Chemical Engineering and Processing*, Vol. 37, pp. 257-263 (1998)) ("Le Person") and Horstmann (U.S.

5,629,003) ("Horstmann") or some combination thereof as set forth in the Office Action. These rejections relied on the Examiner's findings that material claim elements of the '080 Patent's only independent claims in reexamination, Claims 1, 82 and 161, were inherent in the cited references. Two limitations were of paramount importance, namely the limitations of "substantially uniform distribution of components" and of "locking-in or substantially preventing migration of" active.

Patentee maintains that the foregoing claim limitations are sufficent in themselves to establish patentability. Nevertheless, to advance prosecution, Patentee has explicitly added to all the independent claims herein presented specified levels of uniformity of content in the amount of active. Either a 10% limitation on the amount by which an active can vary between individual dosage units sampled from a particular film, and/or a 10% limitation by which the amount of active can vary from a desired amount among individual dosage units sampled from more than one film, which specificed levels of uniformity of content in the amount of active are not disclosed expressly nor are they inherent in the art of record. Patentee has also explicitly required manufacturing resulting pharmaceutical and/or bioactive active-containing films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units. Additional aspects not present in the art of record include, *inter alia*, viscosity ranges, controlled drying, conveying, applying air currents which have forces below the yield value of the polymer matrix during drying, forming a visco-elastic film in about 4 minutes, keeping the polymer matrix temperature below 100 °C, wherein resulting film has a water content of 10% or less. And the foregoing was just a partial listing of new claim elements. Hence, independent claims 1, 82 and 161, as amended, and all the new independent claims, claims 315-318, are not disclosed and/or made obvious, explictly or inherently, in the cited prior art.

The Examiner relies on the Declaration of Edward D. Cohen, Ph.D. under 37 C.F.R. § 1.132, dated September 6, 2012 ("Cohen Declaration) to support the assumption that it would be difficult for a person of ordinary skill in the thin film art not to obtain a film that has uniform content of active. Office Action, pp. 14 and 43. However, Dr. Cohen's assumption is dead wrong on its face or does not apply to the '080 Patent. Importantly, Dr. Cohen does not discuss

the degree of uniformity of content. He refers generally to "substantial uniformity of content of active" and "uniform content of active" per unit dosage. Cohen Declaration, ¶¶ 8-10. Dr. Cohen's statement about uniform content of active, without providing the degree of uniformity of content cannot be applied to the '080 Patent's invention. Especially now that the claims of the '080 Patent expressly require a degree of uniformity of content, namely, that uniformity of content of the resulting film(s) varies (i) no more than 10% with respect to the amount of active within a film (claims 1, 82, 161, 316-318) and/or (ii) no more than 10% from a desired amount with respect to the amount of active; said active sampled from different films in substantially equally sized individual dosage units sampled from different locations of the relevant film(s) (claim 315).

Moreover, as set forth in the Bogue Declaration, ¶¶ 4-11, 730 samples of individual dosage units, ten each from 73 separately manufactured lots of resulting films produced in accordance with Patentee's invention, were tested for active content. The results were that the active content of each individual dosage unit remained well within the control limits of 90% to 110% of the desired amount.

> "The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A. Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.."
>
> Bogue Declaration, ¶ 11.

As noted, the FDA requires that the amount of active vary from dose to dose by no more than a prescribed percentage from the desired amount of active, essentially prescribing a degree

of uniformity of content in the amount of active which must be met. *See* Lin declaration, ¶¶ 9-16. Dr. Cohen provides no support for any prescribed degree of uniformity, and certainly not for the prescribed degree of uniformity of content in the amount of active explicitly recited by Patentee's claims under examination to meet commercial and/or regulatory requirements, or the degree of uniformity present in resulting films manufactured in accordance with Patentee's invention, as clearly demonstrated by the Bogue Declaration.

As held by the Court of Appeals for the Federal Circuit ("Federal Circuit") inherency requires much more than probabilities, possibilities, or for that matter assumptions. In *Crown Operations Intern., Ltd. V. Solutia Inc.*, 289 F.3d 1367 (Fed.Cir. 2002) ("*Crown*"), the patents at issue related to layered films used to create safety and solar control glass. The multi-layer film added properties to the glass assembly, such as impact resistance. An inner layer had solar control properties to reflect, absorb (and thus convert to heat), or transmit defined percentages of certain wavelengths of light. *Crown*, at 1370. The district court had held the only relevant independent claim of one of the patents, the '511 patent, not invalid on the grounds of anticipation and obviousness. It claimed a composite solar/safety film, comprised of a solar control film "wherein said solar control film contributes no more than about 2% visible reflectance". *Crown*, at 1372.

> "Crown [the declaratory judgment plaintiff] argued that U.S. Patent No. 4,017,661 to Gillery (the "Gillery patent") anticipates the '511 patent. The district court held otherwise, because, while the Gillery patent discloses the first three limitations of claim 1 of the '511 patent, it does not disclose the two percent visible reflectance limitation. The court found that neither the Gillery patent claims nor its description expressly disclose a two percent limit on reflectance contribution from the solar control film layer. Crown argued that the two percent limitation was inherently present in the Gillery patent's teachings because the Gillery patent disclosed an assembly with PVB layers, substrate layer, and substrate metal-coating — arguably of the same composition and thickness of the films disclosed by the '511 patent. Thus, Crown argued, because the structure, thickness and materials of the assembly were the same or within the same range(s), the Gillery patent must inherently disclose a two percent limitation. The district court rejected this argument because it found that none of the embodiments disclosed by the Gillery patent meet the two percent visible light reflectance limit."
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> *Crown*, at 1372.

The Federal Circuit, in upholding the decision of the District Court as well as the validity of the '511 patent, discussed the application of inherency to validity that is most relevant here.

> "Regarding alleged anticipation by the Gillery patent, on its face the Gillery patent does not disclose or discuss a two percent limitation for the reflectance contribution of the solar control film. Crown maintains that the '511 patent merely claims a preexisting property inherent in the structure disclosed in the prior art. Crown urges us to accept the proposition that if a prior art reference discloses the same structure as claimed by a patent, the resulting property, in this case, two percent solar control film reflectance, should be assumed. We decline to adopt this approach because this proposition is not in accordance with our cases on inherency. If the two percent reflectance limitation is inherently disclosed by the Gillery patent, it must be necessarily present and a person of ordinary skill in the art would recognize its presence. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed.Cir.1999); *Continental Can*, 948 F.2d at 1268, 20 USPQ2d at 1749. **Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient**." *Id.* at 1269, 20 USPQ2d at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)) (emphasis supplied)."

The alleged inherency of the art cited by the Examiner and discussed below has not been established other than by statements of probabilities and/or possibilities and/or just statements that things are uniform without providing any degree of uniformity that must be present. For example, the assumption that by starting with so-called "uniform" mix of materials, stirring them, then casting and drying as alleged to be disclosed in the prior art is insufficient to establish inherency. Again, inherency requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. Importantly, the mere possibility that some of the films produced as disclosed by the art cited might result in some type of "uniform" film is not sufficent.

1. Chen's alleged inherency.

> "The claimed "substantially uniform distribution of components" and "locking-in or substantially preventing migration" of the active in independent claims 1, 82 and 161, and the variation of active content of 10% or less in dependent claims 254-255,272-273 and 290-291, are inherent in Chen's exemplified films and process. Inherency is based on the following: As discussed above, Chen uses the

> same materials and method as here claimed. Chen's ingredients are mixed until they are uniformly dispersed or dissolved in the hydrocolloid (p. 17, lines 8-11). Chen uses the same criteria discussed above with respect to the '080 patent in the Scope of Claims section for evaluation of substantial uniform distribution, i.e., weight of dosages and visual inspection."
>
> Office Action, p. 13.

The criteria used by Chen as cited by the Examiner for evaluation of "substantial uniform distribution" are physical observations. Such "observations" cannot be used, either inherently or otherwise, to establish the uniformity of content in the actual amount of active in equally sized samples in Chen's examples. Absent statements or data based on analytical chemical testing, not weighing or visual inspection, for the amount of active present in the film, Chen does not and cannot inherently disclose Patentee's resulting film having the claimed levels of uniformity of content. Moreover, even if Chen disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra*, at 1378.

Moreover, Third Party Requester has not provided any proof that Chen's process examples when followed exactly, with all the components exactly as listed, and all other conditions of Chen exactly met, will provide a process suitable for commercial manufacture, a process which produces products which are regulatory approvable by the FDA, and which exhibit the levels of uniformity of content in actual amount of active claimed by Patentee's processes. Indeed, FIG. 5 of Chen describes a release profile of almost 120% of active from a film, which certainly exceeds the levels of uniformity of content in the amount of active that Patentee claims. This single active content result voids all claims to Chen's alleged inherency regarding same.

> "Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity

between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film."

Lin Declaration, ¶ 22.

The Examiner states that the films made in accordance with the claims as issued are inherent in Chen. This conclusion is based on the belief that Chen uses the "same materials and method" as the Patentee, but even if true, much more is required. Patentee respectfully submits that this conclusion is incorrect, and particularly incorrect in light of the claims as amended. The Examiner erroneously states that Chen "uses the same criteria" as the '080 Patent that issued in evaluating substantial uniform distribution, i.e. weights of dosages and visual inspection." Although, a number of ways to test films in the patent are disclosed, in order to test content uniformity of an FDA regulated film product, it is necessary to assay using analytical chemical tests for drug or therapeutic active content of unit film doses. *See*, Lin declaration, ¶¶ 9-16. This is necessary to ensure the amount of active is within acceptable guidelines. Visual observation and physical measurements such as weight is insufficient to determine the active amount in equally sized dosage units at the level of uniformity of content required.

All of Patentees' claims now require analytical chemical testing and that the films have levels of uniformity in the amount of active which varies by no more than 10% from film to film and/or no more than 10% from a desired amount across several films. The Examiner's assumption that visual inspection and weight measurements establish these levels of uniformity of content in and by themselves is therefore incorrect, in so far at least as is required by the FDA, for example. Moreover, "Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products." Lin Declaration, ¶ 21.

Finally, there is a misplaced reliance on the physical terms "glossy" and "transparent" in the Office Action, which the Examiner use to establish the presence of "uniformity" in Chen's films. However, the term "glossy" is purely a visual characteristic ("surface luster or brightness") and is not interchangeable with nor equivalent to the uniformity of content of components of a film, nor the content uniformity of an active in the film. *See,* www.merriam-

webster.com/dictionary/glossy. It is also not interchangeable with specified levels of uniformity of content in amount of active in individual dosage units sampled from a film or sampled from different films. The term transparent is also a purely visual appearance characteristic ("transmitting light without appreciable scattering …"). *See,* www. merriam-webster.com/ dictionary/transparent. It is not indicative of the uniformity of content of the film. As such, Chen can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

2. Staab's alleged inherency.

> "Staab also discloses that "[t]he device of the invention thus is composed of a biologically-compatible material that has been blended homogeneously" with the drug (see col. 6, lines 5-10). In the Example at cols. 11-12, Staab prepares a four-foot wide film which is then cut into two inch by two inch films each weighing 190 mg and containing 19 mg of benzalkonium chloride as the active agent (see col. 11, line 52 through col. 12, line 3). Accordingly, Staab's films inherently have the instantly claimed substantially uniform distribution of components and active. Also, in view of the fact that each film contains 19 mg of benzalkonium chloride and in view of said homogeneous blending, the variation of active in the dosage units is 0% (*sic* 10%), as per claims 254, 255, 272, 273, 290 and 291."
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> Office Action, p. 29.
>
> "In particular, as noted above, the '080 patent teaches that "[t]he addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity, and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size and volume fraction (see col. 8, lines 42-46). Staab uses the same hydrocolloid as in the '080 patent, i.e. said HPMC. Accordingly, Staab's film in the Example at cols. 11-12 is inherently viscoelastic before drying. Accordingly, after drying for about 10 minutes, a viscoelastic film having less water that before drying is formed."
>
> Office Action, p. 30.
>
> "While Staab does not discuss viscoelasticity or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the active, Staab, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process."
>
> Office Action, p. 31.

Again, as with Chen, absent statements based on testing to determine the actual uniformity of content in the amount of active present in the film, so as to meet FDA approval, Staab does not and cannot inherently disclose Patentee's resulting film having the claimed levels of uniformity of content, with respect to the amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film and/or of different resulting films. Staab does not and cannot inherently form a viscoelastic film within about the first 4 minutes, which locks-in the uniformity of content within the recited levels of uniformity of content.

Moreover, even if Staab disclosed, which it does not, the use of the same materials and methods as the '080 Patent, the mere fact that a certain thing may result from a given set of circumstances is not sufficient to support inherency. *Crown, supra*, at 1378. Moreover, Staab just states that there is 19 mg of benzalkonium chloride present in each sample weighing 190 mg. However, Staab does not disclose testing to determine the amount of benzalkonium chloride present in the final film product or even how each and every sample turned out to be 19 mg. Staab, col. 11, l. 35 - col. 12, l. 3. Staab's resulting structure is a foam rather than the recited visco-elastic film formed within 4 minutes and Staab also would not inherently have the recited degree of uniformity of amount of active in substantially equal sized dosage units. Moreover, Staab starts with a composition having 10% by weight of benzalkonium chloride (50% aqueous) yet allegedly obtains a resulting film with 19 mg benzalkonium chloride in a 190 mg film, to once again obtain a 10% benzalkonium chloride resulting composition. A perfect yield must must always be considered suspect. Inherency should never be based on a suspect disclosure. As such, Staab can neither anticipate, explicitly nor inherently, nor make obvious the '080 Patent claims, see discussion below.

3. Le Person's alleged inherency.

> "Le Person discloses that after 5 min of the drying, 'the polymeric network is not turgescent and the meshes are densely packed. The polymer skeleton acts as a filter for the active substance [i.e., pharmaceutical or drug] when the system reequilibrates.' (See p. 262, col. 2, third full paragraph.) Le Person also teaches that '[b]etween the 5th and 10th min of drying the heavy solvent migrates... active substance, slowed down in its migration, stays in the bottom of the layer.' (See the

> last four lines at page 262, col. 2). It is noted that the heavy solvent only accounts for 2% of the wet composition of the coating (see page 258, Table 1). As such, within 5-10 minutes, the solvent has been sufficiently evaporated such that, inherently, a substantial uniform distribution of the active is locked-in and migration is substantially prevented within the film, as here claimed. The active material homogenizes and a quasi-equilibrium is obtained for the components of the Page 38 active phase, taking into account evaporation of the heavy solvent (p. 263, col. 1, lines 8-13), and thus, there is a variation of active content of less than 10%, as per claims 272, 273, 290 and 291.
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> Office Action, pp. 37-38.
>
> "While Le Person does not discuss viscoelasticity or that the films in its process have a 'substantially uniform distribution of components' or disclose 'locking-in or substantially preventing migration' of the active, Le Person, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 82, 89-91,161,171-173, 272-274 and 290-292, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, p. 38.

Le Person is entirely devoid of any details with respect to its process and materials. For example, nowhere does Le Person discuss what type of acrylic polymer he uses nor the molecular weight of the polymer. Thus, Le Person allows for materials which may have such a low molecular weight that forming a visco-elastic film may not be possible. Moreover, Le Person lacks sufficient enabling disclosure to be an effective reference as applied in view of the amended claims. Such deficiencies cannot be used in support of an inherency argument. Again, absent statements and data based on testing for the amount of active present in the film with results establishing a substantial uniformity of content at the claimed levels and suitable for FDA approval, Le Person does not and cannot inherently disclose Patentee's resulting film. Moreover, Le Person does not and cannot inherently form a viscoelastic film in about 4 minutes which locks-in the claimed uniformity of content in the amount of active.

Le Person discloses very little about the acrylic polymer, such as the molecular weight. If the molecular weight was low enough it may not become a viscoelastic material. Patentee asks, how could Le Person anticipate and/or make obvious the '080 Patent which is directed to the commercial manufacture of a regulatory approvable resulting film meeting required specified

levels of uniformity of content in the amount of the active, where Le Person's goal, as noted in its abstract, was devoted to determining "cases of maldistribution of the active substance," in connection with different drying methods, and not to providing a process for manufacturing films with uniformity of content of the desired amount of an active. Importantly, Patentee has added several additional process steps not in the prior art. These new process steps present in the amended independent claim, as well as the new independent claims, further distance Patentee's patent from the prior art. As such, Le Person can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

4. Horstmann's alleged inherency.

> "The claimed substantially uniform distribution of components and active, and locking-in or substantially preventing migration of active, and the variance of active content of 10% or less in dependent claims 254, 272 and 290 are also inherent in Horstmann's Examples 1, 3 and 4. In particular, Horstmann's films before drying are described as being uniform and homogeneous (see col. .3, line 11-19, 29-34 and 37-41; col. 5, lines 1 and 50), and as noted above, Horstmann uses the same components and process steps as here claimed. The '080 patent notes that Horstmann addressed the problem of self-aggregation and nonuniformity by increasing the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film (see col. 2, line 60 through col. 3, line 1).
>
> Office Action, p. 43.
>
> "While Horstmann does not discuss viscoelasticity, water content of its dried films or that the films resulting from its process have a "substantially uniform distribution of components" or disclose "locking-in or substantially preventing migration" of the, active, Horstmann, as cited above, discloses a process which reasonably appears to be either the same as or an obvious variation of the instantly claimed process. Accordingly, claims 1, 5,7-10,12-1423,63,64,82,84,86-89,91-93,102,142,143,161, 166, 168-171, 173-175, 184,224,225,249,254,267,272,285 and 290, if not anticipated under 35 USC 102(b), would be obvious under 35 USC 103(a)."
>
> Office Action, pp. 43-44.

Horstmann forms a gel, rather than a solid film as in the present invention. Thus the gel rheological properties of Horstmann are very different than a solid visco-elastic film having a

water content of 10% or less. Moreover, Horstmann specifically teaches protecting the gels from drying up by placing the cut out gel shapes in a water vapor impermeable sealing material. See Horstmann, col. 5, ll. 11-13. This is a direct teaching away from drying to a water content of 10% or less. Horstmann at col. 2, ll. 25-29, suggests drying may not be necessary.

Again, absent statements based on testing for the amount of active present in the film with results establishing a the claimed levels of uniformity of content in the amount of active, suitable for FDA approval, Horstmann does not and cannot inherently disclose Patentee's resulting film claiming the specified levels of uniformity of content in the amount of active.

Additionally, as the Examiner admits, Horstmann discloses only that its film is alleged to be uniform at a point prior to drying. Horstmann, col. 3, ll. 37-41. Horstmann says nothing about the uniformity of the product during or after drying. Again, *Crown* holds that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* A disclosure of some unspecified degree of uniformity of a film prior to drying in Horstmann does not establish that the product after drying is uniform, let alone the degree of uniformity as claimed by the '080 Patent. As noted throughout the '080 Patent, controlled drying is required for ensuring the claimed levels of uniformity of content. As such, Horstmann can neither anticipate, explicitly or inherently, nor make obvious the '080 Patent claims, see discussion below.

Importantly, Patentee has added several additional process steps also not in the prior art. See above. These new process steps present in the amended independent claims, as well as the new independent claims, further distance Patentee's patent from the prior art, by negating any anticipation and obviousness assertions. Even without the additional process steps, even if it were possible that a resulting film with the proper levels of uniformity of content in the amount of active might possibly result from some manipulations of the disclosures given in any of Chen, Staab, Le Person and/or Horstmann, it is incorrect to rely on these references in an attempt to show they inherently disclosed Patentee's resulting film. See *Crown*, at 1377-1378, *supra*.

As the absence of inherency in and of itself removes Chen, Staab, Le Person and Horstmann as viable prior art for rejecting Patentee's claims under 35 U.S.C. § 102, the Examiner should withdraw his rejections of Patentee's claims 1, 82 and 161 based on same. For the same reasons new independent claims 315-318 are allowable. Moreover, these references for

the same reasons discussed above, as well as the reason discussed below, do not support any finding of obviousness, and thus the rejections of claims 1, 82, and 161 based on 35 U.S.C. § 103 should be withdrawn as well. For the same reasons new independent claims 315-318 are not obvious in light of the prior art. Finally, Patentee's claims 2 through 81, 83 through 160, 162 through 299 and 300 through 314 as they depend from independent claims 1, 82, 161 should all be allowed as well, with any rejections withdrawn.

B. Third Party Requester's Wherein Argument is Wrong

Patentee finds it necessary to address Third Party Requester's attempt to vitiate the '080 Patent's claim language beginning with "wherein". Third Party Requester cites to the Federal Circuit for the premise that "a whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed.Cir.2003). Third Party Requester's Request for Inter Partes Reexamination ("The Request"), p. 16.

However, the Federal Circuit has also strongly held that "when the 'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F. 3d 1326, 1329 (Fed. Cir. 2005). Essentially, Requester proposes that with elimination of the "whereby" clauses, the claims 1, 82 and 161 (before the amendments herein) would not require "wherein said resulting film has a water content of 10% or less and said uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained." The Request, p. 20.

As noted above, "when the whereby clause states a condition that is material to patentability, it cannot be ignored to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326 (Fed. Cir. 2005); *see also Fantasy Sports Properties, Inc. v. Sportsline.com, Inc.*, 287 F.3d 1108, 1111-16 (Fed. Cir. 2002); *Griffin v. Bertina*, 285 F.3d 1029, 1034 (Fed. Cir. 2002). In *Griffin*, for example, the court found that "wherein" clauses were claim limitations "because they relate back to and clarify what is required by the count. Each 'wherein' clause ... expresses the inventive discovery [and] ... elaborates the meaning of the preamble." *Griffin*, 285 F. 3d at 1033-34. Further, "the allegedly inherent properties of the 'wherein clauses' provide the necessary purpose to the steps." *Id.* See also, MPEP, § 2111.04.

The '080 Patent independent claims' wherein clause limitations cannot be disregarded. The '080 Patent claims processes for manufacturing resulting films suitable for commercialization and regulatory approval, said regulatory approval including analytical chemical testing which meets the standards of the U.S. Food and Drug Administration relating to variation of an active in individual dosage units, said films having a substantially uniform distribution of components comprising a substantially uniform distribution of a desired amount of said active in individual dosage units of said resulting films. The ability to make such films with the required level of uniformity in content of active is the essence of Patentee's invention. Thus, such wherein clauses which express the inventive discovery and elaborates the meaning of the preamble cannot be ignored for purposes of patentability.

Finally, Third Party Requester has made many allegations about the '080 Patent and its specifications and claims, and the prior art in The Request. Patent owner believes that the amendments to claims 1, 82 and 161 herein clarifying the scope of same and thereby advancing the prosecution of same, obviate the need to address Third Party Requester's allegations or the Examiner's statements made without the benefit of the amendments. Nevertheless, to the extent that any are not explicitly addressed herein, Patentee hereby asserts they are wrong and unsupported in either fact or law.

C. Claims 1, 4, 5, 8-18, 20-32, 34, 36-40, 44-47, 51, 53, 54, 59, 62-71, 82-84,87-97, 99-111, 113, 115-119, 123-126, 130, 132, 133, 138, 141-150, 161-166, 169-179, 181-193, 195, 197-201, 205-208, 212, 214, 215, 220, 223-232, 243, 244, 246, 247, 249-262, 264, 265, 267-280, 282, 283 and 285-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chen.
Claims 2, 3, 6, 7, 19, 33, 35, 41-43, 48-50, 52, 55-58, 60, 61, 85, 86, 98, 112, 114, 120-122, 127-129, 131, 134-137, 139, 140, 167, 168, 180, 194, 196, 202-204, 209-211, 213, 216-219, 221, 222, 245, 248, 263, 266, 281 and 284 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chen.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Chen, WO 00/42992 ("Chen") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Chen. Patentee incorporates its previous discussions in sections A. and B. above. Chen is a primary reference relied upon by the Examiner in the Office Action. Patentee

respectfully traverses the above rejections on the basis, among others, that Chen does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of a lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Chen also fails to disclose, explicitly or inherently, the additional elements found in Claim 317. Claim 317 generally adds, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Chen discloses two methods of forming a film product, a solvent casting method and an extrusion method. The extrusion method does not rely upon putting a hydrocolloid in a solvent, nor does the extrusion method use a drying oven and is apparently preferred by Chen over the solvent method. Chen, page 15, lines 9-21. In the solvent casting method, Chen states that a hydrocolloid is dissolved or dispersed in water, and mixed to form a homogeneous solution. The active agent and other ingredients may be added and dispersed or dissolved uniformly in the hydrocolloid solution. The coating solution with a solid content of 5-50% and a viscosity of 500-15000cps is degassed and coated onto a polyester film and "dried under aeration" at a temperature between 40-100°C to avoid destabilizing the agents. Chen, p. 15, ll. 19- 29. The dry

film formed by this process is described to be a "glossy, stand alone, self supporting, non-tacky and flexible film". Chen, p. 15, ll. 30-31. These very general statements are all that are given by Chen as to the formation and drying of Chen's film product. These statements cannot support either anticipation or obviousness rejections.

Chen's drying process is so general and devoid of detail so as to provide no guidance other than that to dry, one places a film in a conventional hot air circulating oven at temperatures of from 40-100°C and leaves it for a period of time. Chen does not disclose any other drying methods beyond drying "under aeration", nor does Chen disclose any controlled drying processes whatsoever. Chen showed no recognition of the complexities involved in the commercial manufacturing of films, as Chen's focus relates solely to the ingredients and mechanical properties, not the process. Without any recognition of the problems, and without any appreciation of the difficulties in preventing the settling, migration and/or aggregation or agglomeration of active(s) in the cast flowable mass, Chen neither sought nor found the solution to creating commercial scale films having uniformity of content of pharmaceutical and bioactive actives per individual dosage unit and meet FDA requirements regarding same. Chen lacks substantial disclosure in view of the '080 Patent. Among its deficiencies, Chen lacks any disclosure as to specific processing means (beyond generally drying in a generic oven) or the formation of a visco-elastic film state. Chen only discloses the apparent homogeneity of a blended matrix, and this is prior to the addition of actives. There is no disclosure or suggestion as to how to create a substantially uniform distribution of the pharmaceutical or biological active in the blended matrix and then cast that matrix to maintain uniformity, and then control drying through among other processes conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to rapidly form a visco-elastic film having said pharmaceutical active uniformly distributed throughout by rapidly increasing the viscosity of said polymer matrix upon initiation of drying within about the first 4 to maintain said uniform distribution of said pharmaceutical or biological active by locking-in or substantially preventing migration of said pharmaceutical active within said visco-elastic film and then test it to establish the substantially uniform distribution of pharmaceutical or biological active content, in compliance with FDA regulations.

Among other things, the '080 Patent claims are directed to locking-in an active such as a pharmaceutical or biological active, by controlling drying to form a viscoelastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes. The Examiner has stated in the Reexamination, Reasons for Patentability/ Confirmation ("RFP/C"), in connection with both the '292 Patent and the '891 Patent reexaminations that "Chen does not discuss what happens within the first 4 minutes of drying." Moreover, in the '891 Patent RFP/C the Examiner goes on to state that: "Chen does not discuss uniformity of pharmaceutical or biological active components in its doses. Table 4 of Chen gives the grams per unit dosage film and density for Example 1 with standard deviation based on three or four measurements, but does not give compositional uniformity." Additionally, Chen's Example 1 contains only food flavorings and a sweetener.

Chen does not disclose that the resulting products are compositionally uniform, but only that they are "glossy". As stated above, glossy does not imply or establish compositionally uniformity. In fact, Chen's Figure 5 (Examples 5-8) clearly shows a lack of compositional uniformity of active. Although statistics are not defined in the text, the error bars represent either high or low values, standard deviation or some measure of variation. Given that the compositions of Examples 5-8 are the same, except for the amount of active, it is reasonable to conclude that the active is not uniformly present in the individual films due to the wide variation of release of active from the same film compositions. For example, with regard to the release of nicotine in the same film compositions, the release reaches in excess of 118%. Certainly there is neither disclosure of, nor inherency in, the that the level uniformity of content in the amount of active as sampled in individual dosage units of the same film be 10% or less. "The release profile data presented in Figure 5 show a high degree of variability at each data point. This indicates that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film." Lin Declaration, ¶ 22.

As defined in the specification for the '080 Patent as filed, a visco-elastic solid is one that has been sufficiently dried to lock its active components into a substantially uniform distribution throughout the film. The '080 Patent claims require that this be done within about the first 4

minutes or less. The Examiner has previously acknowledged that Chen does not disclose that the resulting film product has any compositional uniformity of pharmaceutical or biological active at that point in time. See '891 Patent RFP/C. Neither Chen nor the other references teach this step.

As explained throughout the '080 Patent and as summarized above, the present invention is based upon the discovery that certain process parameters, such as, viscosity and controlled drying methods to avoid non-uniformity of content in the amount of active must be employed to provide a commercially and FDA viable film product. Chen does not disclose or suggest such a resulting product. *See* Lin Declaration, ¶¶ 17-22. Chen discloses that various components (absent the active) are combined and that the mixture is blended to form a "uniform" solution. (Chen, p. 20, ll. 19-20). although even the formation of a uniform solution in a blender is beneficial, it is not the end of the process by any means. Further, as explained above, conventional drying methods do not inherently provide uniform films and, in fact, would not be expected to provide resulting films having the claimed uniformity of content in the amount of active.

Patentee's claimed processes are not present in Chen, either expressly or inherently, and Chen cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited Chen reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Chen does not render obvious the pending claims .

D. Claims 2, 3, 16, 32, 55, 72-81, 95, 111, 134, 151-160, 177, 193, 216 and 233-242 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of Chen and Staab.

The Office Action rejected the above claims under 35 U.S.C. § 103(a), as being unpatentable over the combined teaching of Chen and Staab, U.S. 5,393,528 ("Staab"). Patentee incorporates its previous discussions in sections A., B. and C., above, and E., below and traverses all said rejections thereon. As all the above claims depend from one of the independent claims, claims 1, 82 and 161, they are allowable for all the reasons provided in the sections dealing with Chen, above, and Staab, below and even combined Chen and Staab do not render obvious the pending claims of this rejection.

E. Claims 1-5, 10, 12-16, 21, 24, 25, 32, 44-46, 54, 55, 59, 63-70, 72-75, 78- 84, 89, 91-95, 100, 103, 104,111, 123-125, 133, 134, 138, 142-149, 151-154, 157-166, 171,173-177,182,185,186,193,205-207,215, 216, 220, 224-231, 233-236, 239-242, 249-252, 254, 255, 257-260, 267-270, 272, 273, 275-278, 285-288, 290, 291 and 293-299 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Staab.
Claims 8, 9, 76, 77, 87, 88, 155, 156, 169, 170, 237 and 238 were rejected under 35 U.S.C. 103(a) as being unpatentable over Staab.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Staab, or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Staab. Patentee incorporates its previous discussions in sections A., B., C. and D., above, Patentee respectfully traverses the rejection on the basis, among others, that Staab does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the pharmaceutical and/or bioactive active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of the resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Staab certainly does not disclose, explicitly or inherently, the additional claim elements of Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising

drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Moreover, Staab teaches the benefits of using a "gas foamed film" or films. Staab, col. 5, ll.33-35; col. 8, ll. 33. Staab thus teaches away from the '080 Patent by teaching that air bubbles are necessary, which are contraindicated in Patentee's invention requiring a substantially uniform distribution of active. Staab instead teaches that gas bubbles must be added to the polymer/drug mixture prior to casting.

> "It should be noted that heretofore, the significance of the addition of gases in the formation of the film to alter the texture and solubility of the film has not been recognized."
> Staab, col. 3, ll. 15-20.

> "**The fine tuning of dissolution rates and delivery of agent material, by the addition of gases and by altering the grades or mixtures of polymer materials or layers, is an important aspect of the present invention.**
>
> * * * *
>
> **"The gases, for example, air or nitrogen are introduced near the point of application of the liquid polymer material to the stainless steel casting sheet. The gases are added in a closed system by mixing with whipping blades or a motor driven homogenizer to homogenize the mixture of polymer, active material and gas to form a frothy foam. The final mixture then sets up or gels as a foam.** It is also possible to pour the frothy foam mixture into a mold. The mold is then deformed and the formed device such as a diaphragm, is removed."
> Staab, col. 8, ll. 29-64 (emphasis supplied).

In direct conflict with Staab's teaching, the '080 Patent teaches the use of anti-foaming agents to **prevent** gas bubble formation and thereby promote uniformity. Importantly, Patentee's processes, in many cases, avoid the formation of bubbles, without the need to use anti-foaming agents.

> **" Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product."**
>
> '080 Patent, col. 4, ll. 5-21 (emphasis supplied).

> "A number of techniques may be employed in the mixing stage to **prevent bubble inclusions in the final film. To provide a composition mixture with**

substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed.."

'080 Patent, col. 9, ll. 56-65 (emphasis supplied).

See also section of '080 Patent entitled "Anti-foaming and De-foaming Compositions" ('080 Patent, col. 22, l. 47 through col. 23, l. 53).

Staab addresses the fine tuning of dissolution rates and delivery of active agent, by teaching the addition of gases as an important aspect of his invention (Staab, col. 8, ll. 30-34). Staab is silent with respect to the recited levels of uniformity of content. The '080 Patent in connection with achieving uniformity of content in the amount of active teaches avoiding bubble formation and the removal of such gases and bubbles ('080 Patent, col. 9, ll. 56-65). Moreover, Staab uses conventional drying (Staab, col. 11, ll. 64-65) rather than the particular drying methods used to ensure the uniformity of content claimed by the '080 Patent.

The presently claimed process is not disclosed in Staab, either expressly or inherently, and Staab does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Staab does not render obvious the pending claims of the above rejections.

F. Claims 82, 89-91, 161, 171-173, 272-274 and 290-292 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Le Person.
Claims 92 and 174 were rejected under 35 U.S.C. 103(a) as being unpatentable over Le Person.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Le Person, Chemical Engineering and Processing, Vol. 37, pp. 257-263 (1998) ("Le Person") or, under 35 U.S.C. § 103(a), as obvious or unpatentable over Le Person. Patentee incorporates its previous discussions in sections A., B., C., D. and E., above, Patentee respectfully traverses the rejection on the basis, among others, that Le Person does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by

locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of one lot of resulting film, and by no more than 10% from the desired amount across different lots of resulting films, and is in compliance with FDA regulations governing same.

Le Person certainly does not disclose, either explicitly or inherently, the additional claim elements found in Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Le Person does disclose that the drying step used plays a role in the final product, but fails to disclose or suggest how to achieve a uniform final product. In fact, Le Person discloses methods that result in a non-uniform product prior to and at 10 minutes. According to Le Person, the resulting product dried in 9 minutes would not have claimed uniformity of content of active.

Le Person's goal was to determine "cases of maldistribution of the active substance," in connection with different drying methods, said maldistribution having consequences on storage and delivery of a drug and proposes the use of Laser Scanning Confocal Microscopy on the active substance and the heavy solvent to determine same. (Le Person, Abstract). Le Person acknowledges that in the formation of a film product, "drying is the essential unit operation necessary to form the final product." (Le Person, p. 257). Le Person's experimental set-up was composed of two parts, "the drying cell and the wind tunnel. . . . [wherein] the wind tunnel is a conventional drying rig. . . ." Le Person, p. 258, col. 2 & Fig. 1. Le Person's disclosure of the

use of a wind tunnel further negates any argument that Le Place inherently anticipates or makes obvious Patentee's invention.

It is important to note that Le Person simply recognized the overall, general difficulty in obtaining films with a substantially uniform distribution of active. Le Person did not try to solve this problem, only to determine means to identify it. Thus, Le Person did not recognize the specific reasons therefor, nor did Le Person recognize the solutions needed to overcome this difficulty. Le Person's goal was to find ways to best determine whether or not there was homogeneity of film product.

However, the point of Le Person is that, in the time period (i.e., less than 10 minutes), there is non-uniformity of the product. Le Person even states that "intense moisture removal through the exposed surface of the layer to the radiation, during the first 3 min of drying (Le Person, Fig. 7) produces a stress on the polymer skeleton … and as a result the acrylic polymer becomes more and more dense in the upper part of the layer (exposed surface)." (Le Person, p. 261). As a result, this "intense" shrinkage results in displacement of the active phase. As such, Le Person's disclosure is not directed towards achievement of a film having a substantially uniform distribution of an active through drying, and in fact, if anything, teaches away from achieving uniformity of content in the amount of an active.

The presently claimed processes are not present in Le Person, either expressly or inherently, and Le Person does not anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Le Person does not render obvious the pending claims.

G. Claims 1, 5, 7-10, 12-14, 23, 63, 64, 82, 84, 86-89, 91-93, 102, 142, 143, 161, 166, 168-171, 173-175, 184, 224, 225, 249, 254, 267, 272, 285 and 290 were rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hortsmann.

The Office Action rejected the above claims as allegedly anticipated under 35 U.S.C. §102(b) by Horstman, et al. U.S. 5,629,003 ("Horstmann") or, in the alternative under 35 U.S.C. § 103(a), as obvious over Horstmann. Patentee incorporates its previous discussions in sections A., B., C., D., E. and F., above, Patentee respectfully traverses the rejection on the basis, among

others, that Horstmann does not disclose as claimed in the '080 patent: the recited controlled drying; the recited viscoelastic film; substantially uniform distribution of components; or locking-in or substantially preventing migration of the active; or said substantially uniform distribution of said active maintained by locking-in or substantially preventing migration of said active within said visco-elastic film, rapidly increasing the viscosity of the flowable polymer matrix upon initiation of drying within about 4 minutes to maintain said substantially uniform distribution of active, such that uniformity of content of the resulting film varies by no more than 10% in amount of the active present in substantially equally sized individual dosage units sampled from different locations of the resulting film, by no more than 10% from the desired amount across different resulting films, and is in compliance with FDA regulations governing same.

Horstmann certainly does not disclose, either explicitly or inherently, the additional claime elements of Claim 317. Claim 317 generally adds to the above, *inter alia*, conveying said flowable polymer matrix through a drying apparatus at a temperature of at least 60 °C and using air currents, which have forces below the yield value of the polymer matrix, to evaporate at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, such that uniformity of content in the amount of said active in substantially equal sized individual dosage units, sampled from different locations of said visco-elastic film, varies by less than 5%, and further controlling drying through a process comprising drying at a temperature differential ranging from 5 °C to 30 °C between polymer matrix inside temperature and outside exposure temperature.

Moreover, the '080 Patent's description of the differences between Horstmann and Patentee's invention claimed in the '080 Patent is relevant to the Examiner's current rejections as well. For example:

> "In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann . . . incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other

such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. " '080 Patent, col. 2, l. 63 to col. 3, l. 9.

Horstmann's use of conventional drying methods and need for gel formers teaches away from obtaining a resulting film with the desired levels of uniformity of content in the amount of active. Horstmann does not disclose the degree of uniformity of content, merely, for example, in Example 2, referring to film sections containing "approximately" 3 mg of active and a weight of "approximately" 80 mg. Horstmann, col. 5, ll. 15-36. Horstmann does not disclose that these amounts are based on any testing, or for that matter what they are based upon, or that they comply with FDA requirements relating to drug products.

The presently claimed process is not present in Horstmann, either expressly or inherently, and Horstmann cannot anticipate the claims as pending. Moreover, one of ordinary skill in the art, considering the teachings of the cited reference as a whole, would not predictably or rationally arrive at the limitations of the present claims. For these reasons, Horstmann does not render obvious the pending claims.

IX. Conclusion

No reference, either alone or in combination with other references, teaches the processes claimed by the '080 Patent. Entry of the amendments herein is respectfully requested. Patentee traverses all rejections of its claims. For at least the reasons set forth above, independent claims 1, 82, 161, and 315-318 are allowable. Claims 2 - 81, 83 - 160, 162 - 314 are allowable at least based on their dependencies, whether direct or indirect, from independent Claims 1, 82, 161 . Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections to same. Should the Examiner have any questions regarding this response, the undersigned would be pleased to address them.

Respectfully submitted,

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CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **REPLY BY PATENTEE TO A NON-FINAL OFFICE ACTION PURSUANT TO 37 C.F.R. §1.111** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

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EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

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I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, B. Arlie Bogue, Ph.D., do hereby make the following declaration:

I. Technical Background

1. I have worked in the field of pharmaceutical development, and particularly oral dosage form development, for 22 years. I am employed by MonoSol Rx, LLC. ("Patentee" and/or "MonoSol"), the assignee of issued patent U.S. 7,897,080 ("the '080 Patent"), as Senior Director for Manufacturing Strategy and Innovation.

2. I have a BS in Physical Chemistry from Colorado State University and a Ph.D. in Chemical and BioEngineering from Arizona State University. I have participated in postdoctoral studies in Biochemical Engineering at the University of Virginia. During my career, I have been named as an inventor on over 23 U.S. patents and numerous foreign patents directed to the formulation,

processing and/or packaging of pharmaceutical oral disintegrating unit doses (tablets and film strips). I have direct experience with the commercial scale processing of pharmaceutical film systems as well as an understanding of the uniformity of content of active and methods for testing the same.

3. I have read the '080 Patent and the Office Action issued on November 29, 2012 in the reexamination of the '080 Patent ("Office Action") and the references cited therein, and I have also reviewed the amendment as to the independent claims set forth in Patentee's Reply to the Office Action concurrently filed herewith.

II. Producing resulting films in accordance with the '080 Patent

4. Each of the 73 lots of resulting films (Lots 1-73) containing approximately 2,000,000 individual dosage units per lot discussed herein were manufactured: (i) for commercial use and regulatory approval; (ii) in compliance with U.S Food and Drug Administration ("FDA") standards and regulations, including those relating to analytical chemical testing for variation in active in individual dosage units; and (iii) in accordance with the invention disclosed in the '080 Patent, and as claimed by the '080 Patent both as issued and as amended in the Patentee's Reply to the Office Action; by:

(a) forming a flowable polymer matrix comprising a water-soluble polymer, a solvent and a pharmaceutical active, said matrix having a substantially uniform distribution of said active;

(b) casting said flowable polymer matrix, said flowable polymer matrix having a viscosity from about 400 to about 100,000 cps;

(c) controlling drying through a process comprising conveying said polymer matrix through a drying apparatus and evaporating at least a portion of said solvent to form a visco-elastic film, having said active substantially uniformly distributed throughout, within about the first 4 minutes by rapidly increasing the viscosity of said polymer matrix upon initiation of drying to maintain said substantially uniform distribution of said active by locking-in or substantially preventing migration of said active within said visco-elastic film wherein the polymer matrix temperature is 100 °C or less;

(d) forming the resulting pharmaceutical film from said visco-elastic film, wherein said resulting pharmaceutical film has a water content of 10% or less and said substantially uniform distribution of active by said locking-in or substantially preventing migration of said active is maintained, such that uniformity of content in the amount of the active in substantially equal sized individual dosage units, sampled from different locations of said resulting pharmaceutical film, varies by no more than 10%; and

(e) performing analytical chemical tests for uniformity of content of said active in substantially equal sized individual dosage units of said sampled resulting pharmaceutical film, said tests indicating that uniformity of content in the amount of the active varies by no more than 10%, [see Appendix A] said resulting pharmaceutical film suitable for commercial and regulatory approval, wherein said regulatory approval is provided by the U.S. Food and Drug Administration.

5. Additionally, the uniformity of content in the amount of active as sampled from the 73 lots of resulting film varies no more than 10% from the desired amount of the active as indicated by said analytical chemical tests from 4(e) above. [See Appendix B]

III. Analytical Chemical Testing for Uniformity of Content of Patentee's Resulting Films

6. To demonstrate the uniformity of individual dosage unit films, I compiled individual dosage unit assay data for individual Lots 1- 73, all of which were disclosed in MonoSol's 2012 Annual Product Review to the FDA.

7. Ten (10) individual dosage units all having the same dimensions were cut out from different locations of each of the 73 lots of resulting films using a commercial packaging machine, thus providing 730 randomly sampled individual dosage units, ten each from the 73 separate lots. All samples were analyzed by a validated method, in compliance with FDA guidelines and regulations regarding same, using analytical chemical testing, in which the pharmaceutical active

was extracted and analyzed by High Performance Liquid Chromatography (HPLC) against an external standard to quantify the amount of active present in each individual dosage unit.

8. According to the inventive process set forth and claimed in the '080 Patent, and in accordance with FDA nomenclature, I have prepared tables shown as Appendices A, B and C, reflecting the uniformity of content of active of individual dosage units within particular lots and across different lots.

9. First, the uniformity of content of active in a lot is determined through establishing the amount of active ($A_{N(i)}$) actually present in each sampled individual dosage unit from the same lot (N) as determined by taking the difference between the amount of active in the sample with the most active ($Max_{LOT(N)}$) minus the amount of active in the sample with the least amount of active ($Min_{LOT(N)}$) and dividing the difference by the average amount of active in the lot samples ($Lot_{(N)}$ Sample Average). That is: $(Max_{LOT(N} - Min_{LOT(N)}) / ((A_{N(1)} + A_{N(2)} + + + A_{N(10)})/10)$. The results are shown in Appendix A.

10. Second, the uniformity of content across different lots is determined through establishing the amount of active actually present in each sampled individual dosage unit from all 73 lots and comparing that amount of active with a "target" or "desired" amount of active contained therein. The target amount of active, when it is a pharmaceutical, is referred to as the "Label Claim", thus identifying the amount of pharmaceutical active in the film to a user. The desired amount is 100% of the target amount. Each individual dosage unit film cut from any individual lot must have the desired content of pharmaceutical active, varying no more that 10% from the target or desired amount. See Appendix B.

IV. '080 Patent Process Produces Films With Required Uniformity of Content of Active

11. The results shown in the appendices establish that the resulting films produced by the inventive method of the '080 Patent as disclosed and claimed have the required uniformity of content based on analytical chemical testing. First, the amount of active varies by no more than 10% between individual dosage units sampled from a particular lot of resulting film. See Appendix A.

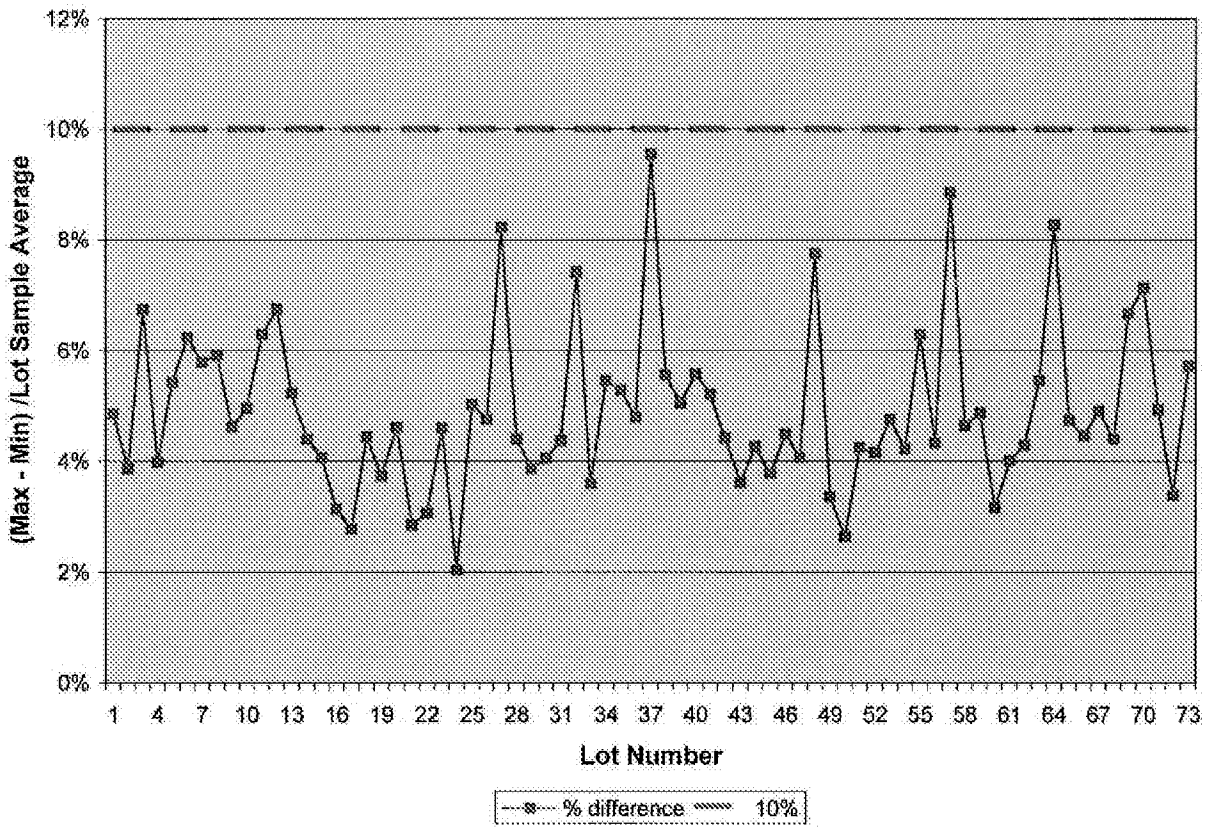
Second, the amount of active across different lots of resulting film varies no more than 10% from the desired amount of the active. See Appendix B. Finally, the uniformity of content of the 73 lots of resulting film meets even more stringent standards, for example, the data shows: (i) 46 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 5%; (ii) 15 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 4%; 4 lots of resulting film wherein the uniformity of content of active is shown with the amount of active varying by less than 3%; and 1 lot of resulting film wherein the uniformity of content of active is shown with the amount of active varying by only 2%. See Appendix C.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

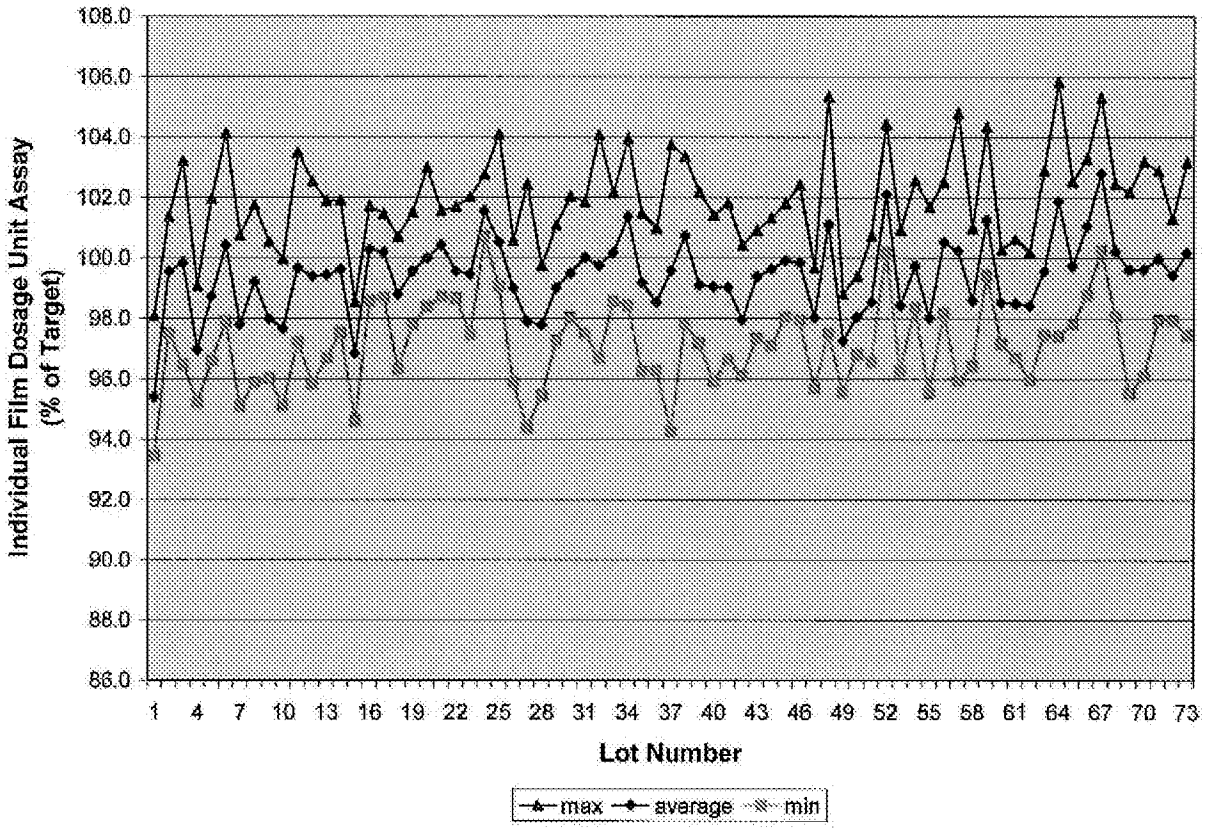
Dated this 13th day of March, 2013

B. Arlie Bogue

APPENDIX A



APPENDIX B



APPENDIX C

Lots less than 5%			lots 5% to 10%	
Lot #	% Difference		Lot #	% Difference
24	2.0%		10	5.0%
45	2.6%		25	5.0%
17	2.8%		39	5.0%
21	2.8%		41	5.2%
22	3.1%		13	5.2%
16	3.1%		35	5.3%
60	3.2%		5	5.4%
50	3.4%		63	5.5%
72	3.4%		34	5.5%
33	3.6%		38	5.6%
43	3.6%		40	5.6%
19	3.7%		73	5.7%
46	3.8%		7	5.8%
29	3.9%		8	5.9%
2	3.9%		6	6.2%
4	4.0%		11	6.3%
61	4.0%		55	6.3%
30	4.0%		69	6.7%
48	4.1%		3	6.7%
15	4.1%		12	6.7%
52	4.2%		70	7.1%
54	4.2%		32	7.4%
51	4.2%		49	7.8%
44	4.3%		27	8.2%
62	4.3%		64	8.3%
56	4.3%		57	8.9%
31	4.4%		37	9.5%
28	4.4%			
14	4.4%			
68	4.4%			
42	4.4%			
18	4.4%			
66	4.5%			
47	4.5%			
23	4.6%			
20	4.6%			
9	4.6%			
58	4.6%			
65	4.7%			
26	4.8%			
53	4.8%			
36	4.8%			
1	4.9%			
59	4.9%			
67	4.9%			
71	4.9%			
total	46		total	27

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF B. ARLIE BOGUE, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	March 13, 2013	M&E Docket:	117744-00023

Mail Stop Inter Partes Reexam
Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO on
March 13, 2013.
Signed: Michael I. Chakansky /Michael I Chakansky/

DECLARATION OF DAVID T. LIN, PH.D. UNDER 37 C.F.R. § 1.132

Madame:

I, David T. Lin, Ph.D. do hereby make the following declaration:

I. SUMMARY OF CREDENTIALS AND EXPERIENCE

1. Since January 2005, I have served as a Senior Consultant to Biologics Consulting Group, Inc. ("BCG"), a team of consultants who provide national and international regulatory and product development advice on the development and commercial production of small molecular weight synthetic drug, biotechnological and biological products.

2. While BCG is being paid for my time, I am not an employee of, nor do I have any financial interest in, MonoSol Rx, LLC ("Patentee" and/or "MonoSol").

3. Before joining BCG, I held various positions with the United States Food and Drug Administration ("FDA"). From 1997-2001, I was a Chemistry Reviewer in the Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research ("CDER"). In 2001, I became the Team Leader in the same Division and served in that role until 2003 when I was promoted to the position of acting Deputy Division Director in the Division of New Drug Chemistry III, Office of New Drug Chemistry (currently referred to as Office of New Drug Quality Assessment). In 2004, I was promoted to the position of acting Division Director.

4. As a Chemistry Reviewer at CDER, I was responsible for the comprehensive review of Chemistry, Manufacturing and Controls ("CMC") data for drugs being investigated during Phase 1, 2, and 3 clinical studies. I was also responsible for the review of CMC data in New Drug Applications and provided regulatory input to CMC reviewers responsible for review of Abbreviated New Drug Applications. This included providing scientific and regulatory guidance during development of small molecular weight drugs and biotechnological/biological drugs across a wide variety of dosage forms. I have reviewed CMC data submitted with respect to over 100 Investigational New Drug Applications and New Drug Applications (original and supplemental) as a chemistry reviewer, contributed to decisions regarding the approval of drugs, made presentations before scientific and regulatory conferences and participated in a variety of special FDA projects and committees, including serving as the co-Chair of the CMC Good Review Practices Committee.

5. As Team Leader, acting Deputy Division Director and acting Division Director in the Office of New Drug Chemistry, I was actively involved in directing the content of FDA guidances that pertained to CMC topics. As acting Deputy Division Director and Division Director, I was directly involved in discussions, regarding the content of the 2003 FDA draft guidance on Drug Product-Chemistry, Manufacturing, and Controls Information, with the committee responsible for writing this guidance. I had signatory authority for this draft guidance prior to public issuance by FDA. As acting Deputy Division Director and Division Director, I was involved in regular meetings with the supervisory staff in the Office of Generic Drugs to discuss regulatory and review policy issues that are common to both New Drug Applications and Abbreviated New Drug Applications.

6. I consider myself an expert in the fields of FDA practice and procedure as applicable to the testing requirements for drugs and review of Investigational New Drug Applications (INDs) and New Drug Applications (NDAs).

7. I received my B.A. in Biochemistry from the University of Pennsylvania in 1984, my Ph.D. in Organic Chemistry from the University of Maryland in 1989 and my M.B.A. from the University of Maryland's RH Smith School of Business in 2002. Attached hereto as Exhibit A is my curriculum vitae, including a list of my publications for the past ten years.

8. I have carefully reviewed Chen (WO 00/42992) ("Chen").

II. U.S. STATUTORY AND REGULATORY BACKGROUND FOR TESTING DRUGS FOR POTENCY AND DOSAGE UNITS FOR UNIFORMITY

9. From a US regulatory perspective, for a drug to be approved for commercial marketing and distribution, specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product must be provided in a New Drug Application.[1] In addition, reference to the current U.S. Pharmacopeia (USP) may satisfy these requirements.

10. Section 501(b) of the Food, Drug, and Cosmetic Act (the Act) deems an official drug (i.e., a drug represented as a drug which is recognized in the U.S. Pharmacopeia) to be adulterated if it fails to conform to compendial standards of quality, strength or purity. Compendial tests or assay methods are used when determining such conformance under 501(b); the standards are stated in individual monographs as well as portions of the General Notices section of the USP/NF. Standards and test methods have been established for such characteristics as potency and content uniformity.

11. Section 501(c) of the Act deems a drug that is not recognized in the USP to be adulterated if it fails to meet the strength, purity or quality which it is represented to possess.

[1] 21 CFR 314.50(d)(1)(ii)(a)

The applicable quality standards for a drug not recognized in the USP can be determined from such sources as the labeling of the drug (or drug product), the manufacturer's written specifications, and new drug applications.

12. The current good manufacturing practice (cGMP) regulations include the minimum requirements for the preparation of drug product for administration to humans. One of the requirements is that the strength[2] of the drug (active ingredient) in the drug product must be determined for each batch of drug product manufactured for commercial distribution.[3] Strength is taken to mean content or assay of the drug.

13. Batch uniformity of the drug products is ensured with procedures that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.[4] FDA also describes in guidance that it is expected the sampling plan for drug product is representative of the batch.[5]

14. Controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that the drug product conform to appropriate standards of identity, strength, quality, and purity.[6]

15. Regulatory specifications must be established to ensure that the dosage form will meet acceptable therapeutic and physicochemical standards throughout the shelf-life of the marketed product.[5] These specifications include tests for strength (content or assay) and uniformity of dosage units.

---

[2] 21 CFR 210.3(b)(16)

[3] 21 CFR 211.165(a)

[4] 21 CFR 211.110(a)

[5] FDA Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products, February 1987

[6] 21 CFR 211.160(b)

16. Testing to establish uniformity of dosage units is defined in the USP under the USP general chapter <905>.[7]

III. CHEN'S DISCLOSURE IS INSUFFICIENT

17. I have been asked to review Chen and render an opinion as to whether there is sufficient information contained within to allow regulatory FDA approval and commercialization of a drug product that is manufactured as described. After review of the patent in light of FDA practice and procedure, it is my opinion that there is insufficient disclosure to allow FDA to determine that a drug product as described can be manufactured for commercial distribution, manufactured in a consistent manner and meet specifications that will ensure the identity, strength, quality, purity, and potency of the drug product. In particular, Chen lacks any disclosure which would necessarily lead to the manufacture of films with uniformity of content (strength) of drug active required for FDA approval.

18. As would be required for FDA approval Chen does not disclose sufficient information that films containing drug can be produced consistently with respect to uniformity of content of the drug. No information was disclosed that demonstrated uniformity of content in the amounts of drug in individual dosage units. Chen discloses no specific test methods, and hence no test results, that could allow for the determination of the actual amount of drug (active) in individual dosage units.

19. As required for FDA approval, Chen's patent did not disclose sufficient information regarding the manufacturing process and process controls. The information disclosed by Chen would not ensure that films containing drug could be manufactured to meet specifications that ensure consistent strength.

20. Even if the information disclosed in Chen could be utilized to develop a manufacturing process for films containing drug, there is no information regarding the test methods that are necessary to determine the amount of drug in individual dosage units.

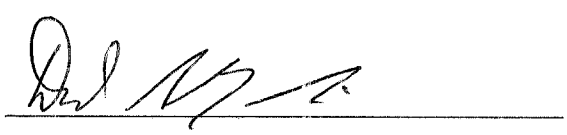
[7] USP General Chapter <905> Uniformity of Dosage Units

21. Therefore, Chen's disclosure is lacking, both explicitly and inherently, the disclosure necessary to provide for the manufacture of drug-containing films with the uniformity of content in amount of drug (active) in individual dosage units to make FDA approvable film products. It is my understanding that an inherent disclosure may not be established by probabilities or possibilities and that the mere fact that a certain thing may result from a given set of circumstances is not sufficient and that to be inherent requires that the missing disclosure is necessarily present.

22. Finally, Chen's patent discloses the release profiles of four active agents from films. See Chen, Figure 5. The release profile data presented in Figure 5 show a high degree of variability at each data point. For example, the release profile for nicotine containing film product show that the amount of nicotine released at the 5 minute and 8 minute time point can be as high as approximately 115-120%. This level of active agent is greater than the 110% level (from an expected amount of 100%) that is considered acceptable to FDA for regulatory approval of a product that purports to be manufactured consistently with acceptable content uniformity. These data indicate that the test method used in the analysis is not reproducible and/or there is a lack of active agent content uniformity between individual dosage units. These deficiencies demonstrate the lack of manufacturing consistency and lack of active agent content uniformity in the film.

23. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and. that such statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 13th day of March, 2013



David T. Lin

CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **DECLARATION OF DAVID T. LIN, PH.D. UNDER 37 C.F.R. § 1.132** has been served, by first class mail, on March 13, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

DANIELLE L. HERRITT
McCARTER & ENGLISH LLP
265 FRANKLIN STREET
BOSTON, MASSACHUSETTS 02110

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
Registration No.: 29,855
Attorney for the Patentee

EXHIBIT A

DAVID TSOCHUNG LIN

9121 Fall River Lane, Potomac, MD 20854 (301) 299-2853 dlin@bcg-usa.com

EXPERTISE

- 18+ years pharmaceutical regulatory experience.
  - 7+ years regulatory chemistry, manufacturing and controls (CMC) experience at CDER/FDA on small molecular-weight drugs, botanical drugs, peptide drugs, and protein drugs formulated in a broad range of sterile and non-sterile dosage forms.
  - 3+ years research experience at CBER/FDA.
  - 8+ years experience as regulatory CMC consultant.
- Unique combination of biologic/biotechnological and small molecular-weight drug regulatory experience, including device/drug and device/biologics combination products.
- Understanding of FDA regulatory requirements and expectations for drug development and marketing approval.
- Performed primary CMC review and assessment of drug products for treatment of reproductive and urologic disorders and diseases.
- Supervised CMC review activities in 7 CDER medical reviewing divisions including Reproductive/Urologic, Anti-viral, Dermatologic/Dental, Anti-inflammatory/ Analgesic/Ophthalmologic, Anti-infective, Special Pathogen/Immunologic, and Over-the-Counter drug products.
- Understanding of drug substance and drug product analytical method development and validation.
- Understanding of drug substance and drug product stability protocol development and stability data analysis.
- Understanding of current Good Manufacturing Practices (cGMPs)
- Experienced in chemical synthesis, small-scale and pilot-scale fermentation, biologics/ biotechnology, and protein chemistry.
- Experienced working in cross-functional teams (i.e., Pharmacology/toxicology, Clinical, Biostatistics, Biopharmaceutics, and Analytical).
- Ph.D. in Organic Chemistry; M.B.A. degree and training for managers.

EXPERIENCE

BIOLOGICS CONSULTING GROUP, INC. Alexandria, VA
January 2005 – Present
Senior Consultant

- Evaluate and provide advice on client CMC scientific and regulatory strategies for a wide range of therapeutic drug products (biologic and non-biologic) in dosage forms that include tablets, topicals, injectables, transdermals, implants, sprays, and inhalation, at all stages of product development, from pre-IND through post-NDA/BLA approval.
- Review and provide advice on IND and NDA/BLA submissions for suitability relative to FDA expectations for CMC data.
- Perform gap analysis audits for deficiencies relative to FDA expectations.
- Conduct regulatory and scientific due diligence audits for business acquisitions and licensing partnerships. Provide assessment of strengths and deficiencies.
- Represent clients in interactions with FDA.
- Prepare and write submissions to FDA, with focus on CMC sections.
- Represent client as FDA regulatory expert in legal proceedings.
- Advise clients on manufacturing contractor and vendor evaluation and selection.
- Provide management and technical oversight of contract manufacturing organizations (CMOs).
- Involved in business development to increase client base.
- Provide scientific and regulatory training and presentations at pharmaceutical/biopharmaceutical conferences.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, OFFICE OF NEW DRUG CHEMISTRY, DIVISION OF NEW DRUG CHEMISTRY III. Rockville, MD
July 2003 – December 2004
Division Director (acting) *March 2004 – December 2004*
Deputy Division Director (acting) *July 2003 – March 2004*

- Supervised 34 employees in 9 therapeutic product classes, includes 6 Team Leaders, review chemists and administrative staff. Responsible for employee work performance review and career development.
- Planned and set long-range plans and schedules for Division work. Directed and coordinated workload, and assured implementation of Division policies, goals and objectives.
- Evaluated budget and fiscal controls to manage Division functions.
- Made critical decisions and provided expert advice concerning regulatory, scientific and compliance approaches and options consistent with Office policies and objectives.
- Represented FDA in dealing and negotiating with the regulated industry, and professional and industry organizations.
- Participated as invited speaker at regulatory and scientific conferences on behalf of FDA.
- Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
October 2001-July 2003
Lead Chemist (Team Leader)

- Managed a team of 4 review chemists in 2 therapeutic product classes.
- Responsible for secondary review, consistency of CMC reviews and adherence to FDA/ONDC policies and guidances.
- Coordinated reviewers' workload of IND and NDA submissions to ensure that reviews were conducted in timely manner.
- Interacted extensively with the regulated industry to provide regulatory direction during IND drug development and NDA post-approval activities.
- Active in the development of FDA guidances for industry and internal good review practices. Served as the Chair of the Stability Guidance Technical Committee, Co-chair of the Conjugated Estrogens Working Group and Co-chair of the Good Review Practices Working Group.

FOOD & DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS. Rockville, MD
April 1997-October 2001
Chemistry Reviewer

- Evaluated the quality of new drug products submitted to the FDA for approval.
- Integral part of a cross-functional review team responsible for evaluating the quality and effectiveness of reproductive and urologic drug products being investigated in clinical studies.
- Major contributor to committees responsible for establishing drug product quality standards and publishing guidances for pharmaceutical companies.
- Provided regulatory guidance to pharmaceutical company representatives during drug development.
- Mentored new reviewers.
- Served as computer focal point to facilitate and troubleshoot computer issues.

FOOD & DRUG ADMINISTRATION, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, LABORATORY OF PARASITIC BIOLOGY AND BIOCHEMISTRY. Bethesda, MD
February 1994-April 1997
National Research Council Fellow

- Investigated the biological role of specific proteins in the sexual differentiation of the malaria parasite. Published three research papers in peer-reviewed journals.
- Presented research data at three separate scientific conferences.
- Supervised the research projects of college students.
- Responsible for the coordination of instrument repairs and the ordering of laboratory supplies.

GENERAL ELECTRIC CO., CORPORATE RESEARCH & DEVELOPMENT, BIOLOGICAL SCIENCES LABORATORY. Schenectady, NY
July 1989-January 1994
Staff Scientist

- Developed recombinant biphenyl-metabolizing microorganisms capable of degrading environmental contaminants. Marketed this technology to the GE business units and government agencies responsible for environmental clean-up.
- Investigated the factors affecting aerobic biodegradation of indigenous PCBs in Hudson River sediment by various bacterial strains.
- Isolated and conducted mechanistic studies of the dioxygenase enzymes involved in biodegradation.
- Investigated the scientific and economic feasibility of biologically synthesizing aromatic monomers for use as a feedstock to produce biodegradable polymers.
- Supervised research projects of summer interns.
- Published research in peer-reviewed journals.
- Recruited at major East Coast universities. Interviewed and screened graduating science Ph.D. students for second round interviews at the Research Center.

UNIVERSITY OF MARYLAND, Dept. of Chemistry/Biochemistry. College Park, MD
May 1985-May 1989
Research Assistant

- Investigated mechanism of action of two bacterial enzymes, mandelate racemase and D-amino acid oxidase.
- Synthesized and tested novel halogenated aromatic hydroxy- and amino- acid analogs as potential irreversible inhibitors.
- Published research in peer-reviewed journals and co-authored one chapter in a biotechnology book. In addition, the research data was presented at two national scientific conferences.
- Served as the computer expert for the laboratory group.

EDUCATION

ROBERT H. SMITH SCHOOL OF BUSINESS. College Park, MD
University of Maryland
Master of Business Administration (MBA), *2002*
Concentration: Finance

UNIVERSITY OF MARYLAND. College Park, MD
Department of Chemistry and Biochemistry
Ph. D. -- Organic Chemistry, *1989*
Research Advisor -- Dr. John W. Kozarich

UNIVERSITY OF PENNSYLVANIA. Philadelphia, PA
Bachelor of Arts with Honors – Biochemistry, *1984*
Dean's List, Phi Lambda Upsilon Chemical Honor Society

TRAINING

- Facilitation Skills, CDER/FDA (Fall 2002)
- Six Sigma Strategy and Methods, Univ. of MD (Summer 2002)
- Group Decision-Making Techniques, CDER/FDA (Feb. 2002)
- Managing Written Communications for Team Leaders, CDER/FDA (Spring 2002)
- Organizational Behavior and Human Resources, Univ. of MD (Fall 1999)
- Management of Human Resources, Univ. of MD (Fall 1999)
- Introduction to Drug Law and Regulation, CDER/FDA (Nov. 1998)
- Basic Statistical Methods, CDER/FDA (Fall 1998)

HONORS/AWARDS

- CDER's Team Excellence Award (Nov 2004)
- FDA's Group Recognition Award (May 2004)
- CDER's Special Recognition Award (Nov 2002)
- CDER's Team Excellence Award (Nov 2002)
- OPS/ONDC Special Recognition Award (Dec 2001)
- CDER's Team Excellence Award (Nov 2000)
- OPS/ONDC Special Recognition Award (Jun 2000)
- CDER's Excellence in Mentoring Award (Nov 1999)

PRESENTATIONS

- Conducting Effective & Compliant Stability Programs for Pharmaceuticals & Biologics, "Stability Studies During Development", "Stability of Biopharmaceuticals", "Development of Specifications for Biopharmaceuticals", and "Extractables, Leachables, and Particulates – Safety Concern for Biotechnology Products", Dubai, UAE (Sep 2012).
- 4th DIA China Annual Meeting, "ICH Guidelines Q1D, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products", and "Q1E, Evaluation of Stability Data", Shanghai, China (May 2012).
- IPA's Current Trends and Practices in Stability Testing, "Stability Testing Requirements for Biopharmaceutical Products", Montreal, Canada (Oct 2011)
- IPA's Current Trends and Practices in Stability Testing, "Stability Program for Combination Products", Montreal, Canada (Oct 2011)
- 3rd DIA China Annual Meeting, "Thinking About Comparability for Biosimilar Proteins", Beijing, China (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Stability Challenges for Combination Products", Boston, MA (May 2011).
- IPA's Current Trends and Practices in Stability Testing, "Country Specific Stability Requirements", Boston, MA (May 2011).
- Stability Programs Forum, "Stability Testing for Biotechnology/Biologic Products", Philadelphia, PA (Dec 2010).
- 11th Annual EuroTIDES/EuroPEPTIDES Conference, "Stability Considerations and Testing for Peptide-and Oligo-Based Therapeutics", Barcelona, Spain (Nov 2010).
- International Summit of China Pharmaceutical Industry, "FDA Requirements for Peptide Product Development: Considerations from Small Molecule and Biological Products", Hangzhou, China (Oct 2010).

- 7th Annual Method Validation Conference, "Ensure Method Validation Compliance through a Review of FDA Warning Letters", San Francisco, CA (Jul 2010).
- 6th Annual BioProcess International European Conference, "Extractables, Leachables and Particulates – Safety Concern for Biotechnology Products," Vienna, Austria (May 2010)
- ISPE-CSAC Meeting, "Biotechnological Drug Development and Interactions with CDER," Raleigh, NC (Oct 2009).
- Seminar on China International Bio-medicine Outsourcing Service, "Product Quality Issues with GLPs and GCPs," Hangzhou, China (Sep 2009).
- Informa Stability Testing for Biologics Conference, "Understanding Product Expiry and Shelf-Life," Prague, Czech Republic (Sep 2009).
- Informa Stability Testing for Biologics Conference Workshop, "Stability Testing Performed Over a Product Lifecycle," Prague, Czech Republic (Sep 2009).
- IVT Lab Compliance Conference, "Implement a Comprehensive and Compliant Stability Program," Philadelphia, PA (Aug 2009).
- OKBio ACCELERATE Workshop, "Product Development – Regulatory CMC Considerations," Oklahoma City, OK (Jun 2009).
- IVT Method Validation Conference, "Challenges in Understanding Impurities and Degradants for Biological/Biotechnological Products," San Francisco, CA (Oct 2008).
- IVT Method Validation Conference, "Strategies for Setting Biological Product Specifications," San Francisco, CA (Oct 2008).
- CBI 3rd Annual Stability Programs Conference, "Complex Stability Programs for Biologics," Philadelphia, PA (Jun 2008).
- IVT Lab Compliance Conference, "Stability Testing Fundamentals and Considerations in the Current Regulatory Environment," Baltimore, MD (Apr 2008).
- R&D Direction's 5th Annual Drug Development Summit, "Looking Forward in 2008: Regulatory Priorities and Considerations," Amelia Island, FL (Feb 2008).
- 2007 AAPS Annual Meeting, "Critical Stability Evaluation of Biopharmaceuticals During Clinical Development Stages," San Diego, CA (Nov 2007).
- 2007 DIA Annual Meeting, "The Impact of FDA's Quality by Design Initiative on Biologics Development," Atlanta, GA (Jun 2007).
- Institute for International Research: Formulation and Forced Degradation Strategies for Biomolecules, "Regulatory Requirements for Successful Product Development," San Diego, CA (Mar 2007).
- International Pharmaceutical Academy: Effective Management of Stability Programs, "Stability Design Considerations for Global Regulatory Filings," Toronto, Canada (Feb 2007).
- Cambridge Healthtech Institute's PepTalk: Optimizing Protein and Antibody Therapeutics, "Regulatory Considerations for the Development of Protein Therapeutic Products," San Diego, CA (Jan 2007).
- 2006 AAPS Annual Meeting, "The Impact of FDA Initiatives on the Development of Biological Products," San Antonio, TX (Nov 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "In-Use Testing of Biotechnological and Biologic Products," Boston, MA (Oct 2006).
- SWE Enterprises: Stability Testing for the FDA Regulated Industry, "Cost Efficient Design of Stability Studies," Boston, MA (Oct 2006).
- Institute for International Research: Chemistry Manufacturing & Controls, "Clarifying and Understanding ICH Guidance to Help Meet International Requirements for Submissions," Philadelphia, PA (July 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Cost Efficient Design of Stability Studies," San Diego, CA (June 2006).
- IVT Stability Testing: Implementing Effective Processes for Stability Program Development, "Stability Requirements for Global Regulatory Filings," San Diego, CA (June 2006).

- CBI Stability Programs: New Approaches to Test, Analyze and Document Data for Improved Program Design and Global Compliance, "In Use Testing of Biotechnological and Biological Products," Princeton, NJ (June 2006).
- IBC/TIDES: Oligonucleotide and Peptide Technology and Product Development, "Stability Considerations and Testing for Oligo- and Peptide-Based Therapeutics," Carlsbad, CA (May 2006).
- IBC Biopharm Manufacturing and Distribution Summit: Logistics for Biopharmaceutics, "Stability Studies to Support the Chain of Custody of Biotechnology Products," Reston, VA (Dec 2005).
- 2005 AAPS Annual Meeting: AAPS Short Course on Degradation and Stability in Small Molecule Active Pharmaceutical Ingredients/Stability Testing for Global Filings, "Stability Requirements for Global Regulatory Filings," Nashville, TN (Nov 2005).
- Therapeutic Strategies Against Neurodegenerative Conditions, "The Regulatory Product Development Process," Burlington, MA (Oct 2005).
- International Pharmaceutical Federation (FIP) Workshop: Harmonizing Clinical Trial GMP and Quality Requirements Across the EU and Beyond, "The US Investigational New Drug (IND) System," Noordwijk Zee, The Netherlands (Mar 2005).
- 2004 AAPS Annual Meeting, "Phase 2 and 3 IND CMC Guidance: FDA Perspective," Baltimore, MD (Nov 2004).
- 64th Annual World FIP Congress, "Clinical Trial Application Process – CMC: US FDA Perspective," New Orleans, LA (Sep 2004).
- AAPS Pharmaceutical Technologies 3rd Summer Conference: Optimizing the Global Clinical Trial Process, "IND Applications – FDA Perspective," Cherry Hill, NJ (Aug 2004).
- 2004 DIA Annual Meeting, "FDA Stability Guidance Update," Washington, DC (Jun 2004).
- DIA Meeting on CM&C/Regulatory and Technical Strategies, "Challenges and Opportunities in CMC Requirements for Phase 2-3," Bethesda, MD (Mar 2004).
- 2003 PDA Annual Meeting, "Draft FDA Stability Guidance," Atlanta, GA (Nov 2003).
- 2003 DIA Annual Meeting, "Product Quality of Non-clinical and Clinical Trial Materials," San Antonio, TX (Jun 2003).
- PARCS Meeting, "Managing CMC Requirements during IND," Irvine, CA (Apr 2003).
- PARCS Meeting, "Use of SUPAC Guidances during IND Development," Irvine, CA (Apr 2003).
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Electronic Patent Application Fee Transmittal

Application Number:	95002170
Filing Date:	10-Sep-2012
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Filer:	Stephen J. Brown
Attorney Docket Number:	117744-00023

Filed as Large Entity

inter partes reexam Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Inter Reexamination	1813	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**0**

Electronic Acknowledgement Receipt

EFS ID:	15215642
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	13-MAR-2013
Filing Date:	10-SEP-2012
Time Stamp:	23:15:29
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response after non-final action-owner timely	FINAL080REPLYTOOA.pdf	653223 8fc8f0e3f49f5bcf46d57581b8d7765071574da1	no	86

Warnings:	
Information:	

2	Response after non-final action-owner timely	Declarations.pdf	9066001 fa617de5bca4c8f01850c9912482145029fb095c	no	26
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30246 0f8873435e13b90bd937cd3b03eb008e2ed9e7c7	no	2
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			Total Files Size (in bytes):	9749470	

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/002,170	09/10/2012	7897080	117744-00023	6418

23869 7590 02/26/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
DIAMOND, ALAN D	

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
02/26/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

NOTICE RE DEFECTIVE PAPER IN INTER PARTES REEXAMINATION	Control No.	Patent Under Reexamination
	95/002,170	7897080
	Examiner	Art Unit
	Alan Diamond	3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

1. ☐ No proof of service is included with the paper filed by ☐ patent owner ☐ requester on _____. 37 CFR 1.248 and 1.903. Proof of service is required within a time period of 30-days or one month from the date of this letter, whichever is longer. Failure to serve the paper may result in the paper being refused consideration. If the failure to comply with this requirement results in a patent owner failure to file a timely and appropriate response to any Office action, the prosecution of the reexamination proceeding will be terminated under 37 CFR 1.957(b) or limited under 37 CFR 1.957(c) (as is appropriate for the case).

2. ☐ The paper filed on _____ by the ☐ patent owner ☐ requester is unsigned. A duplicate paper or ratification, properly signed, is required within a time period of 30-days or one month from the date of this letter, whichever is longer. Failure to comply with this requirement will result in the paper not being considered. If the failure to comply results in a patent owner failure to file a timely and appropriate response to any Office action, the prosecution of the reexamination proceeding will be terminated under 37 CFR 1.957(b) or limited under 37 CFR 1.957(c) (as is appropriate for the case).

3. ☐ The paper filed on _____ by the ☐ patent owner ☐ requester is signed by _____ who is not of record. A ratification or a new power of attorney with a ratification, or a duplicate paper signed by a person of record, is required within a time period of 30-days or one month from the date of this letter, whichever is longer. Failure to comply with this requirement will result in the paper not being considered. If the failure to comply results in a patent owner failure to file a timely and appropriate response to any Office action, the prosecution of the reexamination proceeding will be terminated under 37 CFR 1.957(b) or limited under 37 CFR 1.957(c) (as is appropriate for the case).

4. ☐ The amendment filed by patent owner on _____, does not comply with 37 CFR 1.530. Patent owner is given a time period of 30-days or one month from the date of this letter, whichever is longer, to correct this informality, or the prosecution of the reexamination proceeding will be terminated under 37 CFR 1.957(b) or limited under 37 CFR 1.957(c) (as is appropriate for the case). The amendment will not be entered, although the argument the rein will be considered as it applies to the proceeding without the amendment should the prosecution be limited under 37 CFR 1.957(c).

5. ☐ The amendment filed by patent owner on _____, does not comply with 37 CFR ☐1.20(c)(3) and/or ☐1.20(c)(4), as to excess claim fees. Patent owner is given a time period of 30-days or one month from the date of this letter, whichever is longer, to correct this fee deficiency, or the prosecution of the reexamination proceeding will be terminated under 37 CFR 1.957(b) or limited under 37 CFR 1.957(c) (as is appropriate for the case), to effect the "abandonment" set forth in 37 CFR 1.20(c)(5).

6. ☒ Other: See attached page.

/Alan Diamond/
Patent Reexamination Specialist
Central Reexamination Unit 3991

NOTE: PATENT OWNER EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.956. NO EXTENSION OF TIME IS PERMITTED FOR THIRD PARTY REQUESTER. 35 U.S.C. § 314(b)(2).

All correspondence relating to this *inter partes* reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

With respect to item No. 6, the response filed by patent owner on 01/29/2013 does not comply with 37 CFR 1.943, which requires that responses by patent owner shall not exceed 50 pages, excluding amendments, appendices of claims and reference materials such as prior art references. In particular, the total page count is 56 pages, which includes 52 pages of Remarks (i.e., pages 79-130) and pages 1-4 of the Declaration by Gerald Fuller (Fuller Declaration). The Fuller Declaration is directed to Dr. Fuller's opinion and thus, is counted towards the page count. The Declaration of B. Arlie Bogue is not counted towards the 50-page limit since it is directed to experimental results. Patent owner is required to exercise one of the following two options: (A) submit a re-drafted response that does not exceed the page limit set by 37 CFR 1.943; or (B) file a copy of the supplemental response with pages redacted to satisfy the 37 CFR 1.943 page limit requirement. Patent Owner is given a time period of 15-DAYS from the date of this letter to file the response. If no response is received, the improper patent owner submission will NOT be considered. See MPEP 2667(I)(A)(2).

Transmittal of Communication to Third Party Requester *Inter Partes* Reexamination	Control No.	Patent Under Reexamination	
	95/002,170	7897080	
	Examiner	Art Unit	
	Alan Diamond	3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address. --

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Danielle L. Herritt
McCarter & English LLP
265 Franklin Street
Boston, MA 02110

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above-identified reexamination proceeding. 37 CFR 1.903.

Prior to the filing of a Notice of Appeal, each time the patent owner responds to this communication, the third party requester of the *inter partes* reexamination may once file written comments within a period of 30 days from the date of service of the patent owner's response. This 30-day time period is statutory (35 U.S.C. 314(b)(2)), and, as such, it cannot be extended. See also 37 CFR 1.947.

If an *ex parte* reexamination has been merged with the *inter partes* reexamination, no responsive submission by any *ex parte* third party requester is permitted.

All correspondence relating to this inter partes reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of the communication enclosed with this transmittal.

PTO/SB/08a (03-08)
Approved for use through 07/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4515162		1985-05-07	Yamamoto et al	
	2	4517173		1985-05-14	Kizawa et al	
	3	4529601		1985-07-16	Broberg et al	
	4	4529748		1985-07-16	Wienecke	
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	7	4593053		1986-06-03	Jevne et al	
	8	4608249		1986-08-26	Otsuka et al	

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	Attorney Docket Number	1199-26 RCE/CON/REX

	9	4615697		1986-10-07	Robinson	
	10	4623394		1986-11-18	Nakamura et al	
	11	4652060		1987-03-24	Miyake	
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	14	4695465		1987-09-22	Kigasawa et al	
	15	4704119		1987-11-03	Shaw et al	
	16	4713239		1987-12-15	Babaian et al	
	17	4713243		1987-12-15	Schiraldi et al	
	18	4722761		1988-02-02	Cartmell et al	
	19	4740365		1988-04-26	Yukimatsu et al	

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	20	5028632		1991-07-02	Fuisz	
	21	4748022		1988-05-31	Busciglio	
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	31	4888354		1989-12-19	Chang et al	
	32	4894232		1990-01-16	Reul et al	
	33	4900552		1990-02-13	Sanvordeker et al	
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	41	4937078		1990-06-26	Mezei et al	

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	42	4940587		1990-07-10	Jenkins et al	
	43	4948580		1990-08-14	Browning	
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	46	4981693		1991-01-01	Higashi et al	
	47	4981875		1991-01-01	Leusner et al	
	48	5023082		1991-06-11	Friedman et al	
	49	5024701		1991-06-18	Desmarais	
	50	6488963		2002-12-03	McGinity et al.	

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
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	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	1	20050037055		2005-02-17	Yang et al.	

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	0191721	WO	A2	2001-12-06	A.E. Staley Manufacturing Co.		☐
	2	0170194	WO	A1	2001-09-27	Warner-Lambert Company		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Application Number	95002170
Filing Date	2012-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola, Jr.	Registration Number	29,855

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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Electronic Acknowledgement Receipt

EFS ID:	14825739
Application Number:	95002170
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First Named Inventor/Applicant Name:	7897080
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
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Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Madam:

This Information Disclosure Statement is being submitted pursuant to 37 C.F.R. 1.98, and identifies a number of patents and publication that may be considered relevant. The Patent Holder makes no representation as to the relevance of these documents, but wishes to make these references of record in this reexamination. Consideration of the references recited herein is requested.

If any fee is due with this submission, the Commission is authorized to charge any such fee to Deposit Account No. 08-2461. Should the Examiner have any questions regarding this submission, the undersigned would be pleased to address them.

Respectfully submitted,

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CERTIFICATE OF FIRST CLASS SERVICE

It is certified that a copy of this **INFORMATION DISCLOSURE STATEMENT** has been served, by first class mail, on January 29, 2013, in its entirety on the third party requester as provided in 37 CFR § 1.903 and 37 CFR § 1.248 at the addess below.

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(54) Title: FAST DISSOLVING ORALLY CONSUMABLE FILMS CONTAINING AN ION EXCHANGE RESIN AS A TASTE MASKING AGENT

(57) Abstract: Physiologically acceptable films, including edible films, are disclosed. The films include a water soluble film-forming polymer, such as pullulan, and a taste masked pharmaceutically active agent, such as dextromethorphan. The taste masking agent is preferably a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene, such as AMBERLITE. Methods for producing the films are also disclosed.

FAST DISSOLVING ORALLY CONSUMABLE FILMS CONTAINING AN ION EXCHANGE RESIN AS A TASTE MASKING AGENT

SPECIFICATION

FIELD OF THE INVENTION

This invention relates to fast dissolving orally consumable films containing an agent to mask the taste of a pharmaceutically active agent therein, and more specifically to such films containing an ion exchange resin as the taste masking agent.

BACKGROUND OF THE INVENTION

It has been known to administer pharmaceutically active agents in an edible film vehicle.

For example, WO 99/17753 discloses rapidly dissolving films for delivery of drugs to be adsorbed in the digestive tract.

WO 98/26780 discloses a flat, foil, paper or wafer type presentation for the application and release of active substances in the buccal cavity. The specific active ingredient disclosed in WO 98/26780 is buprenorphine.

WO 98/20862 discloses a film for use in the oral cavity that can contain a cosmetic or pharmaceutical active substance.

WO 98/26763 discloses a flat, foil, paper or wafer like presentation for release of active substances into the buccal cavity. The particular active disclosed is apomorphine.

U.S. Patent Application No. 09/395,104 also discloses the delivery of pharmaceutical agents in a edible film vehicle.

U.S. Patent No. 5,411,945 to Ozaki et al. discloses a pullulan binder and products produced therewith, including edible films (Example B-2). The products can include a variety of ingredients in addition to pullulan, such as other polysaccharides, antibacterial agents, flavor-imparting agents and pharmaceutically active substances (column 4, lines 5-15).

U.S. Patent No. 3,784,390 Hijiya et al. discloses pullulan films and their use in coating and packing materials for foods, pharmaceuticals and other oxygen sensitive materials. All of the examples in this patent teach mixing pullulan in hot water.

It has also been known to combine ion exchange resins with pharmaceutically active agents to provide sustained release formulations.

For example, U.S. Patent No. 6,001,392 to Wen et al. discloses a controlled-release syrup suspension for oral administration containing dextromethorphan adsorbed to a polystyrene sulfonate ion exchange resin. Pharmaceutical films are not disclosed.

U.S. Patent No. 5,980,882 to Eichman discloses a method for improving the stability of a pharmaceutical composition that contains a drug-resin complex, comprising adding a chelating agent in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex. Although Eichman teaches that complexing a drug with an ion exchange resin can mask the taste of the drug. Pharmaceutical films are not disclosed.

The inventors are not aware of any suggestion in the published art that ion exchange resins can act as taste masking agents in a fast dissolving orally consumable film. Accordingly, an object of this invention is to provide fast dissolving orally consumable films containing an ion exchange resin to mask the taste of a pharmaceutically active agent therein.

All references cited herein are incorporated herein by reference in their entireties.

SUMMARY OF THE INVENTION

The invention provides a consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein the film comprises at least one water soluble polymer, at least one pharmaceutically active agent and at least one taste masking agent.

Also provided is a method for preparing the consumable film of the invention, comprising:

dissolving water-soluble ingredients in water to provide an aqueous solution;

mixing at least one water soluble film former and at least one stabilizing agent to provide a film-forming mixture;

combining the film-forming mixture and the aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

adding the oil mixture to the hydrated polymer gel and mixing to provide a uniform gel;

casting the uniform gel on a substrate; and

drying the cast gel to provide the film.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention provides a physiologically acceptable film that is particularly well adapted to adhere to and dissolve in a mouth of a consumer to deliver a pharmaceutically active agent. Preferred films according to the invention comprise a pharmaceutically active agent, an ion exchange resin, a film-forming agent, and at least one of the following additional ingredients: water, antimicrobial agents, plasticizing agents, flavoring agents, saliva stimulating agents, cooling agents, surfactants, stabilizing agents, emulsifying agents, thickening agents, binding agents, coloring agents, sweeteners, fragrances, triglycerides, preservatives, polyethylene oxides, propylene glycol, and the like.

The expression "physiologically acceptable" as used herein is intended to encompass compounds, which upon administration to a patient, are adequately tolerated without causing undue negative side effects. The expression encompasses edible compounds.

The expression "pharmaceutically active agents" as used herein is intended to encompass agents other than foods, which promote a structural and/or functional change in and/or on bodies to which they have been administered. These agents are not particularly limited; however, they should be physiologically acceptable and compatible with the film. Suitable pharmaceutically active agents include, but are not limited to:

A. antimicrobial agents, such as triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA, and the like;

B. non-steroidal anti-inflammatory drugs, such as aspirin, acetaminophen, ibuprofen, ketoprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and the like;

C. anti-tussives, such as benzonatate, caramiphen edisylate, menthol, dextromethorphan hydrobromide, chlophedianol hydrochloride, and the like;

D. decongestants, such as pseudoephedrine hydrochloride, phenylepherine, phenylpropanolamine, pseudoephedrine sulfate, and the like;

E. anti-histamines, such as brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenylpyraline hydrochloride, azatadine meleate, diphenhydramine citrate, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride, acrivastine, loratadine, brompheniramine, dexbrompheniramine, and the like;

F. expectorants, such as guaifenesin, ipecac, potassium iodide, terpin hydrate, and the like;

G. anti-diarrheals, such a loperamide, and the like;

H. H_2-antagonists, such as famotidine, ranitidine, and the like;

I. proton pump inhibitors, such as omeprazole, lansoprazole, and the like;

J. general nonselective CNS depressants, such as aliphatic alcohols, barbiturates and the like;

K. general nonselective CNS stimulants such as caffeine, nicotine, strychnine, picrotoxin, pentylenetetrazol and the like;

L. drugs that selectively modify CNS function, such as phenyhydantoin, phenobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phensuximide, trimethadione, diazepam, benzodiazepines, phenacemide, pheneturide, acetazolamide, sulthiame, bromide, and the like;

M. antiparkinsonism drugs such as levodopa, amantadine and the like;

N. narcotic-analgesics such as morphine, heroin, hydromorphone, metopon, oxymorphone, levorphanol, codeine, hydrocodone, xycodone, nalorphine, naloxone, naltrexone and the like;

O. analgesic-antipyretics such as salycilates, phenylbutazone, indomethacin, phenacetin and the like; and

P. psychopharmacological drugs such as chlorpromazine, methotrimeprazine, haloperidol, clozapine, reserpine, imipramine, tranylcypromine, phenelzine, lithium and the like.

The amount of pharmaceutically active agent that can be used in the rapidly dissolving films, according to the present invention, is dependent upon the dose needed to provide an effective amount of the pharmaceutically active agent. Examples of doses for specific pharmaceutically active agents that can be delivered per one strip of rapidly dissolving oral film are reviewed in Table A.

TABLE A

PHARMACEUTICALLY ACTIVE AGENT	PREFERRED DOSE
Chlorpheniramine Maleate	4 mg.
Brompheniramine Maleate	4 mg.
Dexchlorpheniramine	2 mg.
Dexbrompheniramine	2 mg.
Triprolidine Hydrochloride	2.5 mg.
Acrivastine	8 mg.
Azatadine Maleate	1 mg.
Loratidine	10 mg.
Phenylephrine Hydrochloride	10 mg.
Dextromethorphan Hydrobromide	10-30 mg.
Ketoprofen	12.5-25 mg.
Sumatriptan Succinate	35 - 70 mg.
Zolmitriptan	2.5 mg.
Loperamide	2 mg.
Famotidine	10 mg.
Nicotine	2 mg.
Diphenhydramine Hydrochloride	12.5-25 mg.
Pseudoephedrine Hydrochloride	30 mg.

Ion exchange resins preferred for use in the films of the invention are water-insoluble and consist of a pharmacologically inert organic or inorganic matrix containing covalently bound functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene), or partially synthetic (e.g., modified cellulose and dextrans). The inorganic matrix can also be, e.g., silica gel modified by the addition of ionic groups. The covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., quaternary ammonium), weakly basic (e.g., primary amine), or a combination of acidic and basic groups. In general, those types of ion exchangers suitable for use in ion exchange chromatography and for such applications as deionization of water are suitable for use in these

controlled release drug preparations. Such ion exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp. 312-343). The ion exchange resins useful in the present invention have exchange capacities below about 6 milliequivalents per gram (meq/g) and preferably below about 5.5 meq/g.

The resin is crosslinked with a crosslinking agent selected from difunctional compounds capable of crosslinking polystyrenes; these are commonly known in the art. Preferably, the crosslinking agent is a divinyl or polyvinyl compound. Most preferably the crosslinking agent is divinylbenzene. The resin is crosslinked to an extent of about 3 to about 20%, preferably about 4 to about 16%, more preferably about 6 to about 10%, and most preferably about 8% by weight based on the total resin. The resin is crosslinked with the crosslinking agent by means well known in the art.

The size of the ion exchange resins should preferably fall within the range of about 20 to about 200 micrometers. Particle sizes substantially below the lower limit are difficult to handle in all steps of the processing. Particle sizes substantially above the upper limit, e.g., commercially available ion exchange resins having a spherical shape and diameters up to about 1000 micrometers, are gritty in liquid dosage forms and have a greater tendency to fracture when subjected to drying-hydrating cycles.

Representative resins useful in this invention include AMBERLITE IRP-69 (obtained from Rohm and Haas) and Dow XYS-40010.00 (obtained from The Dow Chemical Company). Both are sulfonated polymers composed of polystyrene cross-linked with 8% of divinylbenzene, with an ion exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H+-form). Their essential difference is in physical form. AMBERLITE IRP-69 comprises irregularly-shaped particles with a size range of 47 to 149 micrometers, produced by milling the parent, large-sized spheres of AMBERLITE IRP-120. The Dow XYS-40010.00 product comprises spherical particles with a size

range of 45 to 150 micrometers. Another useful exchange resin, Dow XYS-40013.00, is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group; its exchange capacity is normally within the range of approximately 3 to 4 meq/g of dry resin.

The most preferred resin is AMBERLITE IRP-69. However, in less preferred embodiments, the taste masking agent need not be an ion exchange resin. In these embodiments, the taste masking agent can be, e.g., magnesium trisilicate. See, e.g., U.S. Patents Nos. 4,650,663 and 4,581,232 to Peters et al. Taste can also be masked by polymers, such as EUDRAGIT E (Rohm and Haas), and/or cellulosics, such as ethylcellulose, and the like.

The film-forming agent used in the films according to the present invention can be selected from the group consisting of pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof. A preferred film former is pullulan, in amounts ranging from about 0.01 to about 99 wt%, preferably about 30 to about 80 wt%, more preferably from about 45 to about 70 wt% of the film and even more preferably from about 60 to about 65 wt% of the film.

Unless specified otherwise, the term "wt%" as used herein with reference to the final product (i.e., the film, as opposed to the formulation used to create it), denotes the percentage of the total dry weight contributed by the subject ingredient. This theoretical value can differ from the experimental

value, because in practice, the film typically retains some of the water and/or ethanol used in preparation.

In embodiments containing relatively high oil content, it is preferable to avoid substantial amounts of humectant in the film (and more preferable to have no humectant in the film), so as to avoid producing an overly moist, self-adhering film. In particular, it is preferred to formulate high oil content films with a plasticizing agent other than glycerin, which is also a humectant, and with a sweetener other than sorbitol, which is a mild humectant.

Saliva stimulating agents can also be added to the films according to the present invention. Useful saliva stimulating agents are those disclosed in U.S. Patent No. 4,820,506. Saliva stimulating agents include food acids such as citric, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acids. Preferred food acids are citric, malic and ascorbic acids. The amount of saliva stimulating agents in the film is from about 0.01 to about 12 wt%, preferably about 1 wt% to about 10 wt%, even more preferably about 2.5 wt% to about 6 wt%.

Preferred plasticizing agents include triacetin in amounts ranging from about 0 to about 20 wt%, preferably about 0 to about 2 wt%. Other suitable plasticizing agents include monoacetin and diacetin.

Preferred cooling agents include monomenthyl succinate, in amounts ranging from about 0.001 to about 2.0 wt%, preferably about 0.2 to about 0.4 wt%. A monomenthyl succinate containing cooling agent is available from Mane, Inc. Other suitable cooling agents include WS3, WS23, Ultracool II and the like.

Preferred surfactants include mono and diglycerides of fatty acids and polyoxyethylene sorbitol esters, such as, Atmos 300 and Polysorbate 80. The surfactant can be added in amounts ranging from about 0.5 to about 15 wt%, preferably about 1 to about 5 wt% of the film. Other suitable surfactants

include pluronic acid, sodium lauryl sulfate, and the like.

Preferred stabilizing agents include xanthan gum, locust bean gum and carrageenan, in amounts ranging from about 0 to about 10 wt%, preferably about 0.1 to about 2 wt% of the film. Other suitable stabilizing agents include guar gum and the like.

Preferred emulsifying agents include triethanolamine stearate, quaternary ammonium compounds, acacia, gelatin, lecithin, bentonite, veegum, and the like, in amounts ranging from about 0 to about 5 wt%, preferably about 0.01 to about 0.7 wt% of the film.

Preferred thickening agents include methylcellulose, carboxyl methylcellulose, and the like, in amounts ranging from about 0 to about 20 wt%, preferably about 0.01 to about 5 wt%.

Preferred binding agents include starch, in amounts ranging from about 0 to about 10 wt%, preferably about 0.01 to about 2 wt% of the film.

Suitable sweeteners that can be included are those well known in the art, including both natural and artificial sweeteners. Suitable sweeteners include, e.g.:

A. water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, and glycyrrhizin;

B. water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2, 2-dioxide, the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (acesulfame-K), the free acid form of saccharin,

and the like;

C. dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame) and materials described in U.S. Pat. No. 3,492,131, L- alpha-aspartyl-N-(2,2,4,4--tetramethyl-3-thietanyl)-D-alaninamide hydrate, methyl esters of L-aspartyl-L-phenylglycerin and L-aspartyl-L-2,5,dihydrophenyl-glycine, L-aspartyl-2,5-dihydro- L-phenylalanine, L-aspartyl-L-(1-cyclohexyen)-alanine, and the like;

D. water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as a chlorinated derivative of ordinary sugar (sucrose), known, for example, under the product description of sucralose; and

E. protein based sweeteners such as thaumatoccous danielli (Thaumatin I and II).

In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with the sweetener selected. This amount will normally be 0.01 % to about 10 % by weight of the composition when using an easily extractable sweetener. The water-soluble sweeteners described in category A above, are usually used in amounts of about 0.01 to about 10 wt%, and preferably in amounts of about 2 to about 5 wt%. Some of the sweeteners in category A (e.g., glycyrrhizin) can be used in amounts set forth for categories B-E below due to the sweeteners' known sweetening ability. In contrast, the sweeteners described in categories B-E are generally used in amounts of about 0.01 to about 10 wt%, with about 2 to about 8 wt% being preferred and about 3 to about 6 wt% being most preferred. These amounts may be used to achieve a desired level of sweetness independent from the flavor level achieved from any optional flavor oils used. Of course, sweeteners need not be added to films intended for non-oral administration.

The flavorings that can be used include those known to the skilled artisan, such as natural and artificial flavors. These flavorings may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Representative flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also useful are artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. These flavorings can be used individually or in admixture. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in admixture. Flavorings such as aldehydes and esters including cinnamyl acetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and so forth may also be used. Generally, any flavoring or food additive, such as those described in Chemicals Used in Food Processing, publication 1274 by the National Academy of Sciences, pages 63-258, may be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamic aldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral, i.e. beta citral (lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream); heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter, cheese); valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal (citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits); aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla);

2,6-dimethyl- 5-heptenal, i.e. melonal (melon); 2-6-dimethyloctanal (green fruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

The amount of flavoring employed is normally a matter of preference subject to such factors as flavor type, individual flavor, and strength desired. Thus, the amount may be varied in order to obtain the result desired in the final product. Such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In general, amounts of about 0.1 to about 30 wt% are useable with amounts of about 2 to about 25 wt% being preferred and amounts from about 8 to about 10 wt% are more preferred.

The compositions of this invention can also contain coloring agents or colorants. The coloring agents are used in amounts effective to produce the desired color. The coloring agents useful in the present invention, include pigments such as titanium dioxide, which may be incorporated in amounts of up to about 5 wt%, and preferably less than about 1 wt%. Colorants can also include natural food colors and dyes suitable for food, drug and cosmetic applications. These colorants are known as FD&C dyes and lakes. The materials acceptable for the foregoing spectrum of use are preferably water-soluble, and include FD&C Blue No. 2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye known as Green No. 3 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-N-ethyl-p-sulfobenzylamino) diphenyl-methylene]-[1-N-ethyl-N-p-sulfonium benzyl)-2,5-cyclo-hexadienimine]. A full recitation of all FD&C and D&C dyes and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, Volume 5, Pages 857-884, which text is accordingly incorporated herein by reference.

The films can also include a triglyceride. Examples of triglycerides include vegetable oils such as corn oil, sunflower oil, peanut oil, olive oil,

canola oil, soybean oil and mixtures thereof. A preferred triglyceride is olive oil. The triglyceride is added to the film in amounts from about 0.1 wt% to about 12 wt%, preferably in a range from about 0.5 wt% to about 9 wt%, of the film.

The films can include a preservative in amounts from about 0.001 wt% to about 5 wt%, preferably from about 0.01 wt% to about 1 wt% of the film. Preferred preservatives include sodium benzoate and potassium sorbate. Other suitable preservatives include, but are not limited to, salts of edetate (also known as salts of ethylenediaminetetraacetic acid, or EDTA, such as disodium EDTA) and parabens (e.g., methyl, ethyl, propyl or butyl-hydroxybenzoates, etc.) or sorbic acid. The preservatives listed above are exemplary, but each preservative must be evaluated on an empirical basis, in each formulation, to assure the compatibility and efficacy of the preservative. Methods for evaluating the efficacy of preservatives in pharmaceutical formulations are known to those skilled in the art.

The films can also include a polyethylene oxide compound. The molecular weight of the polyethylene oxide compound ranges from about 50,000 to about 6,000,000. A preferred polyethylene oxide compound is N-10 available from Union Carbide Corporation. The polyethylene oxide compound is added in amounts from about 0.1 wt% to about 5 wt%, preferably from about 0.2 wt% to about 4.0 wt% of the film.

The films can also include propylene glycol. The propylene glycol is added in amounts from about 1 wt% to about 20 wt%, preferably from about 5 wt% to about 15 wt% of the film.

Methods for preparing films according to the invention are capable of encapsulating the oil ingredients within the film-forming matrix and maintaining the integrity of the film, even when the film contains oils in amounts of 10 wt% or more.

In certain methods for preparing films according to the invention, the film-forming ingredients are mixed and hydrated with water separately from the water-soluble ingredients, which are mixed in aqueous solution separately from the organic ingredients and surfactants. In these methods, the final formulation is preferably produced by mixing the film-forming phase with the aqueous phase, then mixing in the organic phase, which includes surfactants, such as Polysorbate 80 and Atmos 300. This mass is mixed until emulsified. In other embodiments, the aqueous and film forming phases are combined into a single phase by dissolving the water soluble ingredients in the water and then adding the gums to hydrate. The organic phase is then added to this single aqueous phase.

The resulting formulation is cast on a suitable substrate and dried to form a film. The film is preferably air-dried or dried under warm air and cut to a desired dimension, packaged and stored. The film can contain from about 0.1% to about 10 wt% moisture, preferably from about 3 % to about 8 wt% moisture, even more preferably from about 4 to about 7 wt% moisture.

The film-forming phase can include pullulan and stabilizing agents such as xanthan gum, locust bean gum and carrageenan. These ingredients are mixed and then hydrated in water for about 30 to about 48 hours to form a gel. The water is preferably heated to a temperature of about 25 to about 45°C to promote hydration. The amount of water is about 40 to 80% of the gel. The resulting hydrated gel is then chilled to a temperature of about 20 to about 30°C for about 1 to about 48 hours. The water is preferably deionized.

In preferred embodiments, the aqueous phase includes water heated to a temperature of about 60 to 90°C, preferably 70 to 80°C, and ingredients such as the pharmaceutically active agent, ion exchange resin (or other masking agent), coloring agent, preservative and sweetener. The water is preferably deionized and the amount of water used is about 5 to about 80 wt% of the final gel

mixture.

The pharmaceutically active agent is sorbed to the ion exchange resin (or other masking agent) without separating ion exchanged pharmaceutically active agent from unexchanged agent and counter ion salts.

Adsorption of the pharmaceutically active agent onto the ion exchange resin particles to form the pharmaceutically active agent/resin complex is a well known technique as shown in U.S. Pat. Nos. 2,990,332 and 4,221,778. In general, the pharmaceutically active agent is mixed with an aqueous suspension of the resin, and in less preferred embodiments, the complex is then washed and dried. Adsorption of pharmaceutically active agent onto the resin may be detected by measuring a change in the pH of the reaction medium, or by measuring a change in concentration of sodium or pharmaceutically active agent.

Binding of pharmaceutically active agent to resin can be accomplished according to four general reactions. In the case of a basic pharmaceutically active agent, these are: (a) resin (Na-form) plus pharmaceutically active agent (salt form); (b) resin (Na-form) plus pharmaceutically active agent (as free base); (c) resin (H-form) plus pharmaceutically active agent (salt form); and (d) resin (H-form) plus pharmaceutically active agent (as free base). All of these reactions except (d) have cationic byproducts, by competing with the cationic pharmaceutically active agent for binding sites on the resin, reduce the amount of pharmaceutically active agent bound at equilibrium. For basic pharmaceutically active agents, stoichiometric binding of pharmaceutically active agent to resin is accomplished only through reaction (d).

Four analogous binding reactions can be carried out for binding an acidic pharmaceutically active agent to an anion exchange resin. These are: (a) resin (Cl--form) plus pharmaceutically active agent (salt form); (b) resin (Cl--form) plus pharmaceutically active agent (as free acid); (c) resin

(OH--form) plus pharmaceutically active agent (salt form); and (d) resin (OH--form) plus pharmaceutically active agent (as free acid). All of these reactions except (d) have ionic by-products and the anions generated when the reactions occur compete with the anionic pharmaceutically active agent for binding sites on the resin with the result that reduced levels of pharmaceutically active agent are bound at equilibrium. For acidic pharmaceutically active agents, stoichiometric binding of pharmaceutically active agent to resin is accomplished only through reaction (d). The binding may be performed, for example, as a batch or column process, as is known in the art.

In less preferred embodiments, the adsorption complex, including pharmaceutically active agent and resin, is collected and washed with ethanol and/or water to insure removal of any unadsorbed pharmaceutically active agent. The complexes are usually air-dried in trays at room or elevated temperature.

The ratio of the pharmaceutically active agent adsorbate to ion exchange resin adsorbent in the adsorption complex is about 1:3 to about 3:1, preferably about 1:2 to about 2:1, most preferably about 1:1. The only limit to using ratios in excess of 1:3 is an economic and aesthetic one.

The amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 25 to about 75% by weight of the pharmaceutically active agent/resin adsorption complex (hereinafter referred to as the "pharmaceutically active agent/resin complex" or "complex"). More preferably, the amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 33 to about 77% by weight of the pharmaceutically active agent/resin complex. Most preferably, the amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 40 to about 60% by weight of the pharmaceutically active agent/resin complex.

The amount of pharmaceutically active agent/resin complex in the formulation is adjusted to deliver a predetermined dose of the pharmaceutically active agent over a predetermined period of time.

For example, a preferred antitussive film of the invention is administered at one dose every 12 hours to deliver a pharmaceutically effective amount of dextromethorphan over a period of approximately 12 hours to a patient in need of such administration. A typical adult dose of a film of the invention measuring 1" x 1.25" (2.54 cm x 3.18 cm) weighs about 60 to about 190 mg and contains about 20 to about 130 mg of pharmaceutically active agent/resin complex to deliver about 5 to about 65 mg of pharmaceutically active agent (e.g., dextromethorphan hydrobromide) when the average pharmaceutically active agent:ion exchange resin ratio is about 1:1.

In a particularly preferred embodiment of the invention, pullulan is present in the film in an amount of about 2 to about 6 mg/cm^2, dextromethorphan is present in the film in an amount of about 1.4 to about 3 mg/cm^2, and sulfonated polymer ion exchange resin is present in said film in an amount of about 1.4 to about 2 mg/cm^2.

The antitussive pharmaceutically active agents that are suitable for use in these preparations are acidic, amphoteric or most often basic antitussives. Examples of basic pharmaceutically active agents useful in the present invention include, but are not limited to dextromethorphan, diphenhydramine, caramiphen, carbapentane, ethylmorphine, noscapine and codeine. In addition, the antitussive embodiments of the invention can further comprise additional agents that are therapeutically effective to treat conditions other than coughing. That is, more than one type of pharmaceutically active agent can be included in a film of the invention. For example, in the case of a film containing an antitussive agent, the film can further comprise an antihistamine, sympathomimetic pharmaceutically active agent (nasal decongestant,

bronchodilator), analgesic, antiinflammatory, cough suppressant and/or expectorant. Compounds which are antihistamines, sympathomimetic pharmaceutically active agents (nasal decongestant, bronchodilator), analgesic, antiinflammatory, cough suppressants and/or expectorants are well known to those of skill in the art and need not be discussed in detail herein.

In embodiments, a certain percentage of the films disclosed herein will contain non-coated pharmaceutically active agent/resin complexes. The remaining pharmaceutically active agent/resin complexes are further characterized by the presence of a coating. In the preferred embodiment of the present invention, about 20 to about 80% of the pharmaceutically active agent/resin complexes in the sustained-release compositions are coated, most preferably about 40 to about 60% of the pharmaceutically active agent/resin complexes. The coating is a water-permeable, diffusion barrier coating material. The presence of a coating allows one to selectively modify the dissolution profile as desired of a pharmaceutical composition comprising the pharmaceutically active agent/resin complexes of the present invention.

The coating materials can in general be any of a large number of conventional natural or synthetic film-forming materials used singly, in admixture with each other, and in admixture with plasticizers, pigments, etc. with diffusion barrier properties and with no inherent pharmacological or toxic properties. In general, the major components of the coating should be insoluble in water, and permeable to water and pharmaceutically active agent. However, it might be desirable to incorporate a water-soluble substance, such as methyl cellulose, to alter the permeability of the coating, or to incorporate an acid-insoluble, base-soluble substance to act as an enteric coating. The coating materials may be applied as a suspension in an aqueous fluid or as a solution in organic solvents. Suitable examples of such coating materials are described by R. C. Rowe in Materials used in Pharmaceutical Formulation. (A. T. Florence,

editor), Blackwell Scientific Publications, Oxford, 1-36(1984), incorporated by reference herein. Preferably the water-permeable diffusion barrier is selected from the group consisting of ethyl cellulose, methyl cellulose and mixtures thereof Most preferably, the coating material is SURELEASE, manufactured by Colorcon which is water based ethyl cellulose latex, plasticized with dibutyl sebacate or with vegetable oils. Other non-limiting coating materials included within the scope of the present invention are AQUACOAT, manufactured by FMC Corporation of Philadelphia, which is ethylcellulose pseudolatex; solvent based ethylcellulose; shellac; zein; rosin esters; cellulose acetate; EUDRAGITS, manufactured by Rohm and Haas of Philadelphia, which are acrylic resins; silicone elastomers; poly(vinyl chloride) methyl cellulose; and hydroxypropylmethyl cellulose.

Conventional coating solvents and coating procedures (such as fluid bed coating and spray coating) can be employed to coat the particles. Techniques of fluid bed coating are taught, for example, in U.S. Patents Nos. 3,089,824, 3,117,027, and 3,253,944. The coating is normally applied to the pharmaceutically active agent/resin complex, but alternatively can be applied to the resin before complexing with the pharmaceutically active agent. Non-limiting examples of coating solvents include ethanol, a methylene chloride/acetone mixture, coating emulsions, methyl acetone, tetrahydrofuran, carbonetetrachloride, methyl ethyl ketone, ethylene dichloride, trichloroethylene, hexane, methyl alcohol, isopropyl alcohol, methyl isobutyl ketone, toluene, 2-nitropropane, xylene, isobutyl alcohol, n-butyl acetate.

It is preferred that the coated pharmaceutically active agent/resin complexes are coated in the range from about 40 to about 70% w/w pharmaceutically active agent/resin complex. More preferably, the pharmaceutically active agent/resin complex is coated in the range from about 45 to about 55% w/w pharmaceutically active agent/resin complex. Most

preferably, the pharmaceutically active agent/resin complex is coated about 50% w/w pharmaceutically active agent/resin complex. Variation in the amount of coating and/or the use of coated/uncoated complex mixtures can be employed to selectively modify the dissolution profile as desired.

The average particle sizes of the non-hydrated coated and uncoated pharmaceutically active agent/resin complexes is about 60 to about 200 and about 60 to about 250 micrometers, respectively. More preferably, average particle sizes of the coated pharmaceutically active agent/resin complexes is between about 70 and about 190 micrometers, and most preferably about 70 to about 180 micrometers. More preferably, average particle sizes of the uncoated pharmaceutically active agent/resin complexes is between about 55 and about 160 micrometers, and most preferably about 60 to about 150 micrometers. It is desirable that about 85%, preferably about 95%, and most preferably about 98% of the resin particles have sizes within the ranges set forth above. Adjustments within these ranges can be made to accommodate desired aesthetic qualities of the final formulation product. It is more preferable that the resin dextromethorphan complex have particle sizes within these ranges as well.

In embodiments, it is possible to hydrate the film-forming ingredients and combine all of the ingredients without heating. This method comprises dissolving the water-soluble ingredients in water to form an aqueous mixture; mixing the film-forming ingredients in powder form to form a powder mixture; adding the powder mixture to the aqueous mixture to form a hydrated polymer gel; stirring the hydrated polymer at room temperature for about 30 minutes to about 48 hours; mixing the cooling agent, menthol and any other oils to form an oil mixture; adding the oil mixture to the hydrated polymer gel and mixing until uniform; deaerating the film until air bubbles are removed, casting the uniform mixture on a suitable substrate; and drying the cast mixture to form a

film. This method hydrates the film-forming ingredients without heating the water, which can reduce energy costs in the manufacturing process and undesirable losses of volatile ingredients to evaporation. Further, mixing the oils in two steps minimizes the amount of flavor lost.

While not wishing to be bound by any theories, it is believed that the film-forming ingredients can be hydrated and mixed without heating due to an ionic effect known as the Donnan equilibrium. Hydrating the film-forming agents in the presence of electrolytes in solution effectively lowers the viscosity of the polymer gel being formed, thus increasing the efficiency of the hydrating process. The water-soluble ingredients of the formulation provide the electrolytes, which are dissolved in the hydration solution prior to addition of the film-forming ingredients. High-shear mixing also accelerates hydration, which delumps the powders, providing greater surface area for water contact. In addition, local heating effects, generated in the shear regions, provide energy for hydration without substantially raising the temperature of the mass.

Examples

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

Example 1

The ingredients listed in Table 1 were combined to provide a comparative example of an antitussive film in accordance with the following procedure:

A. The water was heated to 50°C. The potassium sorbate and sweeteners were dissolved in the water with mixing. The titanium dioxide was then added with further mixing to form Preparation A.

B. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) were mixed in a separate container to form

Preparation B.

C. Preparation B was slowly added to Preparation A with rapid mixing, followed by overnight mixing at a reduced rate to provide Preparation C.

D. The glycerin and olive oil were combined in a separate container and then the menthol and monoammonium glycyrrhizinate (MAG) were dissolved therein by heating to 45°C to form Preparation D.

E. Preparation D was added to Preparation C with thorough mixing and then the flavor agents were added with continued mixing to provide Preparation E.

F. Dextromethorphan coated with ethyl cellulose was then added to Preparation E with mixing. The pH was adjusted as necessary to 6.0 using 10% citric acid solution to provide Preparation F (Examples 1-3 only).

Preparation F was poured on a mold and cast to form a film of a desired thickness at room temperature. The film was dried under warm air and cut to a desired dimension (dictated by, e.g., dosage and mouthfeel) for taste testing. The film was segmented into 1" x 1.25" (2.54 cm x 3.18 cm) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 70±3 mg.

A placebo film was also prepared in accordance with the foregoing to facilitate evaluation of, e.g., the taste and appearance of the active film.

Table 1

Material	% w/w in batch	g/batch	%w/w*	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (55% DM)		103.6291		27.3000	29.5775	9.3899
Xanthan Gum	0.0600	0.6000	0.2432	0.1581	0.1713	0.0544
Locust Bean Gum	0.0700	0.7000	0.2837	0.1844	0.1998	0.0634
Carrageenan	0.3000	3.0000	1.2159	0.7903	0.8563	0.2718
Pullulan	16.0000	160.0000	64.8466	42.1503	45.6666	14.4976
Potassium Sorbate	0.0600	0.6000	0.2432	0.1581	0.1713	0.0544
Acesulfame Potassium Salt	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
Aspartame NF	1.4000	14.0000	5.6741	3.6882	3.9958	1.2685
Purified Water	75.3264	753.2640				68.2534
Physcool	0.1000	1.0000	0.4053	0.2634	0.2854	0.0906
Menthol	1.0000	10.0000	4.0529	2.6344	2.8542	0.9061
Citric Acid	0.0710	0.7100	0.2878	0.1870	0.2026	0.0643
Cherry Flavor (Givudan)	0.1500	1.5000	0.6079	0.3952	0.4281	0.1359
Peppermint Flavor	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0405	0.0263	0.0285	0.0091
Polysorbate 80 NF	0.3500	3.5000	1.4185	0.9220	0.9990	0.3171
Atmos 300	0.3500	3.5000	1.4185	0.9220	0.9990	0.3171
Glycerine	3.0000	30.0000	12.1587	7.9032	8.5625	2.7183
Olive Oil	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
FD&C green #3	0.0026	0.0260	0.0105	0.0068	0.0074	0.0024
Titanium Dioxide	0.2500	2.5000	1.0132	0.6586	0.7135	0.2265
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1103.6291		92.3000	100.0000	100.0000
* assuming that all water is evaporated						

The active film was gritty and bitter.

Example 2

Comparative films having the ingredients listed in Table 2 were prepared in accordance with the method of Example 1.

Table 2

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (53.5% DM)		106.4239		28.0374	30.1356	9.6187
Xanthan Gum	0.0600	0.6000	0.2432	0.1581	0.1699	0.0542
Locust Bean Gum	0.0700	0.7000	0.2837	0.1844	0.1982	0.0633
Carrageenan	0.3000	3.0000	1.2159	0.7904	0.8495	0.2711
Pullulan	16.0000	160.0000	64.8493	42.1520	45.3065	14.4610
Potassium Sorbate	0.0600	0.6000	0.2432	0.1581	0.1699	0.0542
Acesulfame Potassium Salt	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
Aspartame NF	1.4000	14.0000	5.6743	3.6883	3.9643	1.2653
Purified Water	75.3274	753.2740				68.0819
Physcool	0.1000	1.0000	0.4053	0.2635	0.2832	0.0904
Menthol	1.0000	10.0000	4.0531	2.6345	2.8317	0.9038
Citric Acid (used to adjust pH to 6.0)	0.0700	0.7000	0.2837	0.1844	0.1982	0.0633
Cherry Flavor (Givudan)	0.1500	1.5000	0.6080	0.3952	0.4247	0.1356
Peppermint Flavor	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0405	0.0263	0.0283	0.0090
Polysorbate 80 NF	0.3500	3.5000	1.4186	0.9221	0.9911	0.3163
Atmos 300	0.3500	3.5000	1.4186	0.9221	0.9911	0.3163
Glycerine	3.0000	30.0000	12.1592	7.9035	8.4950	2.7114
Olive Oil	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
FD&C Green #3	0.0026	0.0260	0.0105	0.0069	0.0074	0.0024
Titanium Dioxide	0.2500	2.5000	1.0133	0.6586	0.7079	0.2260
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1106.4239		93.0374	100.0000	100.0000
* assuming that all water is evaporated						

The active film was gritty and bitter.

Example 3

Comparative films having the ingredients listed in Table 3 were prepared in accordance with the method of Example 1.

Table 3

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (60% DM)		94.7292		25.0000	27.7778	8.6532
Xanthan Gum	0.0600	0.6000	0.2436	0.1583	0.1759	0.0548
Locust Bean Gum	0.0700	0.7000	0.2842	0.1847	0.2053	0.0639
Carrageenan	0.3000	3.0000	1.2180	0.7917	0.8797	0.2740
Pullulan	16.0000	160.0000	64.9625	42.2256	46.9174	14.6155
Potassium Sorbate	0.0600	0.6000	0.2436	0.1583	0.1759	0.0548
Acesulfame Potassium Salt	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
Aspartame NF	1.4000	14.0000	5.6842	3.6947	4.1053	1.2789
Purified Water	75.3704	753.7040				68.8484
Physcool	0.1000	1.0000	0.4060	0.2639	0.2932	0.0913
Menthol	1.0000	10.0000	4.0602	2.6391	2.9323	0.9135
Citric Acid	0.0270	0.2700	0.1096	0.0713	0.0792	0.0247
Cherry Flavor (Givudan)	0.1500	1.5000	0.6090	0.3959	0.4399	0.1370
Peppermint Flavor	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0406	0.0264	0.0293	0.0091
Polysorbate 80 NF	0.3500	3.5000	1.4211	0.9237	1.0263	0.3197
Atmos 300	0.3500	3.5000	1.4211	0.9237	1.0263	0.3197
Glycerine	3.0000	30.0000	12.1805	7.9173	8.7970	2.7404
Olive Oil	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
FD&C green #3	0.0026	0.0260	0.0106	0.0069	0.0076	0.0024
Titanium Dioxide	0.2500	2.5000	1.0150	0.6598	0.7331	0.2284
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1094.7292		90.0000	100.0000	100.0000
* assuming that all water is evaporated						

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The active film was very thin, blue and gritty. Sensations of bitterness and numbness were minimal, but the flavor was not entirely agreeable.

Example 4

Films of the invention having the ingredients listed in Table 4 were prepared in accordance with the method of Example 1, except that Step F comprised adding uncoated dextromethorphan hydrobromide and AMBERLITE resin to Preparation E as separate ingredients.

Table 4

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Dextromethorphan		17.0326		15.0000	15.7563	5.0951
Amberlite IRP69		17.2597		15.2000	15.9664	5.1630
Xanthan Gum	0.0600	0.1800	0.2439	0.1585	0.1665	0.0538
Locust Bean Gum	0.0700	0.2100	0.2845	0.1849	0.1943	0.0628
Carrageenan	0.3000	0.9000	1.2194	0.7926	0.8326	0.2692
Pullulan	16.0000	48.0000	65.0338	42.2720	44.4033	14.3587
Potassium Sorbate	0.0600	0.1800	0.2439	0.1585	0.1665	0.0538
Acesulfame Potassium Salt	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
Aspartame NF	1.4000	4.2000	5.6905	3.6988	3.8853	1.2564
Purified Water	75.3974	226.1922				67.6630
Physcool	0.1000	0.3000	0.4065	0.2642	0.2775	0.0897
Menthol	1.0000	3.0000	4.0646	2.6420	2.7752	0.8974
Citric Acid	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Cherry Flavor (Givudan)	0.1500	0.4500	0.6097	0.3963	0.4163	0.1346
Peppermint Flavor	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0300	0.0406	0.0264	0.0278	0.0090
Polysorbate 80 NF	0.3500	1.0500	1.4226	0.9247	0.9713	0.3141
Atmos 300	0.3500	1.0500	1.4226	0.9247	0.9713	0.3141
Glycerine	3.0000	9.0000	12.1938	7.9260	8.3256	2.6923
Olive Oil	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
FD&C green #3	0.0026	0.0078	0.0106	0.0069	0.0072	0.0023
Titanium Dioxide	0.2500	0.7500	1.0162	0.6605	0.6938	0.2244
Total w/o active		300.0000	100.0000	65.0000		
Total with active	100.0000	334.2922		95.2000	100.0000	100.0000
* assuming that all water is evaporated						

The active film had a pleasing appearance and taste.

Example 5

The ingredients listed in Table 5 were combined to provide an example of an antitussive film of the invention in accordance with the following procedure:

A. The water was heated to 75°C. Uncoated dextromethorphan hydrobromide was dissolved with mixing in the water, while maintaining the temperature at 75°C. AMBERLITE resin was then mixed into the water with heating for 4 to 5 hours at 70-80°C. Heating was stopped, water lost to evaporation was replaced, and the potassium sorbate and sweeteners were then added to the composition with mixing to form Preparation A.

B. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) were mixed in a separate container to form Preparation B.

C. Preparation B was slowly added to Preparation A with rapid mixing, followed by overnight mixing at a reduced rate to provide Preparation C.

D. The menthol was dissolved with mixing in the alcohol in a separate container. The Physcool was then dissolved with mixing therein. The MAG, Polysorbate 80, Atmos 300 and flavors were then added to the mixture and mixed to enhanced uniformity to form Preparation D.

E. Preparation D, glycerine and mannitol were added to Preparation C with thorough mixing to provide Preparation E.

Preparation E was poured on a mold and cast to form a film of a desired thickness at room temperature. The film was dried under warm air and cut to a desired dimension (dictated by, e.g., dosage and mouthfeel) for taste testing. The film was segmented into 1.5 in^2 (9.7 cm^2) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 70±3 mg.

A placebo film was also prepared in accordance with the foregoing to facilitate evaluation of, e.g., the taste and appearance of the active film.

Table 5

Material	%w/w in batch	g/batch	mg/dose*	%w/w* film	% w/w actual batch
Dextromethorphan HBr		11.4615	15.0000	21.4286	9.2666
Amberlite IRP69		12.2256	16.0000	22.8571	9.8843
Xanthan Gum	0.0600	0.0600	0.0944	0.1348	0.0485
Locust Bean Gum	0.0700	0.0700	0.1101	0.1573	0.0566
Carrageenan	0.3000	0.3000	0.4718	0.6740	0.2425
Pullulan	16.0000	16.0000	25.1613	35.9447	12.9359
Potassium Sorbate	0.0600	0.0600	0.0944	0.1348	0.0485
Acesulfame Potassium Salt	0.5000	0.5000	0.7863	1.1233	0.4042
Aspartame NF	1.4000	1.4000	2.2016	3.1452	1.1319
Purified Water	70.2000	70.2000			56.7561
Alcohol USP	5.0000	5.0000			4.0425
Physcool	0.1000	0.1000	0.1573	0.2247	0.0808
Menthol	1.5000	1.5000	2.3589	3.3698	1.2127
Peppermint Flavor	0.1000	0.1000	0.1573	0.2247	0.0808
Raspberry Flavor (Givudan)	0.5000	0.5000	0.7863	1.1233	0.4042
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0100	0.0157	0.0225	0.0081
Polysorbate 80 NF	0.3500	0.3500	0.5504	0.7863	0.2830
Atmos 300	0.3500	0.3500	0.5504	0.7863	0.2830
Glycerine	1.5000	1.5000	2.3589	3.3698	1.2127
Mannitol USP	2.0000	2.0000	3.1452	4.4931	1.6170
Total w/o active		100.0000	39.0000		

The active film had a pleasing appearance and taste.

Example 6

Films of the invention having the ingredients listed in Table 6 were prepared in accordance with the method of Example 5.

Table 6

Material	%w/w in batch	g/batch	mg/dose*	%w/w*	%w/w
Dextromethorphan HBr		11.6538	15.0000	21.4286	9.3919
Amberlite IRP69		12.4308	16.0000	22.8571	10.0180
Xanthan Gum	0.0600	0.0600	0.0925	0.1321	0.0484
Locust Bean Gum	0.0700	0.0700	0.1079	0.1542	0.0564
Carrageenan	0.3000	0.3000	0.4625	0.6606	0.2418
Pullulan	16.0000	16.0000	24.6640	35.2343	12.8944
Potassium Sorbate	0.0600	0.0600	0.0925	0.1321	0.0484
Acesulfame Potassium Salt	0.5000	0.5000	0.7708	1.1011	0.4030
Aspartame NF	1.4000	1.4000	2.1581	3.0830	1.1283
Purified Water	69.7000	69.7000			56.1713
Alcohol USP	5.0000	5.0000			4.0295
Physcool	0.1000	0.1000	0.1542	0.2202	0.0806
Menthol	2.0000	2.0000	3.0830	4.4043	1.6118
Peppermint Flavor	0.1000	0.1000	0.1542	0.2202	0.0806
Raspberry Flavor (Givudan)	0.5000	0.5000	0.7708	1.1011	0.4030
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0100	0.0154	0.0220	0.0081
Polysorbate 80 NF	0.3500	0.3500	0.5395	0.7708	0.2821
Atmos 300	0.3500	0.3500	0.5395	0.7708	0.2821
Glycerine	1.5000	1.5000	2.3123	3.3032	1.2089
Mannitol USP	2.0000	2.0000	3.0830	4.4043	1.6118
Total w/o active		0.0000	39.0000		
Total with active	100.0000	124.0846	70.0000	100.0000	100.0000
* assuming that all water and alcohol is evaporated					

The active film had a pleasing appearance and taste.

Example 7

A film of the invention having the ingredients listed in Table 7 were

prepared in accordance with the method of Example 5. The film was segmented into 1" x 1.25" (2.54 cm x 3.18 cm) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 63.6±3 mg.

Table 7

Material	%w/w in batch	kg/batch	mg/dose*	%w/w*	%w/w
Dextromethorphan HBr		1.3567	15.0000	23.5981	9.3918
Amberlite IRP69		1.4472	16.0000	25.1713	10.0180
Xanthan Gum	0.0600	0.0070	0.0772	0.1215	0.0484
Locust Bean Gum	0.0700	0.0081	0.0901	0.1417	0.0564
Carrageenan	0.3000	0.0349	0.3661	0.6075	0.2418
Pullulan	16.0000	1.8627	20.5941	32.3988	12.8944
Potassium Sorbate	0.0600	0.0070	0.0772	0.1215	0.0484
Acesulfame Potassium Salt	0.5000	0.0582	0.6436	1.0125	0.4030
Aspartame NF	1.4000	0.1630	1.8020	2.8349	1.1283
Purified Water	69.7000	8.1145			56.1714
Alcohol USP	5.0000	0.5821			4.0295
Physcool	0.1000	0.0116	0.1287	0.2025	0.0806
Menthol	2.0000	0.2328	2.5743	4.0498	1.6118
Peppermint Flavor	0.1000	0.0116	0.1287	0.2025	0.0806
Raspberry Flavor (Givudan)	0.5000	0.0582	0.6436	1.0125	0.4030
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0012	0.0129	0.0202	0.0081
Polysorbate 80 NF	0.3500	0.0407	0.4505	0.7087	0.2821
Atmos 300	0.3500	0.0407	0.4505	0.7087	0.2821
Glycerine	1.5000	0.1746	1.9307	3.0374	1.2089
Mannitol USP	2.0000	0.2328	2.5743	4.0498	1.6118
Total w/o active + resin		11.6420	32.5644		
Total with active + resin	100.0000	14.4459	63.5644	100.0000	100.0000
* assuming that all water and alcohol is evaporated					

The active film had a pleasing appearance and taste.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

CLAIMS

WHAT IS CLAIMED IS:

1. A consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein said film comprises at least one water soluble polymer, at least one pharmaceutically active agent and at least one taste masking agent.

2. The consumable film according to claim 1, wherein said at least one water soluble polymer is a member selected from the group consisting of pullulan, hydroxyproplymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof.

3. The consumable film according to claim 2, wherein said at least one water soluble polymer is pullulan.

4. The consumable film according to claim 1, wherein said at least one pharmaceutically active agent is a member selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory agents, antitussives, decongestants, anti-histamines, expectorants, anti-diaherrals, H_2-antagonists, proton pump inhibitors, central nervous system agents, analgesics and mixtures thereof.

5. The consumable film according to claim 4, wherein the antimicrobial agent is a member selected from the group consisting of triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA and mixtures thereof.

6. The consumable film according to claim 4, wherein the non-steroidal anti-inflammatory agent is a member selected from the group consisting of aspirin, acetaminophen, ibuprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and mixtures thereof.

7. The consumable film according to claim 4, wherein the antitussive is a member selected from the group consisting of benzonatate, caramiphen edisylate, dextromethorphan, chlophedianol, diphenhydramine, salts thereof and mixtures thereof.

8. The consumable film according to claim 4, wherein the decongestant is selected from the group consisting of pseudoephedrine, phenylepherine, phenylpropanolamine, salts thereof and mixtures thereof.

9. The consumable film according to claim 4, wherein the anti-histamine is selected from the group consisting of brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenhydramine citrate, diphenylpyraline hydrochloride, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride and mixtures thereof.

10. The consumable film according to claim 4, wherein the expectorant is selected from the group consisting of guaifenesin, ipecac, potassium iodide, terpin hydrate and mixtures thereof.

11. The consumable film according to claim 4, wherein the anti-diarrheal is loperamide.

12. The consumable film according to claim 4, wherein the H_2-antagonist is selected from the group consisting of famotidine, ranitidine and mixtures thereof.

13. The consumable film according to claim 4, wherein the proton pump inhibitor is selected from the group consisting of omeprazole,

lansoprazole, and mixtures thereof.

14. The consumable film according to claim 1, wherein the at least one taste masking agent is an ion exchange resin.

15. The consumable film according to claim 14, wherein the ion exchange resin is a sulfonated polymer comprising polystyrene cross-linked with divinylbenzene.

16. The consumable film according to claim 14, wherein the ion exchange resin is a sulfonated polymer comprising polystyrene cross-linked with 8% of divinylbenzene, with an ion exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H^+-form).

17. The consumable film according to claim 16, wherein the ion exchange resin has irregularly-shaped particles ranging in size from about 47 to about 149 micrometers.

18. The consumable film according to claim 16, wherein the ion exchange resin has spherical particles ranging in size from about 45 to about 150 micrometers.

19. The consumable film according to claim 14, wherein the ion exchange resin is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group, and wherein an exchange capacity of said ion exchange resin is normally within a range of about 3 to about 4 meq/g of dry ion exchange resin.

20. The consumable film according to claim 1, wherein the at least one taste masking agent is magnesium trisilicate.

21. The consumable film according to claim 1, wherein said at least one water soluble polymer is pullulan, said at least one pharmaceutically active agent is dextromethorphan, and said at least one taste masking agent is a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene.

22. The consumable film according to claim 21, wherein said pullulan is present in an amount of about 40 to about 80 wt% of said film, said dextromethorphan is present in an amount of about 5 to about 40 wt% of said film, said sulfonated polymer ion exchange resin is present in an amount of about 5 to about 40 wt% of said film, and a ratio of said dextromethorphan to said sulfonated polymer ion exchange resin is 1:3 to 3:1.

23. The consumable film according to claim 22, wherein said pullulan is present in said film in an amount of about 2 to about 6 mg/cm^2, said dextromethorphan is present in said film in an amount of about 1.4 to about 2 mg/cm^2, and said sulfonated polymer ion exchange resin is present in said film in an amount of about 1.4 to about 2 mg/cm^2.

24. The consumable film according to claim 22, further comprising:

about 0.01 to about 5 wt% of at least one stabilizing agent;

about 0.001 to about 0.1 wt% of at least one of at least one coloring agent;

about 0.1 to about 70 wt% of water;

about 0.1 to about 15 wt% of at least one sweetening agent;

about 0.1 to about 15 wt% of at least one flavoring agent;

about 0.1 to about 4 wt% of at least one cooling agent;

about 0.1 to about 5 wt% of at least one surfactant;

about 0.1 to about 12 wt% of a triglyceride;

about 0.001 to about 5 wt% of a preservative;

about 0.1 to about 5 wt% of a polyethylene oxide compound; and

about 1 to about 20 wt% of propylene glycol.

25. A method for preparing the consumable film of claim 1, said method comprising:

dissolving water-soluble ingredients in water to provide an aqueous solution;

mixing at least one water soluble film former and at least one stabilizing agent to provide a film-forming mixture;

combining said film-forming mixture and said aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

adding said oil mixture to said hydrated polymer gel and mixing to provide a uniform gel;

casting the uniform gel on a substrate; and

drying the cast gel to provide said film.

26. The method of claim 25, wherein said at least one pharmaceutically active agent and said at least one taste masking agent are incorporated into said aqueous solution or into said uniform gel.

27. The method of claim 25, wherein said at least one taste masking agent is an ion exchange resin, and said at least one pharmaceutically active agent is sorbed to said ion exchange resin without separating ion exchanged pharmaceutically active agent from unexchanged agent and counter ion salts.

INTERNATIONAL SEARCH REPORT

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 438 147 A (SCLAVO) 24 July 1991 (1991-07-24) claims 1-5,13	1,2, 14-19
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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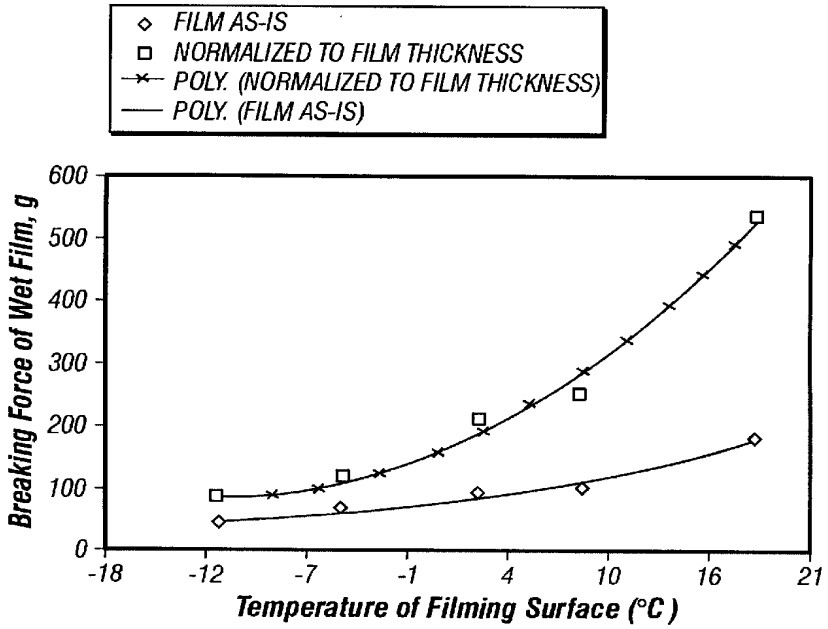
(54) Title: MODIFIED STARCH AS A REPLACEMENT FOR GELATIN IN SOFT GEL FILMS AND CAPSULES



(57) Abstract: Film-forming compositions are disclosed that can comprise, on a dry solid basis, 25 to 75 percent by weight of certain starch derivatives having a DE less than about 1,25 to 75 % plasticizer, and 0.1 to 15 % hydrocolloid gum. The starch derivatives can be chemically modified starches which range in molecular weight from 100,000 to 2,000,000. These starch-based systems can completely replace gelatin in edible film-forming applications such as soft and hard gel capsules.

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MODIFIED STARCH AS A REPLACEMENT FOR GELATIN IN SOFT GEL FILMS AND CAPSULES

BACKGROUND OF THE INVENTION

This invention relates to starch compositions useful in forming flexible films. More particularly, it relates to film-forming compositions containing certain modified starches.

Gelatin is a protein that forms thermo-reversible films. Gel masses composed of gelatin and a plasticizer such as glycerin are formulated to be liquid above room temperature, form a film when cast on a cooled surface, and re-melt when exposed to higher temperatures again. This ability to re-tackify enables encapsulation of liquid materials in gelatin soft capsules. Films formed from plasticized gelatin set very quickly and have high wet film strength. They are also very elastic with good clarity. Plasticized gelatin also has a relatively low viscosity, even when used at high solids concentrations. In addition, when gelatin is in the presence of water at room temperature, it swells but does not go into solution until heat is applied.

In the manufacture of soft gel films and capsules, the soft gel composition must possess the properties of good wet and dry film strength, insolubility in cold water, oil, and alcohol, solubility in hot water, temperature and pressure sealability, film clarity, film flexibility, edibility, inertness to drugs or other materials to be encapsulated, and rapid setting from a hot liquid to form a gel. In the manufacture of photographic elements, the soft gel films must possess the qualities of clarity, strength, setting power, flexibility, and non-interaction with other chemicals in the photographic film.

Although gelatin is useful in soft gel applications because of its rapid gelling ability, excellent film forming properties, and ability to impart oxygen impermeability, it has the disadvantages of high cost, limited availability, non-kosher status for food products and, at times, batch property variations. Because of these shortcomings, those industries where the need for gelatin is greatest have long sought means for replacing gelatin.

A useful gelatin replacer must be compatible with common plasticizers and fill materials used in the industry, and must provide properties equivalent to those of the gelatin which it is replacing for a particular application, e.g., film or binding strength in the pharmaceutical industry, phototransmissibility and resistance to abrasion in the photographic industry, and binding strength in the adhesive industry.

SUMMARY OF THE INVENTION

One aspect of the present invention is a film-forming composition that comprises starch material selected from the group consisting of modified starch and waxy starch; gum; and plasticizer. The modified starch or waxy starch has a dextrose equivalent (DE) of less than about 1, and preferably has no measurable DE. This composition can be, but is not required to be, 100% gelatin-free. Thus, the composition can be used as a gelatin replacement, or as an extender in gelatin formulations.

The composition typically will be prepared with water, and have a solids concentration of about 30-70% by weight. The solids in the composition preferably comprise 25-75% starch material, 25-75% plasticizer, and 0.1-15% gum. In certain preferred embodiments of the invention, the weight ratio of gum to starch is from about 0.1:1 to about 1:1, and the weight ratio of starch and gum to plasticizer is from about 1:0.8 to about 1:3.

The starch material preferably comprises starch which has been chemically modified with a monoreactive moiety to a degree of substitution of least about 0.015. It is also preferred that the starch material has an average molecular weight between about 100,000-2,000,000. In a particularly preferred embodiment, the starch material is selected from the group consisting of ether and ester derivatives of starch, such as hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch. One specific embodiment of the invention comprises hydroxypropylated potato starch having a degree of substitution of about 0.015-0.30 and a molecular weight of about 100,000-2,000,000.

The gum preferably is selected from the group consisting of carrageenan, locust bean, xanthan, gellan, agar, alginates, guar, gum arabic, and pectin. A combination of kappa carrageenan and iota carrageenan, most preferably in a weight ratio of about 1:1, is especially preferred. The plasticizer preferably comprises at least one polyol, such as glycerol, sorbitol, maltitol, or a mixture of one or more of these. The composition of the present invention can optionally also comprise at least one monovalent or divalent cation, such as sodium, potassium, and calcium salts, or mixtures thereof.

Another aspect of the invention is an edible film that comprises the above-described starch-based composition, usually with much of the water removed. Yet another aspect of the invention is a soft gel capsule that comprises a sealed capsule wall and a first substance that is encapsulated by the sealed capsule wall. The capsule wall comprises the above-described starch-based composition. In one embodiment of the invention, the film or the capsule wall consists essentially of the combination of starch material, gum, and plasticizer.

The first substance encapsulated by the capsule wall can be any of a variety of materials which have been encapsulated by gelatin in the past. Many such substances are edible, including drugs, vitamins, nutritional supplements, and pre-measured food ingredients such as flavorings. It can also comprise, for example, photographic or dye solutions.

Another aspect of the invention is a method of encapsulating a first substance. This method comprises the steps of: providing a first substance and an edible film as described above; and encapsulating the first substance in the film. Preferably, the film used in this method has been formed on a surface having a temperature of at least about 38°C (100°F).

One object of this invention to provide an economical means for replacing gelatin in compositions utilized in the production of soft gel for food, pharmaceutical, and industrial applications. It is a further object of this invention to provide starch-based materials which are compatible with the existing application equipment used for manufacture of the various products which are primarily comprised of gelatin films.

The starch-based systems of the present invention, when incorporated as a replacement for gelatin in aqueous solutions, display properties superior to those of their parent base starch. More precisely, modified starches that have been chemically modified with monoreactive moieties to a degree of substitution of at least 0.015 DS, and degraded to molecular weights between 100,000 and 2,000,000, or, alternatively, waxy starches, when combined with gum and plasticizing agents, are a highly functional replacement for gelatin in soft gel film forming applications. The presence of gum increases the rate of film formation and enhances film strength.

In compositions of the present invention, the starch and gum preferably are mixed with plasticizers at ratios ranging from about 1 part starch and gum to about 0.8-3 parts plasticizer. The total solids in the composition preferably range from about 30 to 70% weight. Edible films are prepared by blending together the starch, gum, plasticizer, and water, and heating the mixture to a temperature and for a time sufficient to gelatinize the starch fully, (e.g., 80-100 °C for 10-60 min). A vacuum can be used either during or after cooking to remove entrained air and improve film properties. Additional materials may be added to the mixture of starch and plasticizer in order to impart improved functionality. Furthermore, properties of this system can be modified by the inclusion of various mono and divalent cations, including but not limited to sodium, potassium, and calcium. The mixture is then sheeted, while hot, to form a thin film. This film can be formed into soft gel capsules, encapsulating pharmaceutical, nutritional, photographic, or other materials, using well-known techniques.

The modified starch-based compositions of the present invention provide an acceptable balance of critical variables including mass viscosity and pot life, film rate, wet film strength, dry film strength and flexibility, and thermo-reversibility.

In one embodiment of the invention, wet film strength is significantly improved by increasing the temperature of the surface on which the film is formed. It is preferred in the present invention to use film-forming surface temperatures of about 38°C (100°F) or greater. Commercial capsule filming drum temperatures are often set around 10°C (50°F) for gelatin filming, but can easily be adjusted to 38-43°C (100-110°F). Breaking strengths can be increased by as much as 500% by increasing surface temperature from 12-66°C (53°F to 150°F). Films cast at 41°C (105°F) can have as much as twice the breaking strength films cast on 12°C (53°F) surfaces.

In one particularly preferred embodiment, the gum component of the composition consists essentially of 50% kappa carrageenan and 50% iota carrageenan. This combination can increase film strength by as much as 50% over films formed with 100% kappa carrageenan as the gum component, increase film elasticity, reduce the viscosity of the hot mass, lower the minimum temperature at which the gelled mass can be handled in liquid form, and lower the gel-setting temperature of the mass. This composition also broadens the temperature range over which the mass gels, which can improve the ease of film sealing.

The present invention has a number of benefits. One advantage of the invention is that it is a simple, cost-effective, dependable, intrinsically safe, Kosher, and efficient means for replacing the gelatin used in soft gel capsule compositions.

Another advantage of the invention is that the preparation of the starch-based compositions can be carried out by ordinary means with conventional manufacturing apparatus. The resulting compositions can be utilized in any commercial process requiring gelatin and to which conventional coating and drying methods are adaptable. Examples of end-product uses for the compositions of the present invention include encapsulated bath beads, paint balls, and pharmaceuticals. Therefore, the present invention provides a novel, efficient means for replacing gelatin in these and other applications.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the effect of the temperature of the surface on which a film is formed on the strength of that film.

Figure 2 is a graph showing the effect of temperature on flow and gelation for compositions containing different types of carrageenan.

Figure 3 is a graph showing the effect of mass solids percentage on the flowability of compositions containing different types of carrageenan.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

Examples of modified starches that can be used in the present invention include non-retrograding starches derived by chemical modification of starch from any plant source, including corn, waxy maize, potato, sweet potato, wheat, rice, sago, tapioca, sorghum, high amylose corn, and the like. The particular starch chosen will depend on its performance, availability, and cost. The starch should have a DE less than about 1, and preferably has no measurable DE (using the Lane-Eynon method). Among the useful modified starches are the common ether and ester derivatives of starch, including but not limited to hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch derivatives. Also included among the modified starches suitable for use in the practice of this invention are the thermally converted, fluidity or thin boiling type products derived from the aforementioned types of chemically modified starches. Such materials may be of lower molecular weight, prepared by heating the modified starch alone or by subjecting the starch to a hydrolytic acid and/or heat treatment, or by any other known method designed for the thermal conversion of the starch, such as enzymic heat treatment.

Preferred modified starches are the hydroxypropyl derivatives of potato starch having a degree of substitution from 0.015-0.30 ds and a molecular weight of from 100,000 to 2,000,000. In the case of waxy starches of corn, potato, etc., the branches of the amylopectin replace the function of the ether or ester substituents; these starches are functional in the present invention without additional chemical modification, although their properties are not impaired by additional modification, and are enhanced by molecular weight reduction.

Suitable plasticizers include, but are not limited to, glycerol, sorbitol, and maltitol. Suitable hydrocolloid gums include carrageenan, locust bean gum, xanthan gum, gellan gum, agar, alginates, guar gum, gum arabic, and pectin.

The properties of the composition can be enhanced by the addition of certain cations, including but not limited to sodium, potassium, and calcium. The presence of these cations, in combination with certain gums, generally enhances viscoelastic properties and gel strength.

A variety of optional ingredients may be incorporated into the starch compositions of this invention, before, during, or after cooking the starch. Among the suitable additives which may be utilized are preservatives, colorants, flavoring agents, hardeners, antifoggers, sensitizers, and spreading agents. The inclusion of such additives has no adverse effect upon the properties exhibited by the novel starch-based compositions of the present invention.

A composition of the present invention is formed by combining the dry solids (i.e., the modified starch or waxy starch, gum, and plasticizer, plus any other additives), slurrying in water, and heating at a temperature and for a time sufficient to gelatinize the starch. Optionally, this can take place under a vacuum. Films can be formed from these starch-based compositions by any conventional method designed to solubilize and deposit a continuous coating or layer of the solution onto a substrate or mold of any form. Among the suitable coating techniques are spraying, dipping, air knife, trailing blade, reverse and direct roll coaters, etc. A film, such as an overcoating or capsule shell, may then be formed by drying the coated solution to a desired moisture content, using any means suitable for the particular purpose. Suitable conventional means include warm or cold air impingement, low humidity chamber or oven drying, etc. For example, in the pharmaceutical industry, soft gel capsules are prepared by casting a film of the gelatin solution and then continuously passing two ribbons of the film between two opposing rollers, each of which is equipped with an internal vacuum that draws in the film through half capsule wells engraved in its surface. The capsule contents are deposited between the shell halves as they are formed and sealed. The process is continuous, ending with the filled capsules being automatically conveyed to and through a drying unit that partially dries the capsule. Drying is completed in warm air tunnels.

The films of the present invention can be re-melted, and two or more of these re-melted films can be joined to form a seal.

The invention is particularly efficacious in the soft gel capsule manufacturing process that calls for film-forming materials, but it is not limited thereto. The characteristics exhibited by the present, novel starch formulations, particularly their ability to serve as a total replacement for gelatin, permit them to be used in a wide range of applications.

Although the emphasis has been placed on describing this invention in connection with film-forming gelatin-free compositions, compositions of the present invention can also be utilized as extenders in gelatin compositions such as creams, emulsions, binders, adhesives, etc.

Further compositions of the present invention can be used in the replacement of gelatin in hard shell capsule manufacturing.

EXAMPLES

The invention will be further illustrated by, but is not intended to be limited to, the following examples.

Compositions were prepared containing the component amounts given in Examples 1-7 on a dry solids basis. Starch molecular weights were measured by gel permeation chromatography and weight averaged. In Examples 1-7, the starch, plasticizer, and gum, if used, were mixed with sufficient deionized water (except where indicated) to give a total slurry mass of 35 g. The components were mixed together in the cup of a Rapid Visco Analyzer (Model RVA-4D, Foss Food Technology, Eden Prairie, MN) (hereafter referred to as "RVA"), and heated, using 160 rpm stirring, to 98°C over 4.5 minutes. The mixture was held at 98°C, with continued stirring, for 6.5 minutes, then transferred to a chilled surface and drawn into a film of 0.5 mm thickness for film testing. A second paste of the same composition was cooked in the same way and then transferred into a pre-heated glass jar, tightly capped, and placed into an oven for pot life evaluations.

In particular, in Examples 1-7, the film samples were prepared by casting a layer of the test solution at about 82°C (180°F) onto a Teflon-coated piece of glass (approximately 22.9 x 33 cm (9 in x 13 in)). The bottom of the glass was in contact with circulating cold water so that the surface temperature of the glass was 52°C. The film was formed by pouring the hot paste onto the Teflon surface and then quickly drawing the paste across the glass using a Bird Applicator or similar device, the gap width of which could be adjusted to control film thickness. Wet film thicknesses were typically 0.5-0.8 mm. The films were cast, dried, and aged in a room controlled to 21°C (70°F) and 25-30% relative humidity.

The viscosity of the starch mixture was measured by the RVA instrument, which records viscosity throughout the cook.

Pot life was evaluated by transferring the hot paste into preheated glass jars with screw lids, and placing these in a 82°C (180°F) oven. The fluidity of the mass was evaluated after 2 hours by tipping the jars upside down and assigning a flow rating of 0-5. A mass that flowed with the ease of water was given a rating of 5; a mass which did not flow at all was given a rating of 0. The oven temperature was then lowered by 10°C and the samples allowed to equilibrate for 2 hours, and then their flow properties re-assessed. The oven was lowered in 5.6°C (10 °F) increments until all samples had a flow rating of zero – that is, they had all gelled.

Thermo-reversibility was assessed by reheating the pot life samples, described above, in 5.6°C (10 °F) increments, allowing them to equilibrate at each temperature, and then assigning a flow rating using the same criteria as for pot life.

The films were evaluated for rate of filming using a Gardco Electronic Multicycle Circular Drying Time Recorder, and following test method procedure ASTM D 5895. The recorder was placed above the wet film, and a stylus was lowered onto the surface of the film and allowed to rotate for a defined time of 10 minutes. Three points were determined from this test: tack free, dry hard, and dry through. Tack free is defined as the point in the path made by the stylus on the film where the continuous track ends and a discontinuous track or tear begins. Dry hard is the point in the path where the stylus no longer tears the film, and only leaves a visible trace. Dry through is reached when the stylus no longer leaves any visible track on the film.

The tensile strength of the wet film was measured using a Stable Microsystems TA-XT2 Texture Analyzer. To do this, 1.3 cm x 20.3 cm (0.5 in x 8 in) strips were cut from the wet film 5 minutes after it was cast and these were loaded onto the Texture Analyzer. The tensile test was started 15 minutes after the film was cast.

Film appearance (color and clarity) was evaluated on the basis of visual observation.

Example 1

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g Sorbitol Special (obtained from SPI Polyols, New Castle, Delaware)

Example 2

8.4 g potato starch, substituted with 0.5% hydroxypropyl groups and of 600,000 molecular weight

11.8 g Sorbitol Special

Example 3

8.4 g potato starch, substituted with 3.0% hydroxypropyl groups and of 600,000 molecular weight

11.8 g Sorbitol Special

0.5 mm thickness.

Example 4

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g gellan

9.7 g sorbitol

0.5 mm thickness.

Example 5

5.2 g waxy corn starch of 800,000 molecular weight

0.75 g kappa carrageenan

9.7 g sorbitol

Example 6

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g glycerine

Example 7

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g Sorbitol Special

Sufficient 1% NaCl to bring to 35 g total mass.

The physical properties of the hot starch/plasticizer pastes for Examples 1-7, and the resulting films, are listed below in Table 1.

Table 1

Example number	Peak viscosity during cook, cps	Hot paste final visc, cps, 98°C	Time until tack free, sec	Time until dry hard, sec	Wet film tensile strength, g force	Pot life rating @ 82°C (180°F)	Minimum flowable temp, °C	Re-softening temp, °C
1	18000	1700	<5	<10	75	3.5	71	66
2	14000	2500	65	100	*			
3	13000	1150	4020	5700	*			
4		2300	<5	<10	108	0.5	>82	>82
5	13000	2400	<5	<10	65	3.0	77	66
6	16000	1500	<5	<10	50	4.0	71	66
7	11000	1300	<5	<10	75	3.5	77	66

* Too weak to test

Example 8

A formulation was prepared having the following composition (on an as-is basis):

16% starch which had been acid-thinned to approximately 600,000 mol wt and substituted with about 4 wt % hydroxypropyl groups (approx. 10% moisture).

2.3% kappa carrageenan (approx. 9% moisture)

26% Sorbitol Special (24% moisture)

6.7% glycerine (1% moisture)

49% added water

When the moisture in the components is taken into account, the total solids of the composition was 44%. The starch to carrageenan ratio was 6.75/1, and the ratio of plasticizer to thickener (starch plus carrageenan) was 1.6/1. The plasticizer was composed of 75% Sorbitol Special and 25% glycerine. The components were mixed together and then heated to 98°C for 15 minutes (or to 92°C for 30 minutes), then poured hot onto a surface and drawn down into a film.

To control the temperature of the surface onto which films were cast, a stream of water was passed underneath and in contact with that surface. In this experiment, the water stream heated water, rather than chilled water as in the previous examples. The surface temperature was controlled by adjusting the thermostat in the water reservoir – a conventional re-circulating water bath.

To determine "minimum flow temperature" and "gel temperature", masses were cooked in an RVA, then transferred to preheated glass vials and placed in a 82°C (180°F) oven. After 2 hours equilibration, the vials were tipped and the flow of the mass observed, and a ranking assigned and recorded. The oven temperature was then reduced by 5.6°C (10°F) and the samples allowed to equilibrate for an additional 2 hours. The "minimum flow temperature" was defined as the lowest temperature at which the mass would easily flow in the vial. It was viscous but "pourable". The "gel temperature" was the highest temperature at which the mass did not flow at all. Since the samples were evaluated in 5.6°C (10°F) increments, the temperature assignments are approximate.

The kappa carrageenan used for this experiment was SKW Satiagel RPT 8/60 Kappa Carrageenan. The iota carrageenan used was FMC SD 389 PF Iota Carrageenan.

During conventional production of gelatin soft-gel capsules, the hot gelatin mass is cast onto a cooled drum (10-13°C; 50-55°F). In this experiment, the surface onto which the mass was cast was heated by the circulating water stream, in order to slow the rate of cooling of the

composition. Figure 1 shows the variation in wet strength of the films formed as the surface temperature varied.

Increasing the temperature of the filming surface dramatically increased wet film strength. (Wet film strength is the important strength parameter since the film must have sufficient integrity within 1-4 minutes of casting to survive an open draw and other rigors of capsule production.) At higher temperatures, the film thicknesses were lower (probably due to flow on the heated surface). When the film strengths were normalized to film thickness (g force per mm thickness), the temperature effect was especially dramatic – increasing 5 fold as the surface temperature increased from 12-66°C (53°F to 150°F). The "as-is" film strength, uncorrected for film thickness, increased 4 fold.

Film rates were not quantified, but all conditions generated films which could be lifted and handled in under a minute.

Without being bound by theory, it is possible that the higher film strength observed when the surface temperature was higher is due to larger, greater numbers and/or more perfect helices. When the films cool slowly, they have time and mobility near the gelation temperature to form larger and/or more perfect helices. A higher percentage of the carrageenan may be involved in helices compared to material that is quench-cooled.

Example 9

Experiments were performed using compositions like that of Example 8, but in which the carrageenan content was reduced by 25% and the total mass solids percentage was increased. These compositions had a mass viscosity and wet film strength similar to that exhibited by the formulation of Example 8. The composition and properties of the two soft gels are compared in Table 2 below. The two gel masses have similar viscosity/temperature profiles, and gel at similar temperatures. (As mentioned above, a flow rating of 5 is similar to water. A rating of zero indicates that the sample is gelled and there is no flow. A rating of at least 3 is preferred for handing on commercial equipment.)

Table 2

mass solids, %	% carrageenan	% starch	Flow rating 82°C	Flow rating 77°C	Flow rating 72°C	Flow rating 66°C	Breaking strength, g 12°C filming	Breaking strength, g 41°C filming
44	4.1	37	4.5	4.0	2.0	0.0	57	180
48	5.2	42	4.0	3.0	2.0	0.0	---	78

A 25% reduction in carrageenan makes the composition significantly less costly. Increased mass solids percentage reduces shrinkage and drying costs.

Example 10

Starch-based compositions were prepared containing the same ingredients as in Example 8, except iota carrageenan was used as a complete replacement for kappa carrageenan. However, films formed from such compositions had a slow film formation rate. In addition, the films formed were soft, weak, and very elastic.

Tests were then performed using a composition like that of Example 8, except that it included a combination of kappa and iota carrageenan, rather than only kappa carrageenan. This change resulted in stronger films (higher yield stress) than either of the two types of carrageenan alone. The strongest films comprised a 50/50 (weight) combination of the two. As much as 50% increase in film strength was measured with the 50/50 blend of kappa/iota compared with the kappa-only films.

The temperature at which the kappa-only gel mass became a rigid gel was high - about 160°F for the composition of Example 8 at 44% solids. The mass viscosity builds rapidly as its temperature is dropped below 82°C (180°F). This could be a problem in manufacturing operations, because the hot mass could set up in a location in manufacturing equipment that is inadvertently underheated. Further, even higher temperatures (88°C plus) are needed to re-soften the kappa-only gel for capsule sealing. Moreover, kappa carrageenan has a very sharp liquid-gel transition, whereas iota's transition is rather broad.

Because the strength of films formed from kappa/iota blends were not a mathematical combination of the two individual carrageenans, and a 50/50 combination of the two gave the strongest films, a mixed gel structure was strongly implied. Carrageenan gels by coiling portions of its carbohydrate backbone into helixes with portions of another carrageenan molecule. If the gel is composed of helixes containing one strand of kappa carrageenan and one strand of iota carrageenan, predicting the softening temperature is not straightforward.

We therefore prepared gel masses composed of either kappa carrageenan, or a 50/50 blend of kappa and iota. All other aspects of the formula were held constant (see Example 8 for the formulation details). A series of gel masses with varying total solids were prepared for each carrageenan composition. The effects on gel temperature are illustrated in Table 3 below. ("Minimum flow" and "gel temperature" are as defined above.)

Table 3

Effect of carrageenan on mass flow properties and gel temperature

% ds	approx min. flow temp, deg C		approx gel temp, deg C	
	kappa	kappa/iota	kappa	kappa/iota
42	71	66	66	60
44	74	71	71	66
45	77	71	71	66
46	82	77	71	66
47	85	77	71	66

It can be seen that replacing half of the kappa carrageenan with iota decreased the temperature at which the mass will flow, and decreased its gel temperature, by about 5.6°C (10°F) for each of the solids levels tested.

At 82°C (180°F) the two formulations had similar flow properties, but the kappa-only samples thickened rapidly with drop in temperature. Figure 2 illustrates the effect. Lower gel temperature, and more gradual gelation, should make the films made from kappa/iota mixtures easier to handle and easier to seal.

Table 3 above illustrates the importance of solids control during handling of these formulations. Figure 3 illustrates the rapid decrease in mass flowability at 77°C (170°F) as mass solids increases. The effect is especially pronounced for the kappa-only formulation. Blending iota carrageenan with kappa allows for higher solids while maintaining manageable viscosity.

Example 11

Two films that comprised the same ingredients as Example 10 were dipped in mineral oil and then were re-melted and sealed together. During capsule production, gelatin films are typically coated with oil before they are sealed. Without being bound by theory, it is believed that in the absence of the oil coating, evaporative cooling makes it difficult to seal the films (the rapid evaporation cools the films below their gel point by the time the two surfaces came together). The mineral oil appeared to suppress evaporation and the starch-based films could be readily sealed. Both films made with kappa carrageenan and with kappa/iota blends sealed readily using this technique.

The preceding description of specific embodiments of the present invention is not intended to be a complete list of every possible embodiment of the invention. Persons skilled

in this field will recognize that modifications can be made to the specific embodiments described here that would be within the scope of the present invention.

WHAT IS CLAIMED IS:

1. A film-forming composition, comprising:
starch material having a dextrose equivalent less than about 1 and selected from the group consisting of modified starch and waxy starch;
gum; and
plasticizer.

2. The composition of claim 1, wherein the composition is gelatin-free.

3. The composition of claim 1, further comprising water.

4. The composition of claim 3, wherein the composition comprises 30-70% by weight dry solids.

5. The composition of claim 4, wherein the dry solids in the composition comprise 25-75% starch material, 25-75% plasticizer, and 0.1-15% gum.

6. The composition of claim 1, wherein the weight ratio of gum to starch is from about 0.1:1 to about 1:1.

7. The composition of claim 1, wherein the weight ratio of starch and gum to plasticizer is from about 1:0.8 to about 1:3.

8. The composition of claim 1, wherein the starch material comprises starch which has been chemically modified with a monoreactive moiety to a degree of substitution of least about 0.015.

9. The composition of claim 8, wherein the starch material has an average molecular weight of about 100,000-2,000,000.

10. The composition of claim 9, wherein the starch material is selected from the group consisting of ether and ester derivatives of starch.

11. The composition of claim 10, wherein the starch material is selected from the group consisting of hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch.

12. The composition of claim 1, wherein the starch material comprises hydroxypropylated potato starch having a degree of substitution of about 0.015-0.30 and a molecular weight of about 100,000-2,000,000.

13. The composition of claim 1, wherein the gum is selected from the group consisting of carrageenan, locust bean, xanthan, gellan, agar, alginates, guar, gum arabic, and pectin.

14. The composition of claim 13, wherein the gum comprises a combination of kappa carrageenan and iota carrageenan.

15. The composition of claim 14, wherein the weight ratio of kappa carrageenan to iota carrageenan is about 1:1.

16. The composition of claim 1, wherein the plasticizer comprises at least one polyol.

17. The composition of claim 16, wherein the plasticizer is selected from the group consisting of glycerol, sorbitol, maltitol, and mixtures thereof.

18. The composition of claim 1, further comprising at least one monovalent or divalent cation.

19. The composition of claim 18, wherein the cation is selected from the group consisting of sodium, potassium, and calcium, and mixtures thereof.

20. The composition of claim 1, wherein:
the starch material is selected from the group consisting of (a) ether and ester derivatives of starch having a molecular weight of about 100,000-2,000,000 and a degree of substitution of about 0.015-0.30;
the gum comprises a combination of kappa carrageenan and iota carrageenan; and
the plasticizer comprises at least one polyol.

21. An edible film comprising the composition of any of claims 1-20.

22. A soft gel capsule comprising a sealed capsule wall and a first substance that is encapsulated by the sealed capsule wall;
wherein the capsule wall comprises a composition according to any of claims 1-20.

23. The capsule of claim 22, wherein the capsule wall consists essentially of a composition according to any of claims 1-20.

24. The capsule of claim 22, wherein the first substance is edible.

25. The capsule of claim 21, wherein the first substance is selected from the group consisting of drugs, vitamins, nutritional supplements, and pre-measured food additives.

26. A method of encapsulating a first substance, comprising the steps of:
providing a first substance and an edible film that comprises a composition according to any of claims 1-20; and
encapsulating the first substance in the film.

27. The method of claim 26, wherein the first substance is selected from the group consisting of drugs, vitamins, nutritional supplements, and pre-measured food additives.

28. The method of claim 26, wherein the film is formed at a temperature of at least about 38°C.

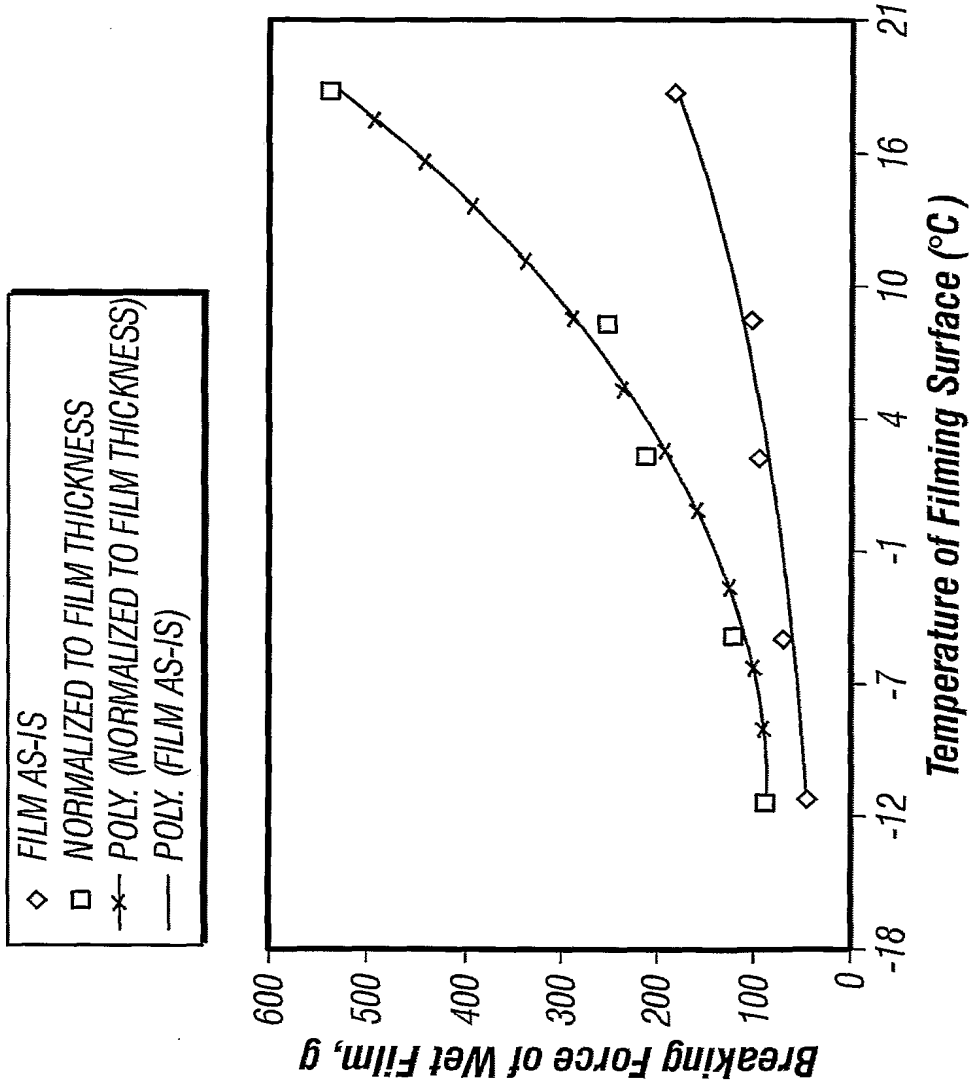

FIG. 1

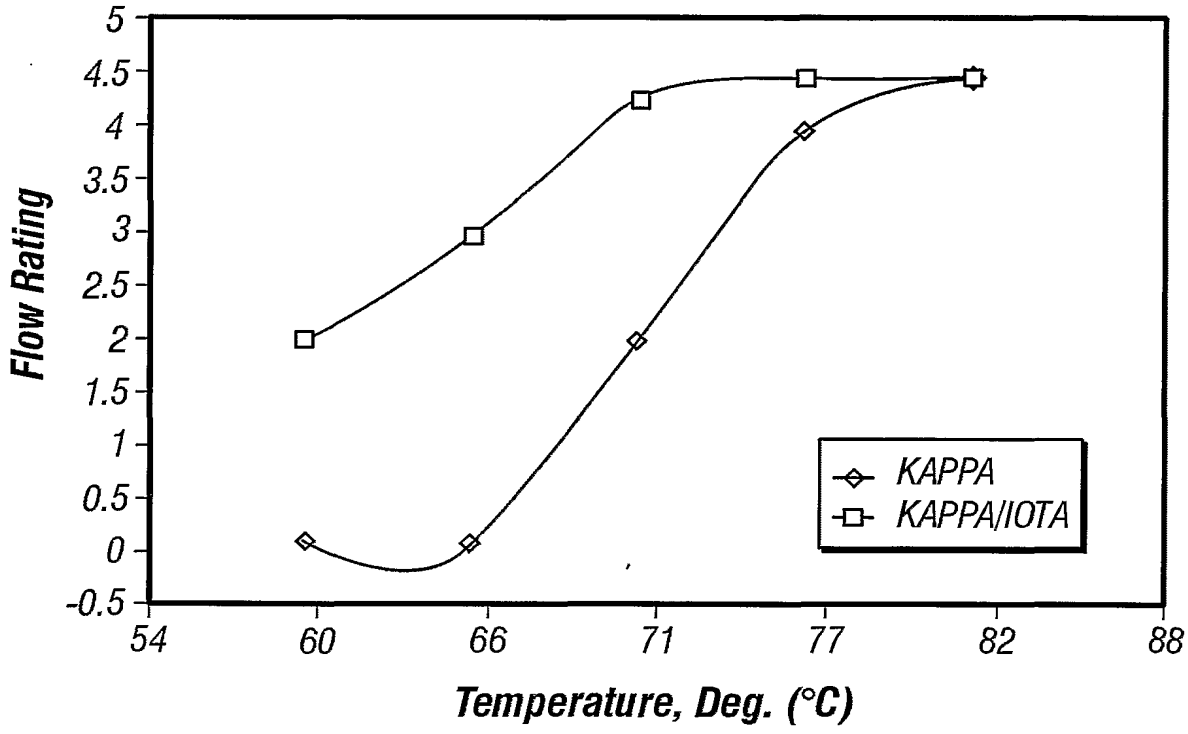

FIG. 2

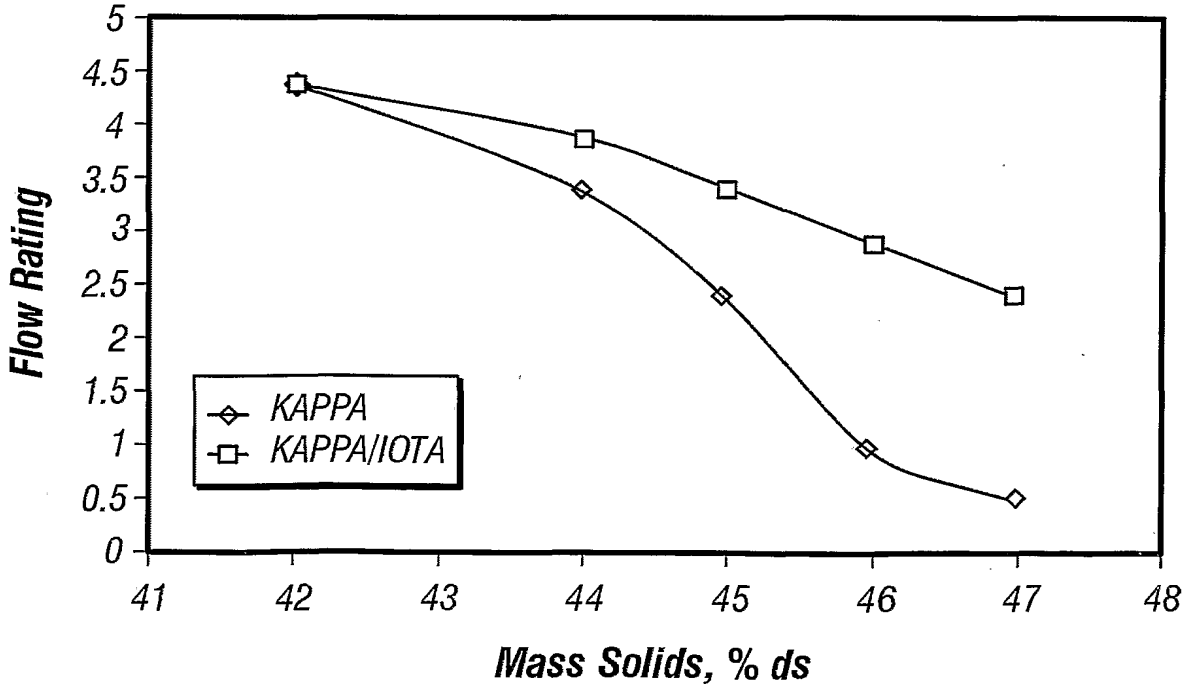

FIG. 3

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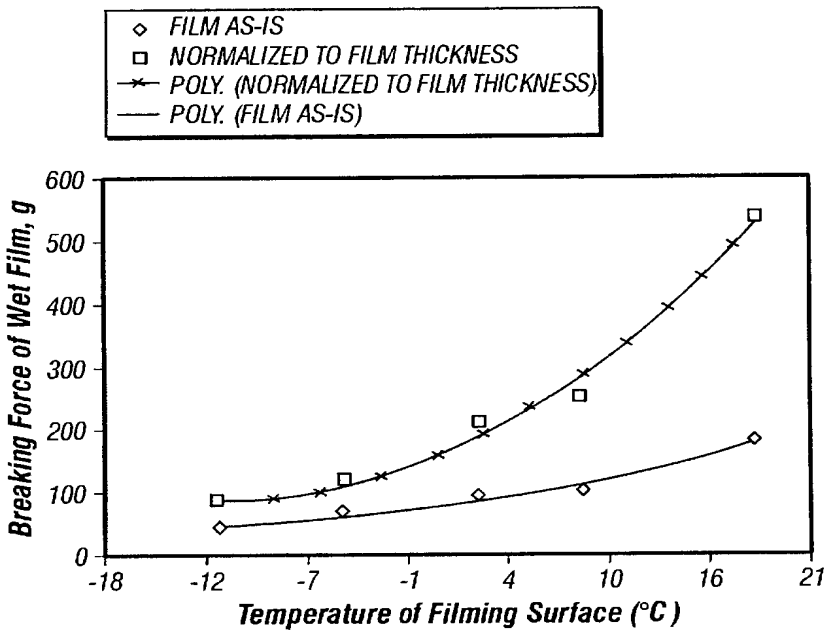
[Continued on next page]

(54) Title: MODIFIED STARCH AS A REPLACEMENT FOR GELATIN IN SOFT GEL FILMS AND CAPSULES



(57) Abstract: Film-forming compositions are disclosed that can comprise, on a dry solid basis, 25 to 75 percent by weight of certain starch derivatives having a DE less than about 1,25 to 75 % plasticizer, and 0.1 to 15 % hydrocolloid gum. The starch derivatives can be chemically modified starches which range in molecular weight from 100,000 to 2,000,000. These starch-based systems can completely replace gelatin in edible film-forming applications such as soft and hard gel capsules.

WO 01/91721 A3

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Inter *ional Application No
PC1/US 01/14888

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08L3/00 C08J5/18 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08L C08J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 451 673 A (MARSHALL L. FISHMAN ET AL.) 19 September 1995 (1995-09-19) column 4, line 10 - line 68	1-7,9, 13, 16-19,21
X	FR 2 783 832 A (WARNER LAMBERT COMPANY) 31 March 2000 (2000-03-31) page 2, paragraph 4 -page 3, paragraph 7	1-28
X	WO 00 10538 A (BANNER PHARMACAPS INC) 2 March 2000 (2000-03-02) page 5, line 29 -page 6, line 1 page 7, line 1 -page 9, line 11	1-28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 2001	05/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lensen, H

1

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INTERNATIONAL SEARCH REPORT

Inter ional Application No
PC1/US 01/14888

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 17, no. 266 (C-1062), 25 May 1993 (1993-05-25) & JP 05 004914 A (ASAHI CHEM IND CO LTD), 14 January 1993 (1993-01-14) abstract & DATABASE WPI Week 199307 Derwent Publications Ltd., London, GB; AN 1993-055171 abstract	1-18
P,X	WO 01 03677 A (R.P.SCHERER TECHNOLOGIES) 18 January 2001 (2001-01-18) page 16, line 4 - line 14 page 10, line 18 -page 11, line 15	1-28
A	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 07, 29 September 2000 (2000-09-29) & JP 2000 116339 A (ITOO KAIGAI JIGYO KK), 25 April 2000 (2000-04-25) abstract & DATABASE WPI Week 200032 Derwent Publications Ltd., London, GB; AN 2000-369392 abstract	
A	US 4 009 291 A (WILLIAM A. MITCHELL ET AL.) 22 February 1977 (1977-02-22)	
E	EP 1 103 254 A (PETER GREITHER) 30 May 2001 (2001-05-30) page 3, line 21 - line 46 page 6, line 1 - line 20	1-28

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ional Application No
PCT/US 01/14888

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 6711094 A	21-11-1994
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PTO/SB/08a (03-08)
Approved for use through 07/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	95002170
Filing Date	2013-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5044761		1991-09-03	Yuhki et al	
	2	5047244		1991-09-10	Sanvordeker et al	
	3	5064717		1991-11-12	Suzuki et al	
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	8	5229164		1993-07-20	Pins et al	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	95002170
	Filing Date	2013-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	9	5234957		1993-08-10	Mantelle	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	95002170
	Filing Date	2013-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	20	5518902		1996-05-21	Ozaki et al	
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	30	6153210		2000-11-28	Roberts et al	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	95002170
	Filing Date	2013-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	31	6177096		2001-01-23	Zerbe et al	
	32	6231957		2001-05-15	Zerbe et al	

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20010046511	A1	2001-11-29	Zerbe et al.	
	2	20050118217		2005-06-02	Barnhart et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2432925	DE	C3	1976-01-22	Schering AG		☐
	2	2449865	DE	B2	1976-04-29	Schering AG Berlin and Bergkamen		☐
	3	3630603	DE	C2	1988-03-10	Desitin Arzneimittel GmbH		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	95002170
	Filing Date	2013-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	4	0200508	EP	B1	1986-12-10	Nitto Denko Corporation		☐
	5	0219762	EP	A1	1987-04-29	Desitin Arzneimittel GmbH		☐
	6	0241178	EP	B1	1987-10-14	Rohto Pharmaceutical Co., Ltd.		☐
	7	0250187	EP	B1	1987-12-23	Johnson & Johnson Consumer Products, Inc.		☐
	8	0259749	EP	B1	1988-03-16	Desitin Arzneimittel GmbH		☐
	9	0273069	EP	B1	1988-07-06	Uni Colloid Kabushiki Kaisha		☐
	10	0381194	EP	A2	1990-08-08	Nitto Denko Corporation		☐
	11	0452446	EP	B1	1991-10-23	Desitin Arzneimittel GmbH		☐
	12	0514691	EP	B1	1992-11-25	Euroresearch S.r.L.		☐
	13	1110546	EP	A1	2001-06-27	Johnson & Johnson Consumer Companies, Inc.		☐
	14	9105540	WO		1991-05-02	Desitin Arzneimittel GMBH		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	95002170
	Filing Date	2013-09-10
	First Named Inventor	Robert K. Yang
	Art Unit	3991
	Examiner Name	Diamond, Alan D.
	Attorney Docket Number	1199-26 RCE/CON/REX

	15	9215289	WO		1992-09-17	Noven Pharmaceuticals, Inc.		☐
	16	9505416	WO		1995-02-23	Cygnus Therapeutic Systems		☐
	17	9518046	WO		1995-07-06	Frank, Richard, D.		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99**)

Application Number	95002170
Filing Date	2013-09-10
First Named Inventor	Robert K. Yang
Art Unit	3991
Examiner Name	Diamond, Alan D.
Attorney Docket Number	1199-26 RCE/CON/REX

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Daniel A. Scola, Jr., Reg. No. 29,855/	Date (YYYY-MM-DD)	2013-01-29
Name/Print	Daniel A. Scola, Jr.	Registration Number	29,855

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Electronic Acknowledgement Receipt

EFS ID:	14825752
Application Number:	95002170
International Application Number:	
Confirmation Number:	6418
Title of Invention:	POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	7897080
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	117744-00023
Receipt Date:	29-JAN-2013
Filing Date:	10-SEP-2012
Time Stamp:	23:36:16
Application Type:	inter partes reexam

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_Statement.pdf	12791 59b32973e93bf159453436a901e1f2f8c14fb4f8	no	2

Warnings:	
Information:	

2	Foreign Reference	DE2432925.pdf	392210 785a64274de8ed518b718c32f2327851641 04446	no	5
Warnings:					
Information:					
3	Foreign Reference	DE2449865.pdf	270911 a7807c93ccf0f1be4d0b4a61f1c71b0962d2 ba2e	no	4
Warnings:					
Information:					
4	Foreign Reference	DE3630603.pdf	410916 43d270c72689866bb57b20e58e53a7c3c07 06535	no	5
Warnings:					
Information:					
5	Foreign Reference	EP0200508.pdf	1584485 7666ec90cf3df74a98aeb01854efeee4d7fd 6b96	no	26
Warnings:					
Information:					
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Warnings:					
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7	Foreign Reference	EP0241178.pdf	709878 a2e84a1b0ff8de4e4da6fbd0a0270bd33be 7cae1	no	10
Warnings:					
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8	Foreign Reference	EP0250187.pdf	785142 537d59477e97922fe8b410b77e308861f28 270b3	no	16
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9	Foreign Reference	EP0259749.pdf	581730 f99b5309a79fc5c86c583c4b8632bec86304 0c46	no	8
Warnings:					
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10	Foreign Reference	EP0273069.pdf	947238 b9299eb58d2fb66b5794d86f534654eb161 610b0	no	14
Warnings:					
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Warnings:					
Information:					
12	Foreign Reference	EP0452446.pdf	291912 b2216a41816d54917057005f51e673acc0c28526	no	5
Warnings:					
Information:					
13	Foreign Reference	EP0514691.pdf	405124 cff1313a7ef94cca28f38ca403cf864c293d42c4	no	7
Warnings:					
Information:					
14	Foreign Reference	EP1110546.pdf	260125 ff9bdaee40d29a40dca8ddb93206165f3fe07a2b	no	15
Warnings:					
Information:					
15	Foreign Reference	WO1991005540.pdf	620295 c06fdd7241d3a9668129186f044b5a614d267ba7	no	17
Warnings:					
Information:					
16	Foreign Reference	WO1992015289.pdf	2707694 147be495a68b814a12fd449142952758c5ab897f	no	62
Warnings:					
Information:					
17	Foreign Reference	WO1995005416.pdf	3478794 33db7779286b087629fea18945c8a4c92863aa8a	no	83
Warnings:					
Information:					
18	Foreign Reference	WO1995018046.pdf	1771071 e30d63c1dd922091acb78c899bd47b14a772a270	no	44
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19	Information Disclosure Statement (IDS) Form (SB08)	080_IDS3.pdf	87522 8845bb0e46fd11523cc6e30114d7d5d24469c425	no	8
Warnings:					
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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee:	Yang et al.	Examiner:	Diamond, Alan D.
Patent No.:	U.S. 7,897,080	Group Art Unit:	3991
Reexamination Control No.:	95/002,170	Confirmation No.	6418
Filed:	September 10, 2012	H&B Docket:	1199-26 RCE/CON/REX
Dated:	January 29, 2013	M&E Docket:	117744-00023

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Central Reexamination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Madam:

This Information Disclosure Statement is being submitted pursuant to 37 C.F.R. 1.98, and identifies a number of patents and publication that may be considered relevant. The Patent Holder makes no representation as to the relevance of these documents, but wishes to make these references of record in this reexamination. Consideration of the references recited herein is requested.

If any fee is due with this submission, the Commission is authorized to charge any such fee to Deposit Account No. 08-2461. Should the Examiner have any questions regarding this submission, the undersigned would be pleased to address them.

Respectfully submitted,

/Daniel A. Scola, Jr./
Daniel A. Scola, Jr.
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DE-PS	14 17 385
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In Betracht gezogenes älteres Patent:
DE-PS 24 59 391;
DE-Z.: Fiedler: Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Aulendorf 1971, S. 24,110,111, 308,376-378,608,609;
Römpp chem. Wörterbuch, Stuttgart 1969, S. 54,682,872;

(54) Folienförmige Arzneimittel

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Patentansprüche:

1. Folienförmige Arzneimittel mit gleichmäßiger Wirkstoffverteilung mit bis zu 60% Wirkstoffen, bezogen auf getrocknete Arzneimittel, auf Basis filmbildender wasserlöslicher Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose, erhalten durch Ausziehen einer Lösung oder Suspension von 48—84 Gewichtsprozent Lösungs- bzw. Suspensionsmittel, 6—20 Gewichtsprozent Folienbildner, 0—30 Gewichtsprozent Füllstoffen und 0,01—2 Gewichtsprozent Polyoxyäthylenpolyoxypropylenpolymeres, Polyoxyäthylenstearate, alkyl- bzw. acylsubstituierte Polyadditionsprodukte des Äthylenoxids als Trennmittel, wobei die Gewichtsprozente auf die Lösung bzw. Suspension bezogen sind, sowie den Wirkstoff und Trocknen und gegebenenfalls Teilen der Folie in Abschnitte.

2. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß sie als Füllstoffe Cellulose, Zucker, Stärken, Mannit, Calciumcarbonat, Calciumphosphat oder Talkum enthalten.

Die Erfindung betrifft den in den Ansprüchen gekennzeichneten Gegenstand.

Aus der belgischen Patentschrift Nr. 6 37 363 sind Papierfolien bekannt, die mit Wirkstoff beschichtet zur oralen Anwendung geeignet sind. Die Folien bestehen aus in Wasser unlöslichen Cellulosefasern und einem wasserlöslichen Bindemittel. Als wasserlösliche Bindemittel wird vorzugsweise Carboxymethylcellulose-Natrium verwendet. Nach den Beispielen der belgischen Patentschrift wird der Wirkstoff durch Auftropfen des gelösten Wirkstoffes, durch Aufstreuen des festen Wirkstoffes oder durch Durchziehen der Folie durch die Wirkstofflösung auf die Papierfolie gebracht. Das diskontinuierliche Verfahren der gesonderten Herstellung der Folie und Aufbringung des Wirkstoffes hat den Nachteil, daß die Dosierungsgenauigkeit nicht sehr gut ist, was bei den heute niedrig dosierten Wirkstoffen jedoch von großer Wichtigkeit ist. Ungenauigkeiten entstehen aber nicht nur bei dem Aufbringen des Wirkstoffes, sondern auch bei der Herstellung und Vorbehandlung des Trägers und durch Veränderungen bei der Lagerung des Trägermaterials. So hat es sich zum Beispiel gezeigt, daß nach der Rezeptur der belgischen Patentschrift bei Verwendung von Folienziehmaschinen keine gleichmäßige Folienschicht entsteht und daß die Folie bei der Trocknung schrumpft.

Aus den deutschen Offenlegungsschriften DE-OS 18 00 580 und DE-OS 19 31 080 sind Arzneimittelzubereitungen in flüssiger und salbenartiger Form bekannt, die erst nach der Applikation auf der Haut einen festen Film bilden.

Die deutsche Offenlegungsschrift DE-OS 20 06 696 bezieht sich auf ein medizinisches Pflaster oder einen Haftverband mit verschiedenen Ausnehmungen oder Hohlräumen, die mit einer Tablette, mit Puder, Salbe, Creme oder ähnlichen Substanzen gefüllt sind und zur Verabreichung von empfängnisverhütenden Substanzen mit Systemwirkung auf dem Wege durch die Haut geeignet sind. Das Pflaster kann auch aus einem Träger- und einem Klebeteil bestehen, wobei die empfängnisverhütenden Stoffe durch Aufsprühen oder Dispergieren der Wirkstofflösung in den Klebeteil eingearbeitet sein können. Die erfindungsgemäßen folienförmigen Arzneimittel bestehen dagegen aus einer einheitlichen Phase mit inkorporiertem Wirkstoff.

Aus der amerikanischen Patentschrift US-PS 38 03 300 sind salbenartige Folien (getrocknete Öl-in-Wasser-Emulsionen) bekannt. Im Gegensatz zu den gelartigen erfindungsgemäßen Arzneimitteln und Placebos enthalten die Folien gemäß US-PS 38 03 300 Öle oder Fette und Emulgatoren.

Ferner ist es bekannt, feste oral applizierbare Arzneimittel mit Überzügen zu versehen, die als Bindemittel sogenannte Filmbildner wie Harze oder Celluloseäther enthalten. Die wirkstofffreien Überzüge schützen das Arzneimittel vor Abrieb, vor Licht und Feuchtigkeit, sie wirken außerdem geruchs- und geschmackshemmend (Fiedler: »Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete«).

In der österreichischen Patentschrift AT-PS 2 79 035 werden Folien zur Erzeugung lokaler Anästhesie beschrieben. Aus einer großen Zahl genannter Folienbildner, die auch Celluloseäther einschließt, werden Polyvinylalkohol, Polyvinylpyrrolidon und Alkalimetallcarboxymethylcellulose besonders herausgestellt. Es hat sich gezeigt, daß die nach der österreichischen Patentschrift bevorzugten Folienbildner für unsere Zwecke wenig geeignet sind, da diese Folienbildner die Wirkstoffe teilweise einschließen und nur verzögert oder überhaupt nicht freigeben. Bei der Verwendung von Polyvinylalkohol als Folienbildner wird die Folie bei Temperaturen um 100°C gegossen und getrocknet; nach dem Abkühlen tritt eine Kristallisation des Wirkstoffes ein, wodurch eine gleichmäßige Wirkstoffverteilung in der Folie nicht mehr gewährleistet ist.

Es ist die Aufgabe der Erfindung, folienförmige Arzneimittel bereitzustellen, in denen bis zu 60% Wirkstoffe gleichmäßig verteilt sind bzw. in denen eine Kristallisation der Wirkstoffe verhindert wird. Die Aktivität der Wirkstoffe muß in der Folie erhalten bleiben, und die Folie darf sich beim Lagern nicht verändern. Das Folienmaterial darf die Wirkstoffe nicht einschließen und muß sie bei Anwendung wieder vollständig freigeben.

Die Aufgabe wird dadurch gelöst, daß man ein Trennmittel einsetzt und als Folienbildner einen nichtionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose verwendet.

Als nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose seien beispielsweise Hydroxypropylcellulose, Hydroxyäthylcellulose und Methylhydroxypropylcellulose genannt.

Geeignete Trennmittel sind Polyoxyäthylenpolyoxypropylenpolymeres, Polyoxyäthylenstearate und alkyl- oder acylsubstituierte Polyadditionsprodukte des Äthylenoxids.

Außer Trennmittel, Folienbildner und Wirkstoffe können die erfindungsgemäßen Folien Füllstoffe enthalten.

Als Füllstoffe sind zum Beispiel Cellulose, Zucker, wie zum Beispiel Lactose, Dextrose, Rohrzucker usw., Stärken, Mannit, Calciumcarbonat, Calciumphosphat, Talkum und Farbstoffe in löslicher Form oder als Pigmente geeignet. Werden lösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine transparente, glatte Folie; werden unlösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine weiße oder farbige, papier-

artige Folie.

Es können alle in der Human- und Veterinärmedizin verwendeten Wirkstoffe eingesetzt werden. Für die innere Anwendung kommt insbesondere die orale Verabreichung infrage. Unter der äußeren Anwendung sollen insbesondere die topikale Verabreichung auf der Haut und in Körperhöhlungen wie Nase, Ohr, Vagina usw., verstanden werden. Als Wirkstoffe seien beispielsweise genannt: Gestagene, Östrogene, Gemische aus Gestagenen und Östrogenen, Tranquilizer, Antidiabetika, Sulfonamide, Antibiotika, Trichomonadenmittel, Entzündungshemmer, wie zum Beispiel Corticoide, usw.

Der Arzneimittelwirkstoff kann im Trägermaterial gelöst oder gleichmäßig suspendiert vorliegen. Der Wirkstoffanteil in der Folie kann bis zu 60% betragen. Als Einzeldosis (Einheit) werden Flächen geschnitten bzw. perforiert, die Wirkstoffmengen enthalten wie sie üblicherweise auch in Tabletten, Dragees, Salben, Zäpfchen usw. enthalten sind. So kann die Wirkstoffmenge pro Einzeldosis je nach Anwendungsart beliebig hoch sein und zwischen etwa 1 µg und 0,5 g betragen, wobei die untere und obere Dosis leicht unter- oder überschritten werden können.

Zur Herstellung der erfindungsgemäßen folienförmigen Arzneimittel werden bis zu 60% Wirkstoffe, bezogen auf getrocknete Arzneimittel, und das Trennmittel gelöst bzw. suspendiert, der Folienbildner und gegebenenfalls der Füllstoff eingetragen, gegebenenfalls homogenisiert und die Lösung bzw. Suspension auf einer Folienziehmaschine zu einem Ausstrich ausgezogen. Die durch Trocknung des Ausstrichs erhaltene Folie wird durch Schneiden bzw. Perforieren in Einzeldosen geteilt.

In der Lösung bzw. Suspension wird der Folienbildner in Gewichtsmengen von 6 – 20%, der Füllstoff in Gewichtsmengen von 0 – 30% und das Trennmittel in Gewichtsmengen von 0,01 – 2% eingesetzt.

Das Lösungs- bzw. Suspensionsmittel ist zu etwa 48 – 84 Gewichtsprozent enthalten und besteht aus Wasser und/oder einem oder mehreren organischen Lösungsmitteln. Als organische Lösungsmittel kommen physiologisch verträgliche Lösungsmittel oder solche Lösungsmittel in Betracht, die bei der Trocknung bis auf einen physiologisch unbedenklichen Rest entfernt werden können. Solche Lösungsmittel sind zum Beispiel Äthylalkohol, Isopropanol, Methylenchlorid usw. und ihre Mischungen. Wasser und Äthylalkohol bzw. Gemische aus Wasser und Äthylalkohol werden bevorzugt angewandt.

Die Schichtdicke des nassen Ausstrichs beträgt etwa 0,1 – 2 mm und die der trockenen Folie etwa 0,05 – 1 mm, vorzugsweise 0,07 – 0,3 mm.

Das Verfahren zur Herstellung des Arzneimittels in Folienform in einem Arbeitsgang (kontinuierliches Verfahren) bietet den Vorteil, daß der Wirkstoff homogen und gleichmäßig verteilt in dem Wirkstoffträger vorliegt. Durch die Konzentration des Wirkstoffs im Träger, die Dicke der Folie und die Fläche kann man die Einzeldosis sehr einfach variieren.

Beispiel 1

Herstellung für 1000 Einheiten:

0,25 g D-Norgestrel
0,05 g Äthinylöstradiol
und
0,84 g Polyoxyäthylenpolyoxypropylenpolymeres
werden in
95,00 g Äthylalkohol unter Rühren gelöst, in diese Lösung wird eine Pulvermischung aus
16,93 g Hydroxypropylcellulose und
16,93 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,25 mg D-Norgestrel
0,05 mg Äthinylöstradiol
0,84 mg Polyoxyäthylenpolyoxypropylenpolymeres
16,93 mg Hydroxypropylcellulose
16,93 mg Cellulose
35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm². Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 2

Herstellung für 1000 Einheiten:

1,10 g Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid) werden in
152,00 g Wasser gelöst. In dieser Lösung werden
0,25 g mikronisiertes D-Norgestrel und
0,05 g mikronisiertes Äthinylöstradiol suspendiert und evtl. homogenisiert. In diese Suspension werden
22,10 g Hydroxypropylcellulose und
16,50 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,25 mg D-Norgestrel
0,05 mg Äthinylöstradiol
1,10 mg Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 ml Äthylenoxid auf 1 Mol Glycerid)
22,10 mg Hydroxypropylcellulose
16,50 mg Cellulose
40,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 3

Herstellung für 1000 Einheiten:

0,03 g D-Norgestrel und
0,84 g Polyoxyäthylenmonostearat-40 werden in
95,00 g Äthylalkohol unter Rühren gelöst.
In diese Lösung wird eine Pulvermischung aus
16,93 g Hydroxypropylcellulose und
17,20 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,03 mg D-Norgestrel
0,84 mg Polyoxyäthylenmonostearat-40
16,93 mg Hydroxypropylcellulose
17,20 mg Cellulose

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 4

Herstellung für 1000 Einheiten:

1,10 g Polyoxyäthylenpolyoxypropylenpolymeres werden in
152,00 g demineralisiertem Wasser gelöst.
In dieser Lösung werden
0,03 g mikronisiertes D-Norgestrel suspendiert und evtl. homogenisiert.
In die Suspension werden
22,10 g Hydroxypropylcellulose und
16,77 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,03 mg D-Norgestrel
1,10 mg Polyoxyäthylenpolyoxypropylenpolymeres
22,10 mg Hydroxypropylcellulose
16,77 mg Cellulose

40,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 5

Herstellung für 1000 Einheiten:

10,00 g 7-Chlor-2-methylamino-5-phenyl-3H-1,4-benzo-diazepin-4-oxid und
0,84 g Polyoxyäthylenpolyoxypropylenpolymeres werden in
95,00 g Äthylalkohol gelöst.
In diese Lösung wird ein Pulvergemisch aus
16,93 g Hydroxypropylcellulose und
7,23 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

10,00 mg 7-Chlor-2-methylamino-5-phenyl-3H-1,4-benzo-diazepin-4-oxid

0,84 mg Polyoxyäthylenpolyoxypropylenpolymeres
16,93 mg Hydroxypropylcellulose
7,23 mg Cellulose

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: gelb, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 6

Herstellung für 1000 Einheiten:

1,00 g Norethisteronacetat
0,03 g Äthinylöstradiol und
0,84 g Polyoxyäthylenpolyoxypropylenpolymeres werden in
95,00 g Äthylalkohol gelöst.
In diese Lösung wird ein Pulvergemisch aus
16,93 g Hydroxypropylcellulose und
16,20 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00 mg Norethisteronacetat
0,03 mg Äthinylöstradiol
0,84 mg Polyoxyäthylenpolyoxypropylenpolymeres
16,93 mg Hydroxypropylcellulose
16,20 mg Cellulose

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 7

Herstellung für 1000 Einheiten:

1,00 g Norethisteronacetat
0,03 g Äthinylöstradiol und
0,84 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einem Gemisch aus
101,60 g Methylenchlorid und
25,40 g Äthylalkohol gelöst.
In diese Lösung wird ein Pulvergemisch aus
16,93 g Hydroxyäthylcellulose und
16,20 g Stärke eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00 mg Norethisteronacetat
0,03 mg Äthinylöstradiol
0,84 mg Polyoxyäthylenpolyoxypropylenpolymeres
16,93 mg Hydroxyäthylcellulose und
16,20 mg Stärke

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 8

Herstellung für 1000 Einheiten:

1,00 g Norethisteronacetat
0,03 g Äthinylöstradiol und
0,84 g Polyoxyäthylenmonostearat-40 werden in
95,00 g Äthylalkohol gelöst.
In diese Lösung wird ein Pulvergemisch aus
16,93 g Hydroxypropylcellulose
8,10 g Lactose und
8,10 g Maisstärke eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00 mg Norethisteronacetat
0,03 mg Äthinylöstradiol
0,84 mg Polyoxyäthylenmonostearat-40
16,93 mg Hydroxypropylcellulose
8,10 mg Lactose
8,10 mg Maisstärke
35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 9

Herstellung für 1000 Einheiten:

25,0 g 5-Morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl)-methylenamino-2-oxazolidinon · HCl
werden in
2,1 g Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid) gelöst in
152,0 g Alkohol und Wasser 1 : 1 suspendiert. In diese Suspension werden
42,3 g Methylhydroxypropylcellulose und
18,1 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und getrocknet.

Zusammensetzung für eine Einheit:

25,0 mg 5-Morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl)-methylenamino-2-oxazolidinon · HCl
2,1 mg Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid)
42,3 mg Methylhydroxypropylcellulose
18,1 mg Cellulose
87,5 mg

Eine Einheit entspricht einer Fläche von ca. 8 cm².
Aussehen der Folie: hellgelb, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 10

Herstellung für 1000 Einheiten:

4,0 g Glisoxepid in mikronisierter Form werden in
0,9 g Polyoxyäthylenmonostearat-40 gelöst in
152,0 g Wasser suspendiert und eventuell homogenisiert.
In die Suspension werden
15,0 g Hydroxyäthylcellulose und
15,1 g Calciumcarbonat eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und getrocknet.

Zusammensetzung für eine Einheit:

4,00 mg Glisoxepid
0,90 mg Polyoxyäthylenmonostearat-40
15,00 mg Hydroxyäthylcellulose
15,10 mg Calciumcarbonat
35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

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(54) Folienförmiges Arzneimittel

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BUNDESDRUCKEREI BERLIN 04 81 130 125/104

Patentansprüche:

1. Folienförmiges Arzneimittel auf Basis filmbildender Celluloseäther gemäß Patentanmeldung P 24 32 925.7-41, dadurch gekennzeichnet, daß die Folie nebeneinander Dosierungseinheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff aufweist.

2. Verfahren zur Herstellung eines folienförmigen Arzneimittels auf Basis filmbildender Celluloseäther durch Ausziehen von Lösungen bzw. Suspensionen auf einer Folienziehmaschine, durch nachträgliches Trocknen des nassen Ausstrichs und Teilen der Folie in Abschnitte gemäß Patentanmeldung P 24 32 925.7-41, dadurch gekennzeichnet, daß man zwei oder mehrere unterschiedliche Lösungen bzw. Suspensionen aus Trennmittel, Folienbildner und gegebenenfalls Füllstoffen und/oder Wirkstoffen herstellt, die unterschiedlichen Lösungen bzw. Suspensionen mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, zu einem Ausstrich auszieht und die durch Trocknung des Ausstrichs erhaltene Folie in Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff teilt.

Gegenstand der Patentanmeldung P 24 32 925.7-41 sind folienförmige Arzneimittel mit gleichmäßiger Wirkstoffverteilung bzw. folienförmige Placebos auf Basis filmbildender Celluloseäther, dadurch gekennzeichnet, daß sie bis zu 60% Wirkstoffe, ein Trennmittel und als Folienbildner einen nicht-ionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose enthalten sowie ein Verfahren zu deren Herstellung.

In Weiterentwicklung des Gegenstandes der Patentanmeldung P 24 32 925.7-41 betrifft die vorliegende Erfindung das in den Ansprüchen näher gekennzeichnete folienförmige Arzneimittel und dessen Herstellung.

Es werden in einem Ausstrich Folien hergestellt, die nebeneinander Dosierungseinheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff aufweisen. Mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, werden unterschiedliche Lösungen bzw. Suspensionen ohne Vermischen zu einem zusammenhängenden Ausstrich ausgezogen. Die Breite und die Dicke des Ausstrichs ist für jede Kammer separat einstellbar. Gewünschtenfalls können Zonen (Streifen) mit unterschiedlichen Wirkstoffen bzw. verschiedenen Konzentrationen durch unterschiedliche Farbstoffe sichtbar gemacht werden. Durch Trocknung des nassen Ausstrichs wird eine Folie erhalten, die bei entsprechender Teilung, zum Beispiel durch Perforation, Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff liefert. Folien mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen werden zur Herstellung von Mehrphasenpräparaten benötigt, beispielsweise zur

Herstellung von Präparaten zur Konzeptionsverhütung.

Durch die Möglichkeit der räumlichen Trennung von miteinander inkompatiblen Wirkstoffen in einer Folieneinheit wird die Stabilität der einzelnen Wirkstoffe verbessert.

Das folienförmige Arzneimittel enthält ein Trennmittel und als Folienbildner einen nichtionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose.

Als nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose seien beispielsweise Hydroxypropylcellulose, Hydroxyäthylcellulose und Methylhydroxypropylcellulose genannt.

Geeignete Trennmittel sind u. a. Polyoxyäthylenpolyoxypropylenpolymeres, Polyoxyäthylenstearate, alkyl- bzw. acylsubstituierte Polyadditionsprodukte des Äthylenoxids, zum Beispiel das Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid), Silikone, Silikontrennemulsionen und Metallseifen.

Außer Trennmittel und Folienbildner können die erfindungsgemäßen Folien Füllstoffe und Wirkstoffe enthalten.

Als Füllstoffe sind zum Beispiel Cellulose, Zucker, wie zum Beispiel Lactose, Dextrose, Rohrzucker usw., Stärken, Mannit, Calciumcarbonat, Calciumphosphat, Talkum und Farbstoffe in löslicher Form oder als Pigmente geeignet. Werden lösliche Füll- bzw. Wirkstoff verwendet, entsteht eine transparente, glatte Folie; werden unlösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine weiße oder farbige, papierartige Folie.

Es können alle in der Human- und Veterinärmedizin verwendeten Wirkstoffe eingesetzt werden. Für die innere Anwendung kommt insbesondere die orale Verabreichung in Frage. Unter der äußeren Anwendung sollen insbesondere die topikale Verabreichung auf der Haut und in Körperhöhlungen wie Nase, Ohr, Vagina usw., verstanden werden. Als Wirkstoffe seien beispielsweise genannt: Gestagene, Östrogene, Gemische aus Gestagenen und Östrogenen, Tranquilizer, Antidiabetika, Sulfonamide, Antibiotika, Trichomonadenmittel, Entzündungshemmer, wie zum Beispiel Corticoide, usw.

Der Arzneimittelwirkstoff kann im Trägermaterial gelöst oder gleichmäßig suspendiert vorliegen. Der Wirkstoffanteil in der Folie kann 0 – 60% betragen. Als Einzeldosis (Einheit) werden Flächen geschnitten bzw. perforiert, die Wirkstoffmengen enthalten, wie sie üblicherweise auch in Tabletten, Dragées, Salben, Zäpfchen usw. enthalten sind. So kann die Wirkstoffmenge pro Einzeldosis je nach Anwendungsart beliebig hoch sein und zwischen etwa 1 µg und 0,5 g betragen, wobei die untere und obere Dosis leicht unter- oder überschritten werden können. Selbstverständlich können auch wirkstofffreie Träger (Placebos) hergestellt werden.

Zur Herstellung des folienförmigen Arzneimittels mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen werden zwei oder mehrere unterschiedliche Lösungen bzw. Suspensionen aus Trennmittel, Folienbildner und gegebenenfalls Füllstoffen und/oder Wirkstoffen bereitet, die unterschiedlichen Lösungen bzw. Suspensionen mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, auf einer Folienziehmaschine zu einem Ausstrich ausgezogen und die durch Trocknung des Ausstrichs erhaltene Folie in Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff geteilt.

Pro Lösung bzw. Suspension wird der Folienbildner in Gewichtsmengen von 6–20%, der Füllstoff in Gewichtsmengen von 0–30% und das Trennmittel vorzugsweise in Gewichtsmengen von 0,01–2% eingesetzt.

Das Lösungs- bzw. Suspensionsmittel ist zu etwa 48–84 Gewichtsprozent enthalten und besteht aus Wasser und/oder einem oder mehreren organischen Lösungsmitteln. Als organische Lösungsmittel kommen physiologisch verträgliche Lösungsmittel oder solche Lösungsmittel in Betracht, die bei der Trocknung bis auf einen physiologisch unbedenklichen Rest entfernt werden können. Solche Lösungsmittel sind zum Beispiel Äthylalkohol, Isopropanol, Methylenchlorid usw. und ihre Mischungen. Wasser und Äthylalkohol bzw. Gemische aus Wasser und Äthylalkohol werden bevorzugt angewandt.

Die Schichtdicke des nassen Ausstrichs beträgt etwa 0,1–2 mm und die der trockenen Folie etwa 0,05–1 mm, vorzugsweise 0,07–0,3 mm.

Das kontinuierliche Verfahren zur Herstellung des folienförmigen Arzneimittels bietet den Vorteil, daß der Wirkstoff homogen und gleichmäßig verteilt in dem Wirkstoffträger vorliegt. Durch die Konzentration des Wirkstoffs im Träger, die Dicke der Folie und die Fläche der Folie kann man die Einzeldosis sehr einfach variieren.

Beispiel 1

Zweiphasenpräparat

Teil 1: 21 Einheiten mit Wirkstoff
Teil 2: 7 Einheiten ohne Wirkstoff

Herstellung für 3000 Einheiten Teil 1

0,75 g D-Norgestrel,
0,15 g Äthinylöstradiol und
0,54 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
237,00 g Äthylalkohol und
12,00 g Wasser gelöst. In diese Lösung werden
44,28 g Hydroxypropylcellulose und
44,28 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2

0,18 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
79,00 g Äthylalkohol und
4,00 g Wasser gelöst. In diese Lösung werden
14,91 g Hydroxypropylcellulose und
14,91 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Zweikammer-Spezialrakel (Breite der Kammern: 1 = 54 mm; 2 = 18 mm) zu einem Ausstrich von 0,5 mm ausgezogen und anschließend getrocknet. Bei entsprechender Teilung in Einheiten zu 18 × 18 mm, zum Beispiel durch Perforation, können über die Breite der Folie drei Einheiten mit Wirkstoff und eine wirkstofffreie Einheit abgeteilt werden. Aus dem Folienband lassen sich nun beliebig viele Abschnitte im Verhältnis von drei Einheiten mit Wirkstoff und einer Einheit ohne Wirkstoff herstellen.

Zusammensetzung für je eine Einheit:

Teil 1 (wirkstoffhaltig)		Teil 2 (wirkstofffrei)
0,25 mg	D-Norgestrel	–
0,05 mg	Äthinylöstradiol	–
14,76 mg	Hydroxypropylcellulose	14,91 mg
14,76 mg	Cellulose	14,91 mg
0,18 mg	Polyoxyäthylenpolyoxypropylenpolymeres	0,18 mg
30,00 mg	Gewicht pro Einheit	30,00 mg

Fläche pro Einheit: ca. 3 cm^2.
Aussehen: weiß.

Beispiel 2

Dreiphasenpräparat (Zweiwirkstoffstufenpräparat)

Teil 1: 11 Einheiten mit 0,05 mg D-Norgestrel
0,05 mg Äthinylöstradiol
Teil 2: 10 Einheiten mit 0,125 mg D-Norgestrel
0,050 mg Äthinylöstradiol
Teil 3: 7 Einheiten ohne Wirkstoff

Herstellung für 1100 Einheiten Teil 1:

0,055 g D-Norgestrel,
0,055 g Äthinylöstradiol und
0,198 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
86,900 g Äthylalkohol und
4,400 g Wasser gelöst. In diese Lösung werden
16,346 g Hydroxypropylcellulose und
16,346 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2:

0,125 g D-Norgestrel,
0,050 g Äthinylöstradiol und
0,180 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
79,000 g Äthylalkohol und
4,000 g Wasser gelöst. In diese Lösung werden
14,823 g Hydroxypropylcellulose und
14,822 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 700 Einheiten Teil 3:

0,189 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
82,950 gÄthylalkohol und
4,200 g Wasser gelöst. In diese Lösung werden
15,656 g Hydroxypropylcellulose und
15,655 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Dreikammer-Spezialrakel (Breite pro Kammer 18 mm) zu einem Ausstrich ausgezogen und getrocknet. Bei entsprechender Teilung, zum Beispiel durch Perforation, zu Einheiten von 18 × 18 mm für Teil 1, 18 × 19,8 mm für Teil 2 und 18 × 28 mm für Teil 3 können über die Breite der Folie drei Einheiten mit unterschiedlichem Wirkstoffgehalt abgeteilt werden. Aus dem Folienband lassen sich Präparate mit 11 Einheiten Teil 1, 10 Einheiten Teil 2 und 7 Einheiten Teil 3 abtrennen.

Zusammensetzung pro Einheit:

Teil 1	Teil 2	Teil 3	Inhaltsstoffe
0,050 mg	0,125 mg	–	D-Norgestrel
0,050 mg	0,050 mg	–	Äthinylöstradiol
0,180 mg	0,180 mg	0,270 mg	Polyoxyäthylenpolyoxypropylenpolymeres
14,860 mg	14,823 mg	22,366 mg	Hydroxypropylcellulose
14,860 mg	14,822 mg	22,364 mg	Cellulose
30,000 mg	30,000 mg	45,000 mg	Gewicht pro Einheit
ca. 3 cm^2	ca. 3,5 cm^2	ca. 5 cm^2	Fläche pro Einheit
weiß	weiß	weiß	Aussehen

Beispiel 3

Dreiphasenpräparat

Teil 1: 11 Einheiten mit 0,05 mg D-Norgestrel
0,05 mg Äthinylöstradiol
Teil 2: 10 Einheiten mit 0,125 mg D-Norgestrel
0,050 mg Äthinylöstradiol
Teil 3: 7 Einheiten mit 50,00 mg Eisen(II)fumarat

Herstellung für 1100 Einheiten Teil 1:

0,066 g Lebensmittelgelb Nr. 2 (Tartrazin; E 102) werden in
4,400 g Wasser gelöst und anschließend in
86,900 g Äthylalkohol eingetragen. In dieser Lösung werden
0,055 g D-Norgestrel,
0,055 g Äthinylöstradiol und
0,198 g Polyoxyäthylenpolyoxypropylenpolymeres gelöst.
In diese Lösung werden
16,313 g Hydroxypropylcellulose und
16,313 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2:

0,065 g Lebensmittelorange Nr. 2 (Sunset Yellow; E 110) werden in
4,000 g Wasser gelöst und anschließend in
79,000 g Äthylalkohol eingetragen. In dieser Lösung werden
0,125 g D-Norgestrel,
0,050 g Äthinylöstradiol und
0,180 g Polyoxyäthylenpolyoxypropylenpolymeres gelöst.
In diese Lösung werden
14,790 g Hydroxypropylcellulose und
14,790 g Cellulose eingetragen und gegebenenfalls *homogenisiert*.

Herstellung für 700 Einheiten Teil 3:

0,042 g Saccharin,
0,042 g Sahne-Essenz und
0,406 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
55,300 g Äthylalkohol und
2,800 g Wasser gelöst. In diese Lösung werden
35,000 g Eisen(II)fumarat,
17,500 g Hydroxypropylcellulose,
5,950 g Kakao und
4,060 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Dreikammer-Spezialrakel (Breite pro Kammer 18 mm) zu einem Ausstrich ausgezogen und anschließend getrocknet. Bei entsprechender Teilung, zum Beispiel durch Perforation, zu Einheiten von 18 × 18 mm für Teil 1, 18 × 19,8 mm für Teil 2 und 18 × 28 mm für Teil 3 können über die Breite der Folie drei Einheiten mit unterschiedlichem Wirkstoffgehalt abgeteilt werden. Aus dem Folienband lassen sich Präparate mit 11 Einheiten Teil 1, 10 Einheiten Teil 2 und 7 Einheiten Teil 3 abtrennen.

Zusammensetzung pro Einheit:

Teil 1	Teil 2	Teil 3	Inhaltsstoffe
0,050 mg	0,125 mg	–	D-Norgestrel
0,050 mg	0,050 mg	–	Äthinylöstradiol
–	–	50,000 mg	Eisen(II)fumarat
0,180 mg	0,180 mg	0,580 mg	Polyoxyäthylenpolyoxypropylenpolymeres
0,060 mg	–	–	Lebensmittelgelb Nr. 2
–	0,065 mg	–	Lebensmittelorange Nr. 2
14,830 mg	14,790 mg	25,000 mg	Hydroxypropylcellulose
14,830 mg	14,790 mg	5,800 mg	Cellulose
–	–	8,500 mg	Kakao
–	–	0,060 mg	Saccharin
–	–	0,060 mg	Sahne-Essenz
30,000 mg	30,000 mg	90,000 mg	Gewicht pro Einheit
ca. 3 cm^2	ca. 3,5 cm^2	ca. 5 cm^2	Fläche pro Einheit
gelb	orange	braun	Aussehen

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(54) Dosierungsform für Wirkstoffe sowie Verfahren zu deren Herstellung

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Beschreibung

Arzneimittel können in Form von Pulvern, Tropflösungen, oder Säften oral verabreicht werden. Da bei diesen Abgabeformen eine genaue Dosierung jedoch schwierig ist, werden vom Hersteller dosierte Applikationsformen wie Tabletten, Dragees oder Kapseln generell bevorzugt. Auch Reagentien und andere Wirkstoffe, z. B. Süßstoffe, werden für eine genaue dosierte Anwendung häufig tablettiert. Die Herstellungstechnik für Tabletten, Dragees, Kapseln und dergleichen ist zwar weitgehend ausgereift, doch ist eine Reihe von systembedingten Nachteilen nicht zu übersehen.

Für niedrig dosierte Wirkstoffe muß ein großer Anteil an Hilfsstoffen zugesetzt werden, um zu einer handhabbaren Größe der Einzeldosis zu gelangen. Weiterhin ist eine genaue Kennzeichnung einzelner Tabletten oder Dragees praktisch nicht möglich. Es haben sich deshalb Durchdrückpackungen durchgesetzt, welche eine Mehrzahl von Tabletten, Dragees oder auch Kapseln enthalten und welche mit den notwendigen Informationen, insbesondere dem Namen des Präparates bedruckt sind. Die Herstellung solcher Verpackungen erfordert naturgemäß einen zusätzlichen Arbeitsgang und es werden Umverpackungen in Form von Faltschachteln benötigt, welche ein beträchtliches Leervolumen aufweisen und dadurch zusätzlich Lagerraum beanspruchen. Ein besonders gravierender Nachteil von Dragees und Kapseln besteht darin, daß eine Zerteilung praktisch unmöglich ist, die kleinste Dosis somit vorgegeben ist. Auch bei Tabletten ist eine genaue Zerteilung schwierig, lediglicht größere Tabletten mit einer Kerbe als Sollbruchstelle lassen sich allenfalls teilen, wobei häufig ungleichgroße Bruchstücke entstehen.

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekannt geworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-PS 6 37 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Aus den deutschen Offenlegungsschriften 24 32 925 und 24 49 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Auch die so erhaltenen wirkstoffhaltigen Folien lassen sich durch Perforation in einzelne Abschnitte zur Dosierung aufteilen. In der CH-PS 6 24 846 wird vorgeschlagen, eine Einheitsdosierungsform dadurch zu schaffen, daß ein Arzneimittelwirkstoff zwischen mehreren Lagen aus eßbarem Trägermaterial angeordnet wird, um den Wirkstoff gegen Einflüsse von außen zu schützen. Darüber hinaus ermöglicht die Ausbildung in mehreren Lagen die Einbringung verschiedener Wirkstoffe in voneinander getrennten Schichten. Wie die Betonung der Eßbarkeit der Trägermaterialien verdeutlicht, soll die gesamte auf diese Weise erhaltene schichtförmige Dosierungsform zur oralen Applikation dienen.

Alle diese Vorschläge haben keinen Eingang in die Praxis gefunden und in dem neuesten Lehrbuch der "Arzneiformenlehre" von P. H. List, 4. Auflage, Stuttgart, 1985, finden sie keine Erwähnung. Dies beruht ersichtlich darauf, daß die bislang bekanntgewordenen Formen es nicht ermöglichen, die geforderte Gewichtskonstanz und gleichmäßige Wirkstoffverteilung zu erreichen, welche heute gefordert werden. Die Pharmakopoea Europea setzt zum Beispiel Maßstäbe für die Gleichförmigkeit des Gewichtes einzeldosierter Arzneiformen, wobei diese dem jeweiligen Durchschnittsgewicht entsprechend nach höchstzulässigen Abweichungen in % gestaffelt sind. Die Forderung liegt im allgemeinen bei +/—5% bis max. 10%. Entsprechende Werte für feste Arzneiformen bestehen auch hinsichtlich anderer Parameter wie Zerfallzeit und Lösungsgeschwindigkeit.

Die oben erwähnten Vorschläge des Standes der Technik führen zur Produkten ungenügender Akzeptanz durch die Patienten (Papierabschnitte lassen sich nur schlecht einnehmen) und erlauben keine exakte Dosierung pro Flächeneinheit, wie sie unbedingt gefordert werden muß. Bei Inkorporieren des Wirkstoffes in eine Folie bereitet nicht nur die genaue Dosierung Schwierigkeiten, sondern ein wesentlicher weiterer Nachteil besteht darin, daß für jeden Wirkstoff eine entsprechende Folie gesondert hergestellt werden muß, so daß die Wirtschaftlichkeit des Herstellungsverfahrens nicht gegeben ist.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine dünnflächige Dosierungsform zu schaffen, welche die genannten Nachteile nicht aufweist, sich leicht herstellen läßt und mit großer Flexibilität unter Verwendung verschiedener Wirkstoffe an die Anforderungen des Marktes angepaßt werden kann.

Gegenstand der Erfindung ist eine Dosierungsform für Wirkstoffe aus einem flächigen Trägermaterial mit einer wirkstoffhaltigen Beschichtung, wobei diese Dosierungsform dadurch gekennzeichnet ist, daß das Trägermaterial ein Trennpapier, ein Trennfilm oder eine Trennfolie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

Die erfindungsgemäße Dosierungsform weist mehrere wesentliche Vorteile auf:

— Da der Träger im Gegensatz zu den vorbekannten Ausführungsformen keinen Teil der Darreichungsform bildet, kann er die erforderliche Festigkeit aufweisen, ohne die Akzeptanz des Arzneimittels durch Patienten zu beeinträchtigen,
— die wirkstoffhaltige Schicht kann bei hochwirksamen Arzneimitteln verhältnismäßig dünn sein, da das Trägermaterial die mechanische Festigkeit gewährleistet.
— mit Hilfe moderner Auftragverfahren läßt sich die wirkstoffhaltige Beschichtung mit konstanter Schichtdicke aufbringen, so daß die erforderlichen Toleranzen eingehalten werden können,
— falls eine Sterilisierung erforderlich ist, kann diese wegen der geringen Schichtdicke problemlos mittels Strahlenbehandlung erreicht werden,
— der Träger läßt sich auf der Vorder- und insbesondere der Rückseite mit verschiedenen Informationen bedrucken,
— aufgrund der relativ großen Fläche von beispielsweise 4 bis 10 cm^2 lassen sich ausführliche Informationen für den Benutzer auf das Trägermaterial vor oder auch nach der Beschichtung aufdrukken,
— die Dosiseinheiten lassen sich durch entsprechende Vorzerteilung flexibel gestalten, so daß für verschiedene Dosierungen (z. B. für Erwachsene

und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

Mit den vorbekannten Darreichungsformen in Folienform hat die erfindungsgemäße Darreichungsform darüber hinaus den Vorteil des äußerst geringen Platzbedarfes gemeinsam. Statt Faltschachteln können daher beispielsweise Taschen oder Beutel aus Kunststoffolie oder kunststoffbeschichtetem Papier verwendet werden, in welche das Produkt eingesiegelt wird, ähnlich wie feuchte Erfrischungstücher.

Als Trägermaterialien eignen sich die verschiedensten Materialien, beispielsweise Papiere mit einem Gewicht von etwa 80 bis 120, vorzugsweise 100 g/m², Kunststoffilme bzw. -folien auf Basis von Polyethylen, Polyvinylchlorid, Polyvinylidenchlorid, Polyester und anderen indifferenten Polymeren oder dünne Metallfolien, beispielsweise solche aus Aluminium. Bevorzugt werden siliconisierte Papiere, welche in unterschiedlichen Qualitäten im Handel erhältlich sind, und welche insbesondere zur Abdeckung von selbstklebenden Produkten wie Pflastern, Klebebändern oder Haftetiketten Verwendung finden. Die an sich auch geeigneten, mit Wachs oder Paraffin beschichteten Trennpapiere sind dagegen in der Praxis weitgehend durch die mit inerten Siliconen beschichteten Papiere ersetzt worden. Bei einem Auftrag der wirkstoffhaltigen Beschichtung auf nur eine Seite der Trägerfolie reicht es aus, wenn nur diese mit einer nicht haftenden Beschichtung versehen ist. Die Rückseite sollte dagegen vorzugsweise so beschaffen sein, daß sie mit Informationen unterschiedlicher Art gut und dauerhaft bedruckbar ist.

Die Möglichkeit der vorder- und rückseitigen Bedruckung ist ein besonderer Vorteil der erfindungsgemäßen Darreichungsform. Beispielsweise können die Kennzeichnung, Angaben über die Inhaltsstoffe sowie Dosierungsangaben aufgedruckt werden. Gegebenenfalls läßt sich sogar der ganze Inhalt eines Beipackzettels rückseitig aufdrucken mit der Folge, daß ein separater Beipackzettel, der auch häufig verlorengeht, überflüssig wird. Bei Arzneimitteln, welche regelmäßig genommen werden müssen, beispielsweise bei hormonalen Contrazeptiva, kann der gesamte Verabreichungsplan so angebracht werden, daß eine einfache Einnahmekontrolle gewährleistet ist. Da die einzelnen Dosiseinheiten von dem Träger abgezogen werden, bleibt dieser bis zum vollständigen Aufbrauch des Arzneimittels erhalten und es gehen keine der aufgedruckten Informationen verloren.

Für die wirkstoffhaltige Beschichtung findet vorzugsweise eine wäßrige Beschichtungsmasse Verwendung, die physiologisch inert ist und deren Einzelkomponenten für Arzneimittel bzw. Lebensmittel geeignet sind. Dabei handelt es sich zum einen um wasserlösliche Quellstoffe in der Art polymerer Filmbildner, vorzugsweise Gelatine, Zellulosen oder Hemizellulosen, quellende oder lösliche Stärken. Vorzugsweise werden ferner Weichmacher zugesetzt, insbesondere mehrwertige Alkohole wie Glycerin oder Sorbitol. Zur Einstellung der gewünschten Viskosität der Beschichtungsmasse, welche etwa die Konsistenz eines Schleimes aufweist, finden polymere Quellstoffe Verwendung, vorzugsweise Alginate, Pectine, Chitine, Lecithine oder Polyethylenglykole. Diese letzteren Stoffe können gleichzeitig als Haftvermittler dienen. Andererseits können auch wasserlösliche Gumme oder Gummi arabicum zugesetzt werden, um die Haftung der Beschichtung auf dem Trägermaterial zu verbessern. Schließlich können noch Konservierungsmittel wie z. B. p-Hydroxybenzoesäureester, Farbstoffe (Lebensmittelfarbstoffe), Pigmente wie Titandioxid oder Aroma- und Süßstoffe zugesetzt werden.

Beschichtungsmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10 000 mpa · s haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

Folgende Rahmenrezeptur hat sich bewährt:

Gelatine	8 bis 10 g
Stärke	3 bis 8 g
Glycerin	1 bis 2 g
Wasser	30 bis 50 g

In dieser Grundmasse wird der Wirkstoff gelöst bzw. dispergiert. Im Fall der Verwendung einer Dispersion muß der Wirkstoff für eine gleichmäßige Verteilung äußerst feinteilig sein. Vorzugsweise liegt die mittlere Teilchengröße im Bereich von etwa 1 bis 20 µm.

Die gewünschte Dosis des Wirkstoffes und die angestrebte Fläche der Dosiseinheiten bestimmen letztlich die Dicke der Schicht, wobei der Feuchtigkeitsgehalt der Beschichtungmasse und der fertigen Beschichtung zu berücksichtigen sind.

Im Rahmen der Erfindung ist es auch möglich, die Beschichtungsmasse zu einer wirkstoffhaltigen Folie zu verarbeiten und diese anschließend, gegebenenfalls unter Verwendung eines physiologisch einsetzbaren inerten Klebstoffes, auf das Trägermaterial aufzukaschieren. Diese Ausführungsform kommt insbesondere dann in Betracht, wenn die wirkstoffhaltige Beschichtung eine größere Dicke aufweisen soll, so daß die Verarbeitung zu einer Folie möglich und sinnvoll ist.

Die erfindungsgemäße Darreichungsform ist besonders geeignet für Arzneimittel, welche niedrig dosiert verabreicht werden, d. h. bei welchen die Einzeldosis für die orale Applikation zwischen 0 mg (Placebo) und etwa 20 mg liegt. Geeignete Arzneimittelwirkstoffe finden sich in allen Bereichen der oralen Therapie; hervorzuheben sind u. a. Analeptika, Antibiotika, Antidiabetika, Antiemetika, Antiepileptika, Antihypertonika, Cortikoide, Geriatrika, Hypnotika, Cardiaka, Hypostatika und Biowirkstoffe.

Die Beschichtung kann einen oder mehrere Arzneimittelwirkstoffe enthalten. Falls bei Verwendung mehrerer Wirkstoffe diese nicht ohne weiteres miteinander verträglich sind, ist es bei der erfindungsgemäßen Darreichungsform möglich, die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufzubringen und die Wirkstoffe dadurch voneinander zu trennen, wobei erforderlichenfalls eine wirkstofffreie Zwischenschicht vorgesehen werden kann. Weiterhin ist es möglich, über der wirkstoffhaltigen Schicht noch eine weitere Schutzschicht vorzusehen, welche den/die Wirkstoff(e) gegen eine Berührung mit der Atmosphäre und/oder gegen Licht schützt. In diesen Fällen muß die Schutzschicht demgemäß luft- und feuchtigkeitsundurchlässig und/oder durch Zusatz entsprechender

Farbstoffe bzw. Pigmente lichtundurchlässig sein.

Weiterhin kann durch entsprechenden Aufbau der Beschichtung die Wirkstoffabgabe nach Verabreichung des Arzneimittels gesteuert werden. Beispielsweise ist es möglich, eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten anzuordnen, welche die Wirkstoffresorption im Magen/Darmtrakt in an sich bekannter Weise steuern. Dabei kann die Wirkstoffschicht z. B. zwischen zwei säureunlöslichen Schichten angeordnet werden, so daß bei Verabreichung der Magen passiert wird und die Resorption erst im Darmtrakt erfolgt. In ähnlicher Weise können unterschiedliche Wirkstoffe in verschiedenen Schichten übereinander auf die Trägerfolie aufgebracht werden, damit die Resorption nacheinander und/oder verzögert erfolgt. Ähnliche pharmakokinetische Effekte lassen sich durch das Einarbeiten (z. B. Suspendieren) von unterschiedlich vorbehandelten mikroverkapselten Wirkstoffen erzielen.

Die Aufbringung der wirkstoffhaltigen Beschichtungen auf den Träger, z. B. auf ein Trennpapier oder eine Trenn-Kunststoffolie, erfolgt vorzugsweise mit Hilfe eines Glattwalzen-Beschichtungsverfahrens. Die vorzugsweise auf ca. 60 bis 80°C erwärmte Beschichtungsmasse wird dabei bei geschlossenem Auftragsystem auf eine beheizte Walze in dünner Schicht übertragen. Mit verzögertem Gleichlauf in bestimmten wählbaren Verhältnissen wird die Masse auf eine parallel angeordnete Walze übertragen, wobei eine Reduzierung der Schichtdicke im Verhältnis 1 : 2 bis 1 : 10 erfolgen kann, wodurch gleichzeitig die Toleranzen bei der Auftragung um diese Faktoren verringert werden. Im Gleichlauf erfolgt dann über ein weiteres Walzensystem die Beschichtung des Trägermaterials. Bei einer Anpassung der Wirkstoffbeschichtungsmasse an den Release-Wert des Trägermaterials kann auf den Zusatz eines Klebemittels völlig verzichtet werden. Gegebenenfalls können jedoch auch geeignete Haftvermittler zugesetzt werden.

Bei Aufbringung mehrerer Schichten, wie dies oben bereits beschrieben wurde, werden diese nacheinander aufgebracht, wobei ggf. jede Beschichtung zuvor eine Trocknungsstation durchläuft. Diese kann beispielsweise aus einem temperierten Walzenpaar und einem in Sektionen steuerbaren Trockentunnel bestehen. Nach dem letzten Beschichtungsvorgang wird das beschichtete Material auf Rollen aufgewickelt.

Die wirkstoffhaltige Beschichtung wird anschließend in Dosiseinheiten vorzerteilt, welche ähnlich wir Haftetiketten vom Trägermaterial abziehbar sind. Normalerweise wird diese Vorzerteilung beim Arzneimittelhersteller erfolgen; es ist jedoch auch denkbar, das beschichtete Material beispielsweise an Krankenhäuser oder Apotheken auszuliefern, wo dann die Vorzerteilung dosisabhängig oder auch individuell nach ärztlicher Vorgabe durchgeführt werden kann.

Die Vorzerteilung erfolgt in besonders einfacher Weise durch Stanzung, wobei es möglich ist, diesen Schritt mit der Bedruckung des Trägermaterials zu kombinieren. In vielen Fällen wird es allerdings günstiger sein, die Bedruckung des Trägermaterials vor der Beschichtung vorzunehmen.

Vor oder besser nach Vorzerteilung der wirkstoffhaltigen Beschichtung in Dosiseinheiten wird das beschichtete Trägermaterial zu gebrauchsfertigen Abschnitten zerschnitten, welche eine bestimmte Anzahl von Dosiseinheiten enthalten. Es ist auch denkbar, das Material auf Rollen zu schmalen Bändern zu zerschneiden. Vor einer solchen Einzelrolle können dann die einzelnen Dosiseinheiten ähnlich wie einzelne Haftetiketten abgezogen werden.

Vorstehend wurde die Erfindung im wesentlichen im Zusammenhang mit Arzneimitteln beschrieben, worauf sie jedoch keineswegs beschränkt ist. Beispielsweise lassen sich in derselben Weise auch Dosierungsformen für chemische Reagentien, Aromastoffe und dergleichen herstellen.

Zur näheren Erläuterung der Erfindung sollen die nachfolgenden Ausführungsbeispiele dienen.

Beispiel 1

Herstellung eines Cardiakum

Zum Naßauftrag auf ein Trennpapier (Siliconpapier mit einem Flächengewicht von 100 g/m²) wurde eine Beschichtungsmasse gemäß folgender Rezeptur hergestellt:

Gelatine	10,0 Gew.-Teile	= 22,22%
Kartoffelstärke	3,0 Gew.-Teile	= 6,67%
Glycerin	1,5 Gew.-Teile	= 3,33%
Titandioxid	0,3 Gew.-Teile	= 0,67%
α-Acetyldigoxin	0,2 Gew.-Teile	= 0,44%
Wasser	30,0 Gew.-Teile	= 66,67%

Diese Beschichtungsmasse wurde in einer Schichtdikke von 90 g/m² mittels Walzen auf das Trennpapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Das Beschichtungsgewicht lag bei 34 g/m², was einem Arzneimittelanteil von 0,4 g/m² entspricht. Ein Abschnitt von 2 cm × 2,5 cm = 5 cm² (entsprechend den Abmessungen einer üblichen Briefmarke) enthält 0,2 mg α-Acetyldigoxin, was mit dem Gehalt der handelsüblichen Tabletten übereinstimmt.

Beispiel 2

Herstellung eines Contrazeptivum

Zum Naßauftrag auf ein Trennpapier (einseitig silikonisiertes Papier von 110 g/m²) wurde eine Beschichtungsmasse von schleimartiger Konsistenz nach folgender Rezeptur hergestellt:

Gelatine	10,00 Gew.-Teile	= 22,222%
Maisstärke	3,17 Gew.-Teile	= 7,044%
Glycerin	1,50 Gew.-Teile	= 3,333%
Titandioxid	0,30 Gew.-Teile	= 0,667%
Levonorgestrel	0,03 Gew.-Teile	= 0,067%
Wasser	30,00 Gew.-Teile	= 66,663%

Die Beschichtungsmasse wurde mittels eines Walzenübertragungsverfahrens mit einem Beschichtungsgewicht von 45 g/m² auf das Trennpapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Bei einem Beschichtungsgewicht von 17 g/m² betrug der Arzneimittelanteil 0,03 g/m².

Ein Abschnitt von 2,5 × 4 cm bzw. zwei Abschnitte von je 2,5 cm × 2 cm, also 10 cm² der Beschichtung, enthalten somit 0,03 Levonorgestrel, was dem Gehalt der handelsüblichen Dragees entspricht.

Patentansprüche

1. Dosierungsform für Wirkstoffe aus einem flächigen Trägermaterial mit einer wirkstoffhaltigen Beschichtung, **dadurch gekennzeichnet,** daß das Trägermaterial ein Trennpapier, ein Trennfilm oder eine Trennfolie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

2. Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß das Trägermaterial ein silicon- oder wachsbeschichtetes Trennpapier ist.

3. Dosierungsform nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die wirkstoffhaltige Beschichtung durch Stanzung in Dosiseinheiten vorzerteilt ist.

4. Dosierungsform nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die Beschichtung einen oder mehrere Arzneimittelwirkstoffe enthält.

5. Dosierungsform nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Beschichtung wasserlösliche Quellstoffe als polymere Filmbildner und gegebenenfalls Weichmacher enthält.

6. Dosierungsform nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß die Beschichtung zur Viskositätseinstellung polymere Quellstoffe enthält, welche gleichzeitig als Haftvermittler dienen können.

7. Dosierungsform nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufgebracht ist.

8. Dosierungsform nach Anspruch 7, dadurch gekennzeichnet, daß miteinander inkompatible Wirkstoffe in getrennten Schichten nacheinander auf das Trägermaterial aufgebracht sind.

9. Dosierungsform nach Anspruch 7, dadurch gekennzeichnet, daß eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten angeordnet ist, welche die Wirkstoff-Resorption im Magen/Darmtrakt in an sich bekannter Weise steuern.

10. Dosierungsform nach Anspruch 7, dadurch gekennzeichnet, daß über der Wirkstoffschicht eine weitere Schicht aufgebracht ist, die den Wirkstoff gegen Berührung mit der Atmosphäre und/oder gegen Licht schützt.

11. Dosierungsform nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß die Rückseite des Trägermaterials mit die Wirkstoffzusammensetzung und/oder deren Einnahme betreffenden Informationen bedruckbar ist.

12. Verfahren zur Herstellung der Dosierungsform der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß man eine wirkstoffhaltige Zusammensetzung mit Hilfe von Walzen auf die nichthaftend ausgerüstete Seite eines Trennpapiers, eines Trennfilms oder einer Trennfolie bringt.

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