IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

RECKITT BENCKISER PHARMACEUTICALS INC., RB PHARMACEUTICALS LIMITED, and MONOSOL RX, LLC,	)	CA. No. 14-01451-RGA
Plaintiffs,	)	
v.	)	
TEVA PHARMACEUTICALS USA, INC.,	)	
Defendant.	)	

JOINT CLAIM CONSTRUCTION STATEMENT

The parties hereby submit the attached Joint Claim Construction Chart, which sets forth: (i) the disputed claim terms; (ii) the parties' respective proposed constructions for the disputed claim terms; and (iii) the intrinsic evidence on which each party will rely to support its respective proposed constructions and/or to rebut the opposing party's proposed constructions. In addition to the materials disclosed in the Joint Claim Construction Chart, each party reserves the right to rely on other portions of the specifications and prosecution histories of the patents-in-suit during claim construction briefing and argument. A copy of the Joint Claim Construction Chart is attached as Exhibit A. Copies of United States Patent Nos. 8,017,150 ("the '150 patent"), 8,475,832 ("the '832 patent"), and 8,603,514 ("the '514 patent) and those portions of their prosecution histories cited by the parties are attached as Exhibits B- and organized as follows:

Exhibit B	U.S. Patent No. 8,017,150
Exhibit C	U.S. Patent No. 8,475,832
Exhibit D	U.S. Patent No. 8,603,514
Exhibit E	'514 Patent File History, December 9, 2010 Amendment and Response Pursuant to 37 C.F.R. §1.111 at 10-20

Exhibit F	'514 Patent File History, April 4, 2011 Amendment and Response Pursuant to 37 C.F.R. §1.116
Exhibit G	'832 Patent File History, September 9, 2009 IDS
Exhibit H	'832 Patent File History, February 29, 2012 Amendment and Response
Exhibit I	'832 Patent File History, October 22, 2012 Amendment and Response After Final Office Action
Exhibit J	'832 Patent File History, April 30, 2013 Amendment and Response with Request for Continued Examination
Exhibit K	'588 Patent Reexamination, Decision on Appeal, Reexamination Application No. 95/001,753 (Reexamination of U.S. Patent No. 7,824,588)

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EXHIBIT A
JOINT CLAIM CONSTRUCTION CHART

Disputed Claim Terms, Proposed Constructions, and Citations to Intrinsic Evidence

The parties reserve the right to rely on any intrinsic evidence cited for a term, regardless of which party provided the same and the right to further amend these charts as necessary. The parties further reserve the right to rely on any figures, tables, examples, or any reference incorporated by reference in cited portions of the patents-in-suit or the respective file histories, even if not explicitly referred to herein.

	Term/Phrase	Plaintiffs' Proposed Construction	Plaintiffs' Intrinsic Evidence	Defendants' Proposed Construction	Defendants' Intrinsic Evidence
1.	"a taste-masking agent coated or intimately associated with said particulate [active]" ('514 cls. 1 and 28)	The Court previously construed "taste-masking of the active" as having its plain and ordinary meaning. Plaintiffs do not believe further, separate construction of this term by the Court is necessary in this case. If the Court determines to further construe the term, the plain and ordinary meaning is a taste-masking agent sufficiently surrounding the particulate active,	**Ex. D ('514 Patent)** ***passim*** **where referencing "taste-masking";** ***see, e.g.,*** **at**: 5:43-49 5:55-59 6:11-12 9:37-41 16:31-39 38:23-39:60 54:1-10 62:1-6, 19-25, 44-46 70:37-39	The taste masking agent is coated on, or in contact with, the particles of active ingredient.	**'514 Patent**: 4:27-30; 5:64-66; 6:11-12; 6:21-26; 6:29-36; 6:49-52; 7:13-22; 9:16-36; 14-4-21; 14-25-51; 15:6-16:3; 16:63-17:3; 17:32-39; 38:21-39:60. **Prosecution of '514 Patent:** December 9, 2010 Amendment and Response Pursuant to 37 C.F.R. §1.111 at 10-20 (Ex. E).

	Term/Phrase	Plaintiffs' Proposed Construction	Plaintiffs' Intrinsic Evidence	Defendants' Proposed Construction	Defendants' Intrinsic Evidence
		e.g., by being dissolved and homogenously distributed.			
2.	"said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix" ('514 cls. 1, 16, 28, 48, 58 and 62)	The Court previously construed "viscosity sufficient to aid in substantially maintaining non-self aggregating uniformity of the active in the matrix" as "viscosity sufficient to provide little to no aggregation of the active within the film." Plaintiffs do not believe further construction of this term by the Court is necessary in this case.	**Ex. D ('514 Patent), *see, e.g.*, at**: 2:27-46 8:56-64 11:35-37 18:4-5 36:55-61 37:14-18 54:11-15	Indefinite.	Decision on Appeal, Reexamination Application No. 95/001,753 (Reexamination of U.S. Patent No. 7,824,588) (Ex. K) at 9-10, 16, 18-19.
3.	Plaintiffs' proposed term: "dried without loss of substantial uniformity" Defendants' proposed term: "dried without the loss of substantial uniformity"	The Court previously construed "capable of being dried without loss of substantial uniformity" as "the film matrix is capable of being dried such that individual dosage units do not vary by more than 10% from the	**Ex. D ('514 Patent), *see, e.g.*, at**: 2:27-46 11:35-37 18:4-5 36:55-61 37:14-18 54:11-15	Dried without employing conventional convection air drying from the top.	**'514 Patent**: 2:60-62; 3:1-34; 4:48-57; 8:56-64; 9:4-9; 22:27-67; 23:4-20; 25:27-31; 28:51-29:1; 30:37-44,61-62; 31:59-32:12; 52:26-50 **Prosecution of '514 Patent:** December 9, 2010 Amendment and Response Pursuant to 37

	Term/Phrase	Plaintiffs' Proposed Construction	Plaintiffs' Intrinsic Evidence	Defendants' Proposed Construction	Defendants' Intrinsic Evidence
	('514 cls. 28 and 62)	intended amount of active for that dosage unit." Plaintiffs do not believe further, separate construction of this term by the Court is necessary in this case.			C.F.R. §1.111 at 10-20 (Ex. E); April 4, 2011 Amendment and Response Pursuant to 37 C.F.R. §1.116 (Ex. F) at 12-21.
4.	"wherein said local pH is from about 3 to about 3.5 in the presence of saliva" ('832 cls. 1 and 9) Teva's proposed term: "about 3 to about 3.5"	The Court previously construed "provide a local pH for said composition of a value sufficient to optimize absorption of said buprenorphine, wherein said local pH is from about 3 to about 3.5 in the presence of saliva" as "provide a local pH for the composition sufficient to optimize absorption of said buprenorphine wherein said local pH is about 3 to about 3.5 in the presence of saliva in the mouth, where local pH refers to the pH of the region of the carrier matrix immediately surrounding the active	**Ex. C ('832 Patent), *see, e.g.*, at**: 3:14-21 3:27-32 3:35-38 3:42-47 3:48-50 11:44-61 12:26-36 13:5-7 15:51-52 17:51-18:16 18:35-41 18:49 19:3-22 20:4-9 20:18-20 21:19-21 21:35-44 22:20-22 23:1-23:55 23:64-67 24:33-37	Greater than 2.95 and less than 3.54.	**'832 Patent:** 11:53-57; 12:26-36; 13:5-7; 15:51-52; 18:11-15; 21:38-44; 23:1-1. **Prosecution of '832 Patent:** September 9, 2009 IDS (Ex. G); February 29, 2012 Amendment and Response (Ex. H) at 2-5, 7-13; October 22, 2012 Amendment and Response After Final Office Action (Ex. I) at 7-10; April 30, 2013 Amendment and Response with Request for Continued Examination (Ex. J) at 2-3 and 5-10.

	Term/Phrase	Plaintiffs' Proposed Construction	Plaintiffs' Intrinsic Evidence	Defendants' Proposed Construction	Defendants' Intrinsic Evidence
		agent as the matrix hydrates and/or dissolves, for example, in the mouth of the user." Plaintiffs do not believe further, separate construction of this term by the Court is necessary in this case. To the extent that further construction is necessary, these terms should be construed to mean "wherein said local pH is above 2.5 and below 4.0."			
5.	"at least one water-soluble polymer component consisting of polyethylene oxide in combination with a hydrophilic cellulosic polymer; wherein: the water-soluble polymer component comprises greater than 75% polyethylene oxide and up to 25%	This term means "at least one water-soluble polymer component consisting of polyethylene oxide and optionally hydrophilic cellulosic polymer, wherein the polyethylene oxide is in an amount of greater than 75% of the polymer component and there may be up to	**Ex. B ('150 Patent), *see, e.g.*, at**: Abstract 1:34-36 4:27-33 17:27-42 17:52-18:5 47:60-48:33 49:10-17 50:6-33 57:39-45	"at least one water-soluble polymer component consisting of polyethylene oxide in combination with a hydrophilic cellulosic polymer; wherein: the water-soluble polymer component comprises greater than 75% polyethylene oxide and up to 25%	**'150 Patent:** 15:43-56, 17:27-29

	Term/Phrase	Plaintiffs' Proposed Construction	Plaintiffs' Intrinsic Evidence	Defendants' Proposed Construction	Defendants' Intrinsic Evidence
	hydrophilic cellulosic polymer" ('150 cl. 1)	25% hydrophilic cellulosic polymer in the polymer component."		hydrophilic cellulosic polymer"	
6.	"at least one water-soluble polymer component consisting of polyethylene oxide in combination with a hydrophilic cellulosic polymer; wherein: the water-soluble polymer component comprises the hydrophilic cellulosic polymer in a ratio of up to about 4:1 with the polyethylene oxide" ('150 cl. 10)	This term means "at least one water-soluble polymer component consisting of polyethylene oxide and optionally hydrophilic cellulosic polymer, wherein the ratio of hydrophilic cellulosic polymer to polyethylene may be up to about 4:1."	**Ex. B ('150 Patent), *see, e.g.*, at**: Abstract 1:34-36 4:47-53 17:27-42 17:52-18:5 47:60-48:33 49:10-17 50:6-33 58:32-38	"at least one water-soluble polymer component consisting of polyethylene oxide in combination with a hydrophilic cellulosic polymer; wherein: the water-soluble polymer component comprises greater than 75% polyethylene oxide and up to 25% hydrophilic cellulosic polymer"	**'150 Patent:** 15:43-56, 17:27-29
7.	Defendants' proposed term: "A film dosage composition" ('832 patent, claim 1)	This term has its plain and ordinary meaning, and limits the claims.	**Ex C ('832 Patent) *passim*; *see, e.g.*, at**: 1:6-15 1:65-3:2 4:46-60 6:60-7:3 15:60-67	This term in the preamble is non-limiting.	

	Term/Phrase	Plaintiffs' Proposed Construction	Plaintiffs' Intrinsic Evidence	Defendants' Proposed Construction	Defendants' Intrinsic Evidence
			23:57-67 4:46-60		

Agreed Upon Constructions:

1. "a hydrophilic cellulosic polymer"('150 Patent, cls. 1 and 10): a polymer made from cellulose that is hydrophilic.

2. "molecular weight" ('150 patent, claims 1, 10): The Court previously construed "molecular weight" as "average molecular weight."[1]

[1] Consistent with the Court's claim construction ruling in the Watson/ Par cases, Teva expressly reserves the right to argue that this term is indefinite at a later stage in the proceeding.

EXHIBIT B

US008017150B2

(12) **United States Patent**
Yang et al.

(10) **Patent No.: US 8,017,150 B2**
(45) **Date of Patent: Sep. 13, 2011**

(54) **POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM**

(75) Inventors: **Robert K. Yang**, Flushing, NY (US); **Richard C. Fuisz**, McLean, VA (US); **Garry L. Myers**, Kingsport, TN (US); **Joseph M. Fuisz**, Washington, DC (US)

(73) Assignee: **MonoSol Rx, LLC**, Portage, IN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 364 days.

(21) Appl. No.: **12/107,389**

(22) Filed: **Apr. 22, 2008**

(65) **Prior Publication Data**

US 2008/0260809 A1 Oct. 23, 2008

Related U.S. Application Data

(60) Division of application No. 10/856,176, filed on May 28, 2004, now Pat. No. 7,666,337, which is a continuation-in-part of application No. PCT/US02/032575, filed on Oct. 11, 2002, and a continuation-in-part of application No. PCT/US02/32594, filed on Oct. 11, 2002, and a continuation-in-part of application No. PCT/US02/32542, filed on Oct. 11, 2002.

(60) Provisional application No. 60/473,902, filed on May 28, 2003, provisional application No. 60/414,276, filed on Sep. 27, 2002, provisional application No. 60/371,940, filed on Apr. 11, 2002.

(51) **Int. Cl.**
A61K 9/14 (2006.01)

(52) **U.S. Cl.** **424/484**; 424/486; 424/488; 424/434; 424/435

(58) **Field of Classification Search** 424/434, 424/435, 436, 443, 484
See application file for complete search history.

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Primary Examiner — Gina C Yu
(74) *Attorney, Agent, or Firm* — Hoffmann & Baron, LLP

(57) **ABSTRACT**

The invention relates to the film products and methods of their preparation that demonstrate a non-self-aggregating uniform heterogeneity. Desirably, the films disintegrate in water and may be formed by a controlled drying process, or other process that maintains the required uniformity of the film. The films contain a polymer component, which includes polyethylene oxide optionally blended with hydrophilic cellulosic polymers. Desirably, the films also contain a pharmaceutical and/or cosmetic active agent with no more than a 10% variance of the active agent pharmaceutical and/or cosmetic active agent per unit area of the film.

18 Claims, 34 Drawing Sheets

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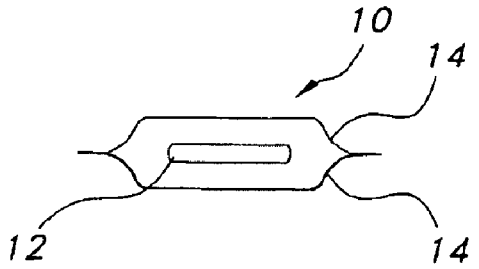


FIG. 1

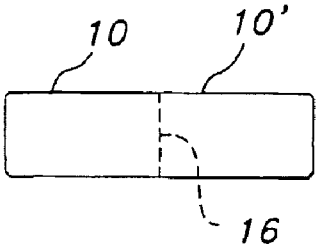


FIG. 2

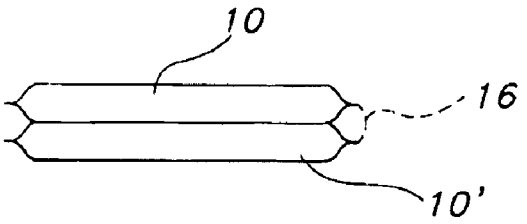


FIG. 3

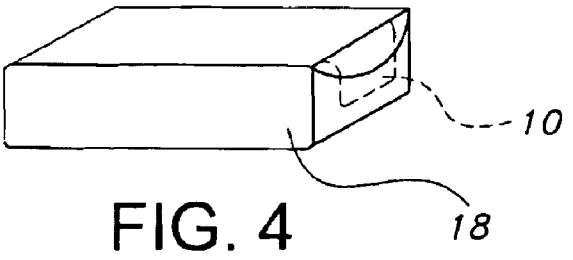


FIG. 4

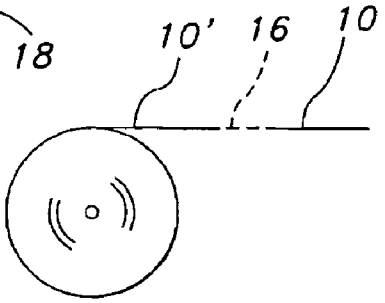


FIG. 5

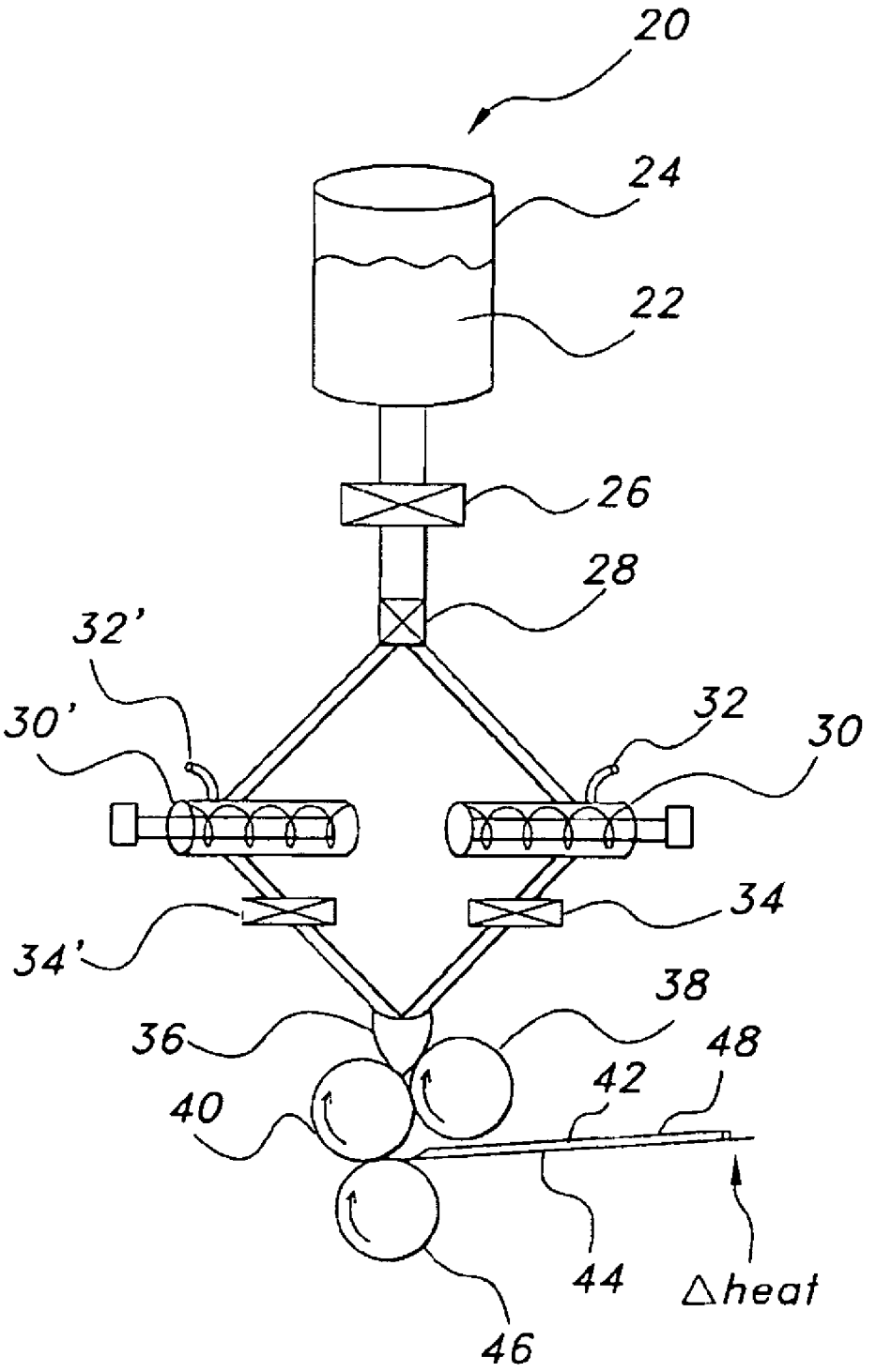


FIG. 6

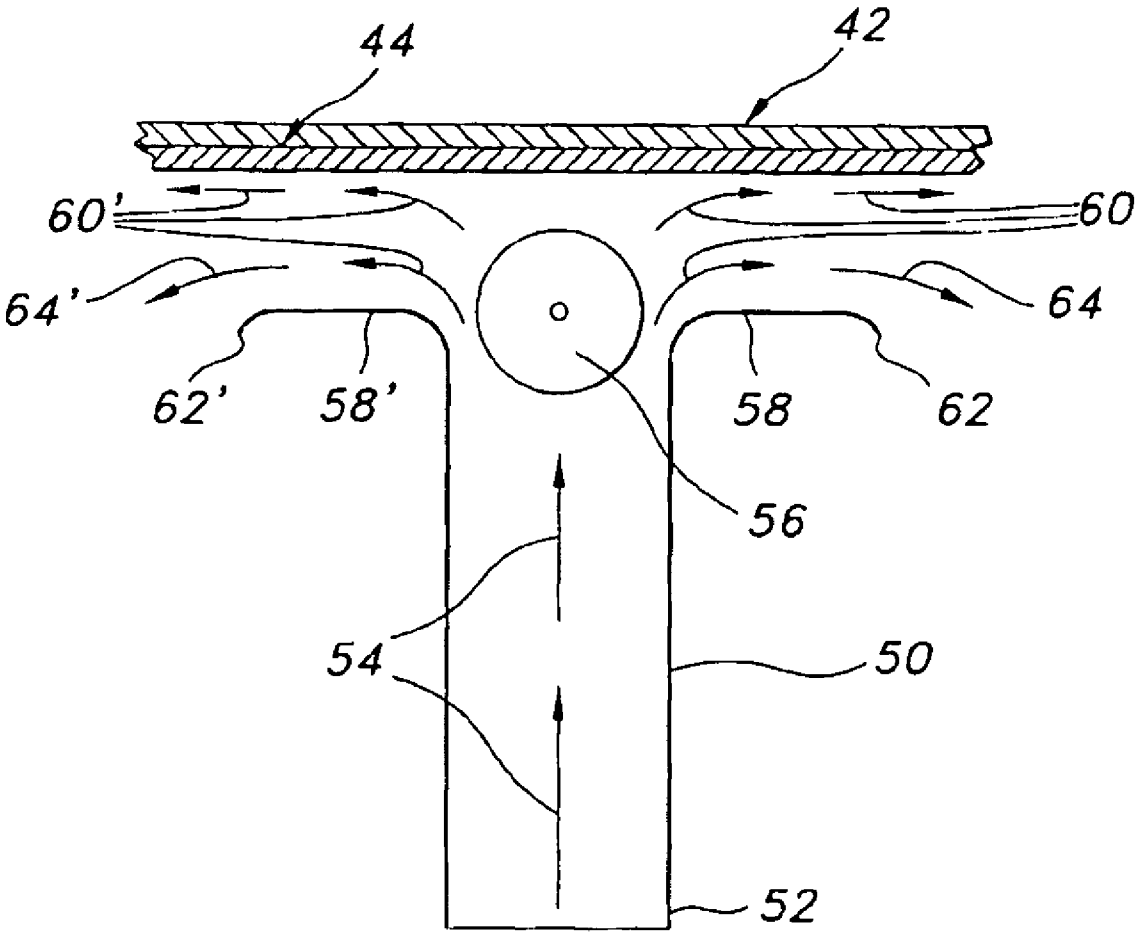


FIG. 7

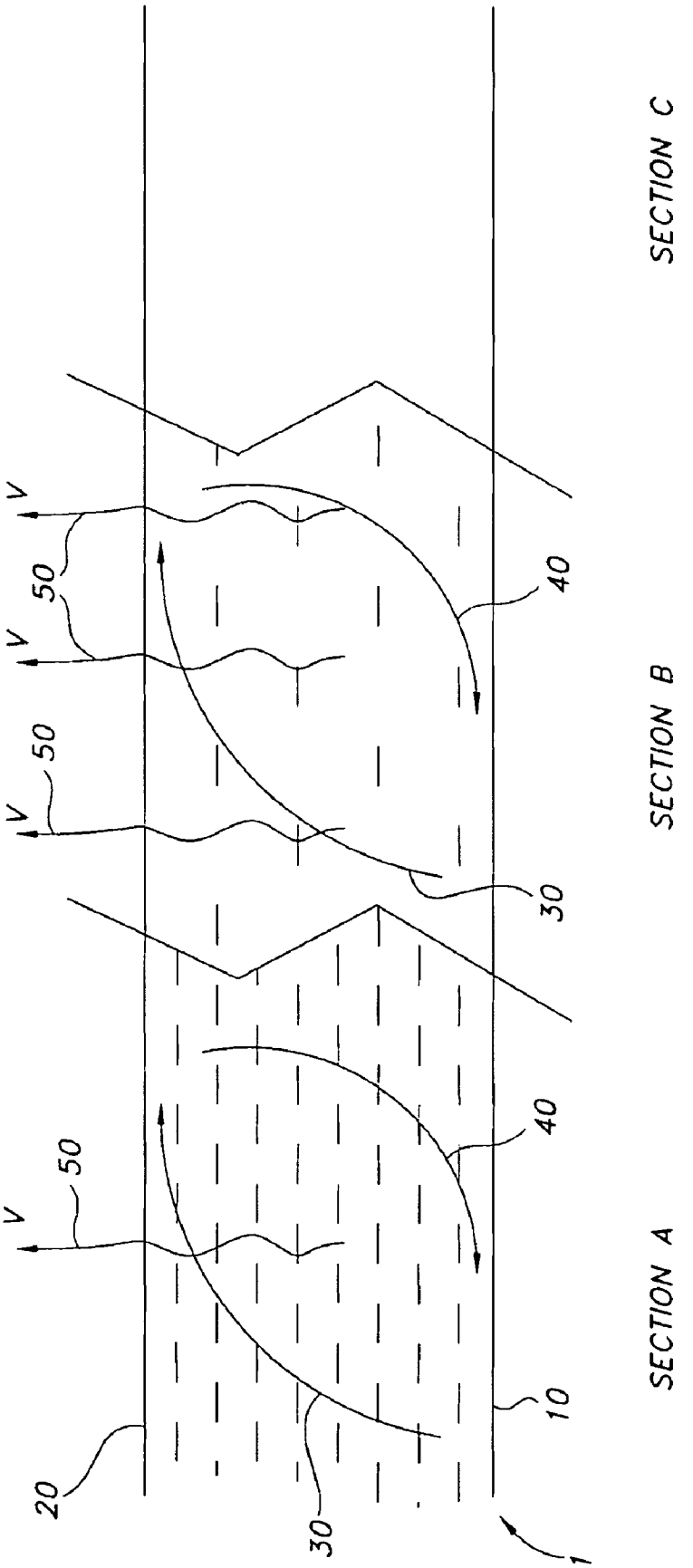


FIG. 8

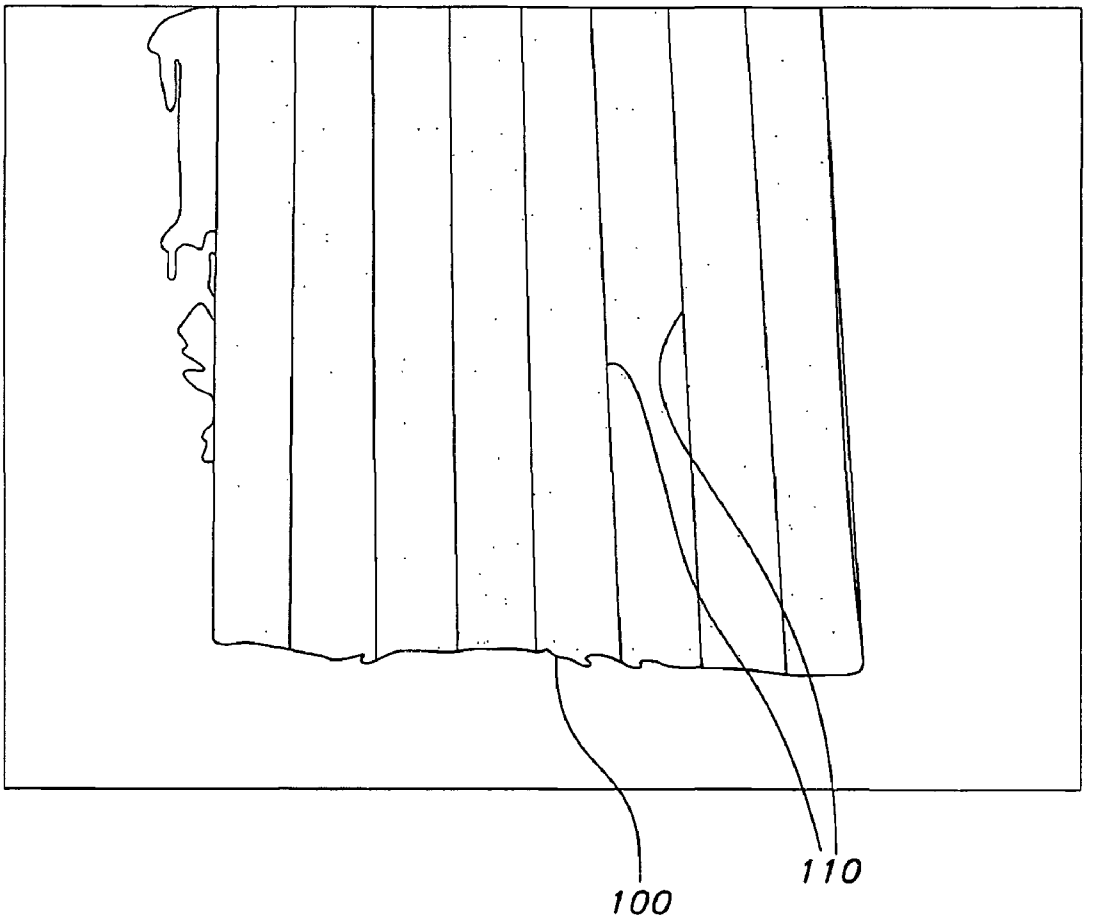


FIG. 9

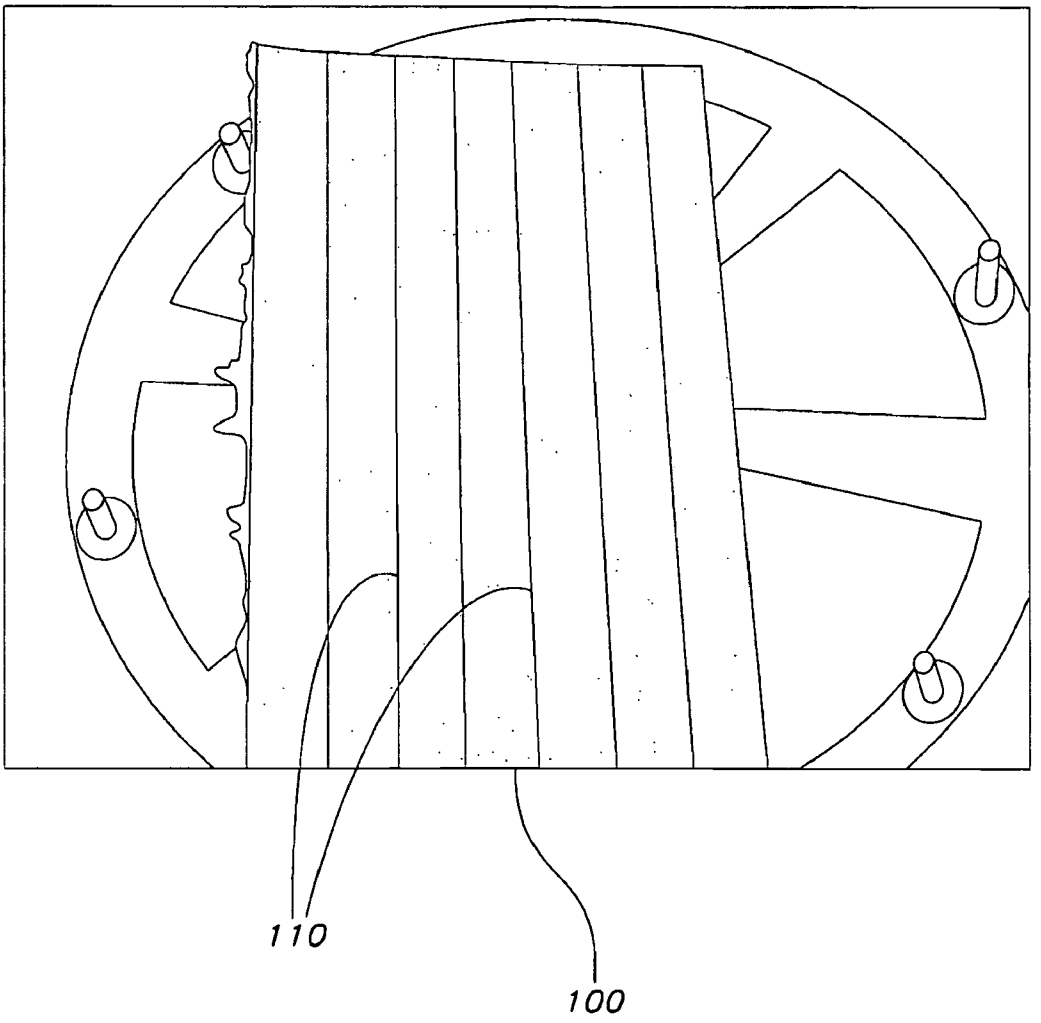


FIG. 10

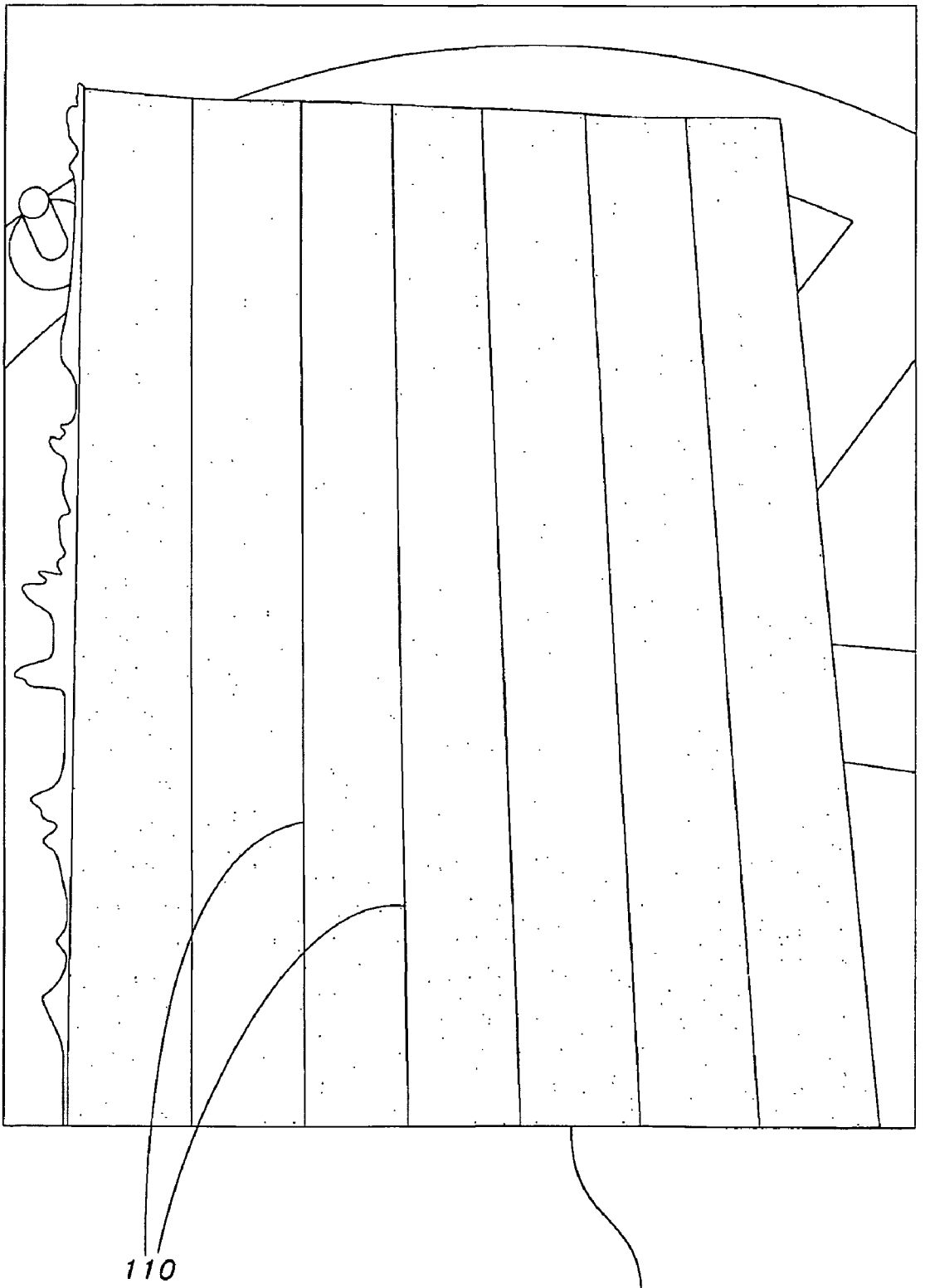


FIG. 11

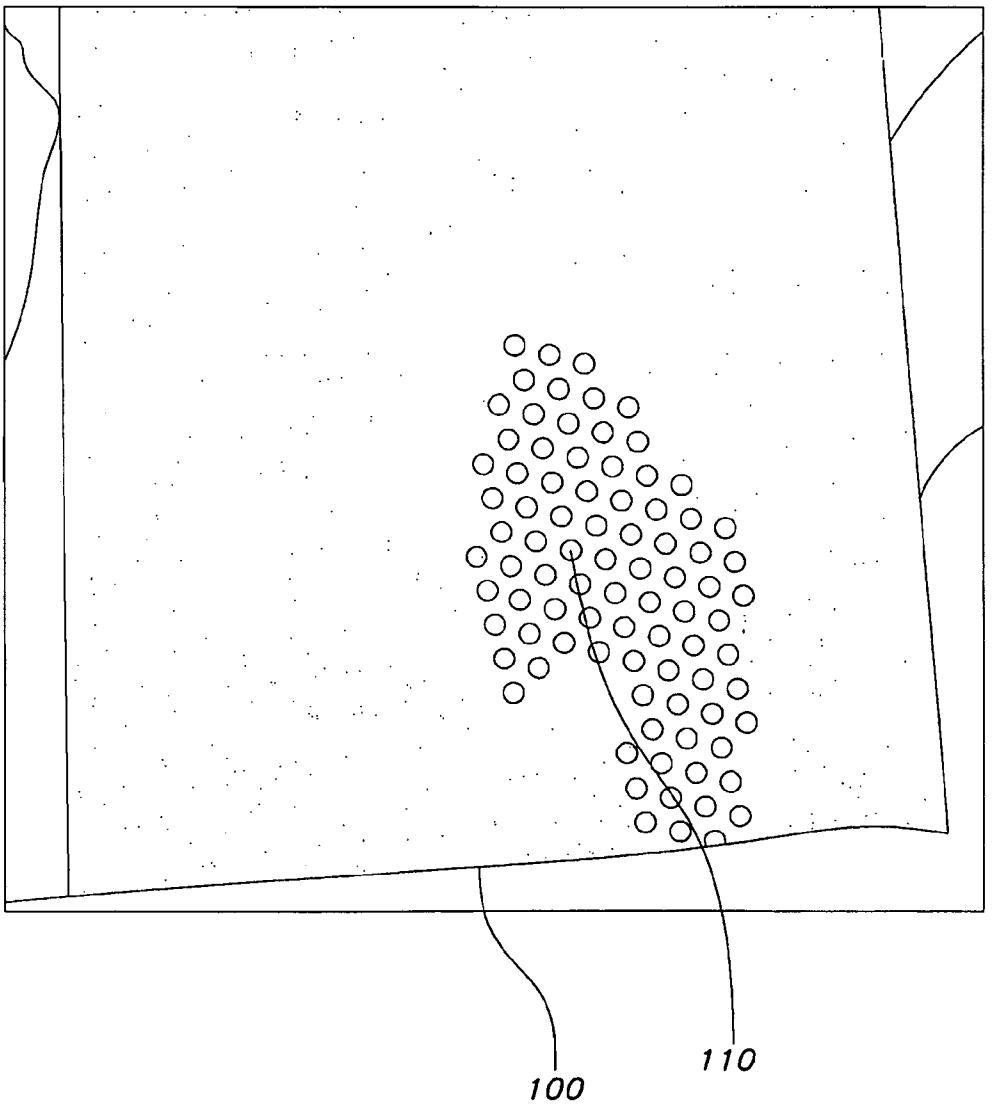


FIG. 12

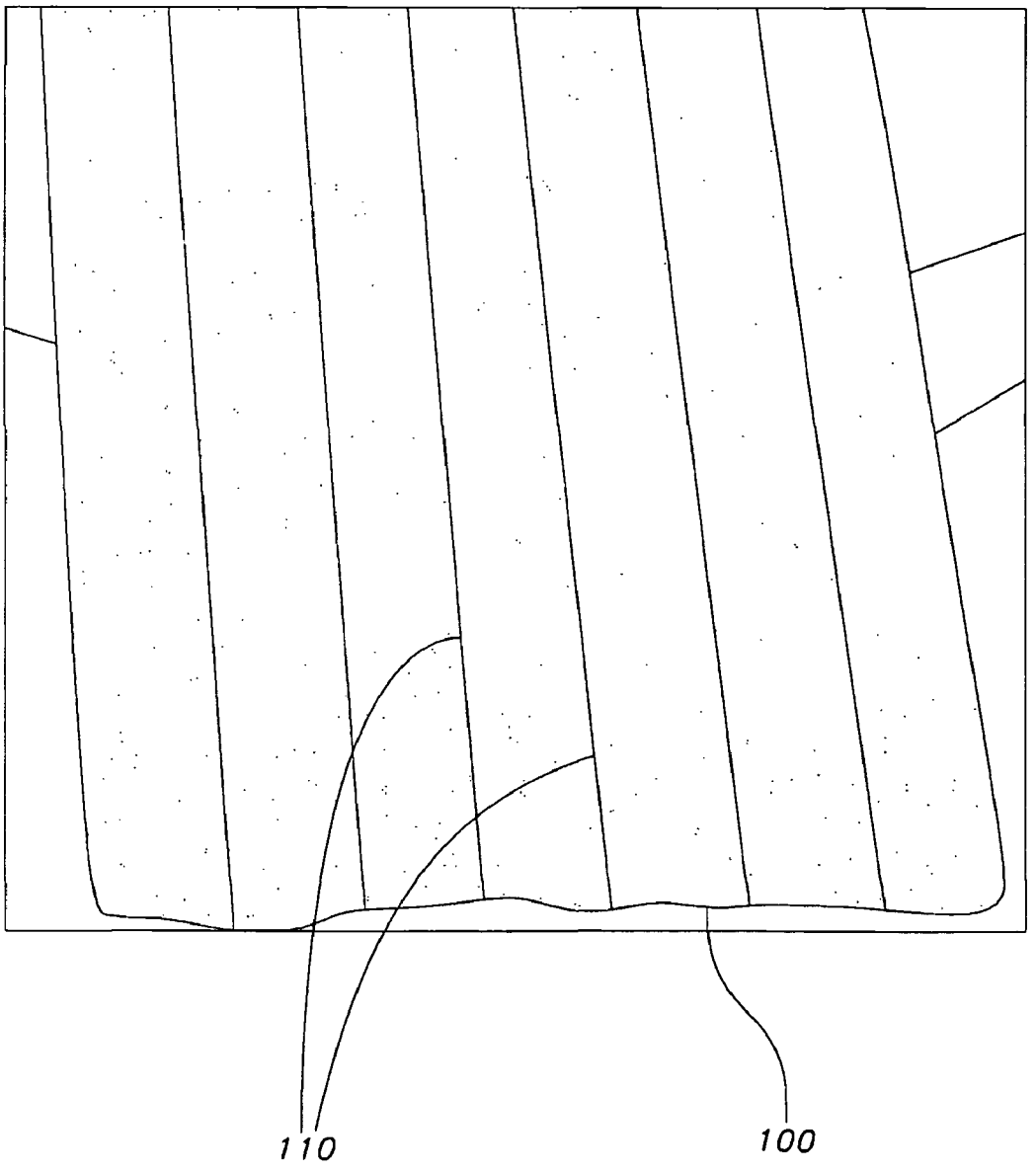


FIG. 13

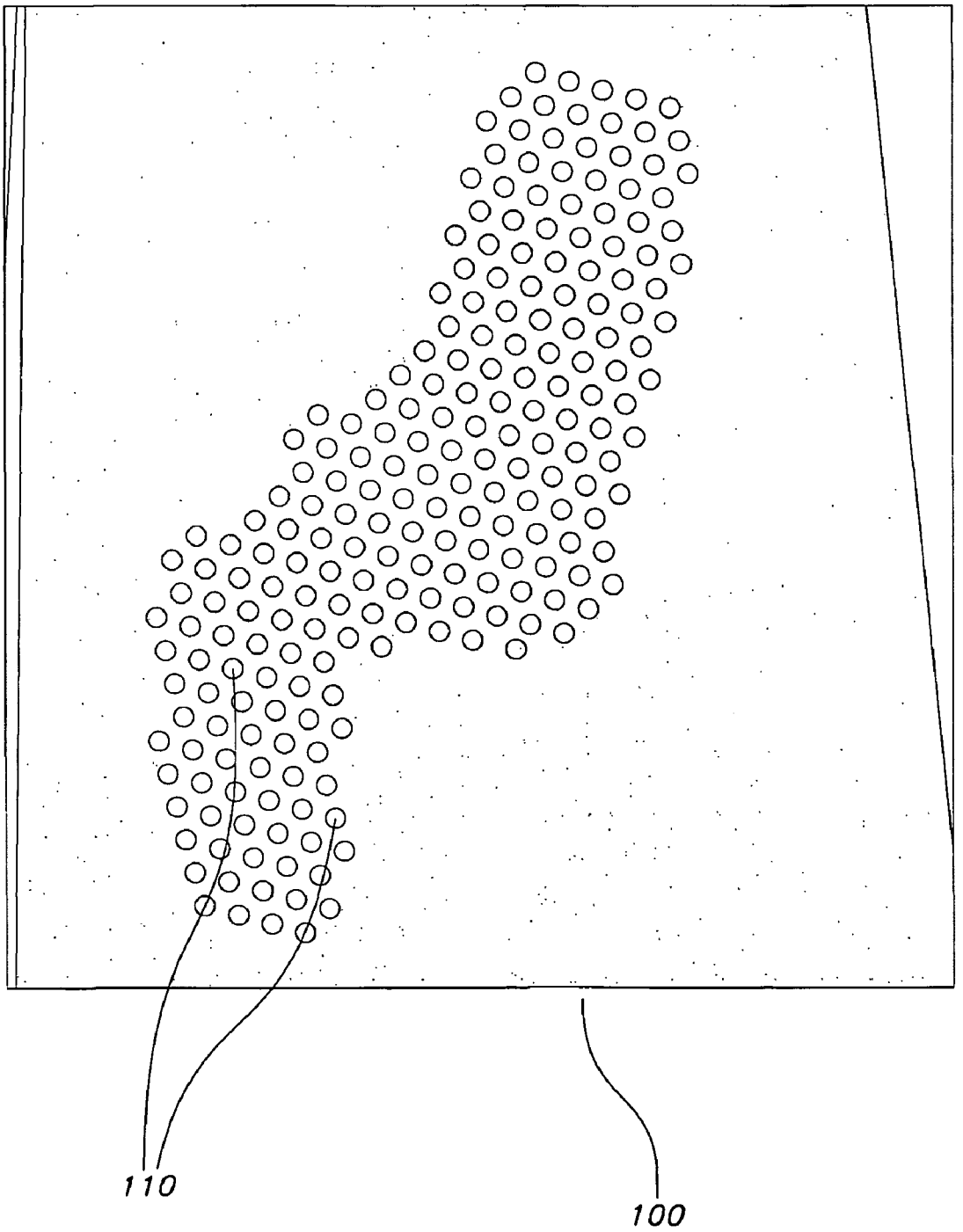


FIG. 14

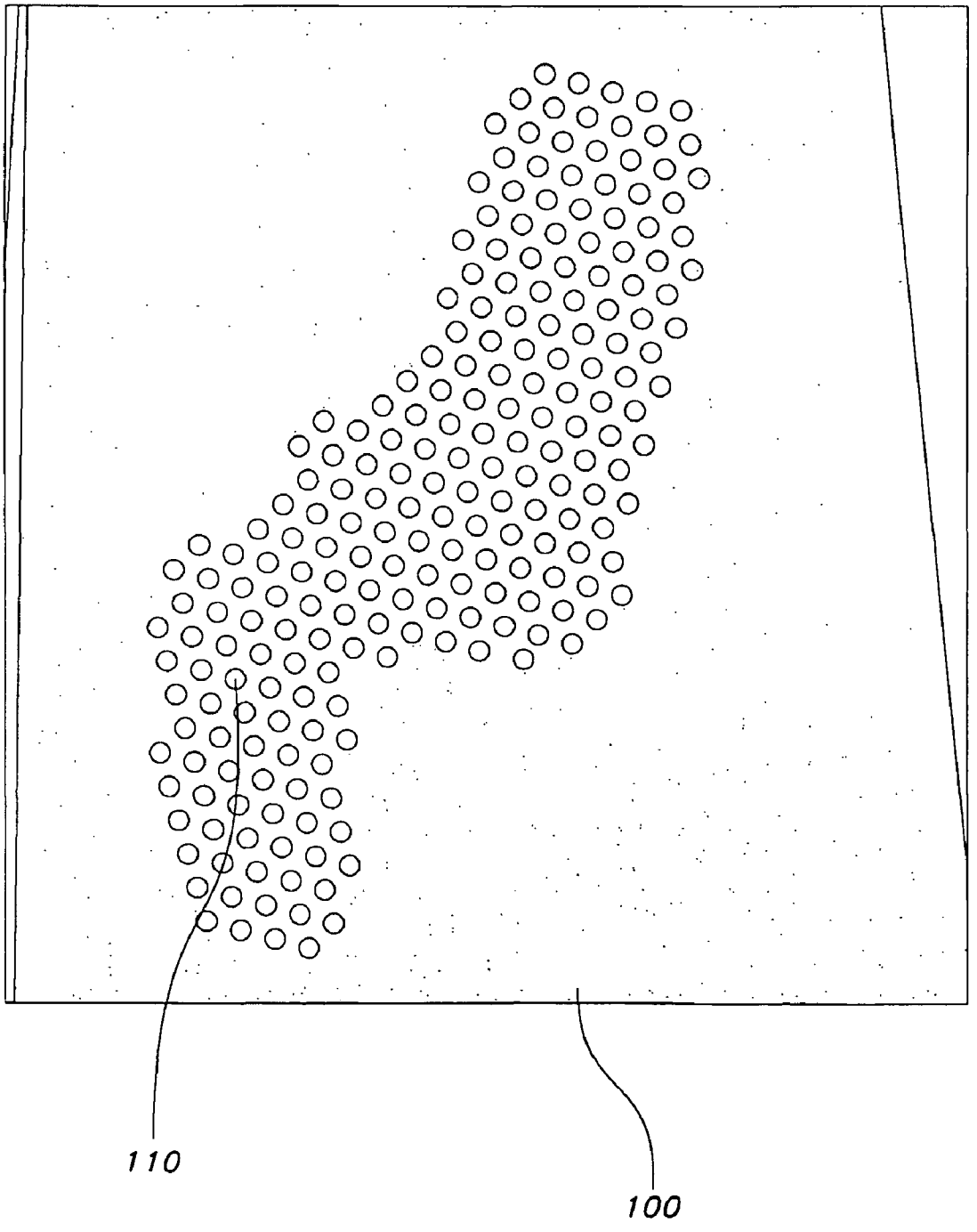


FIG. 15

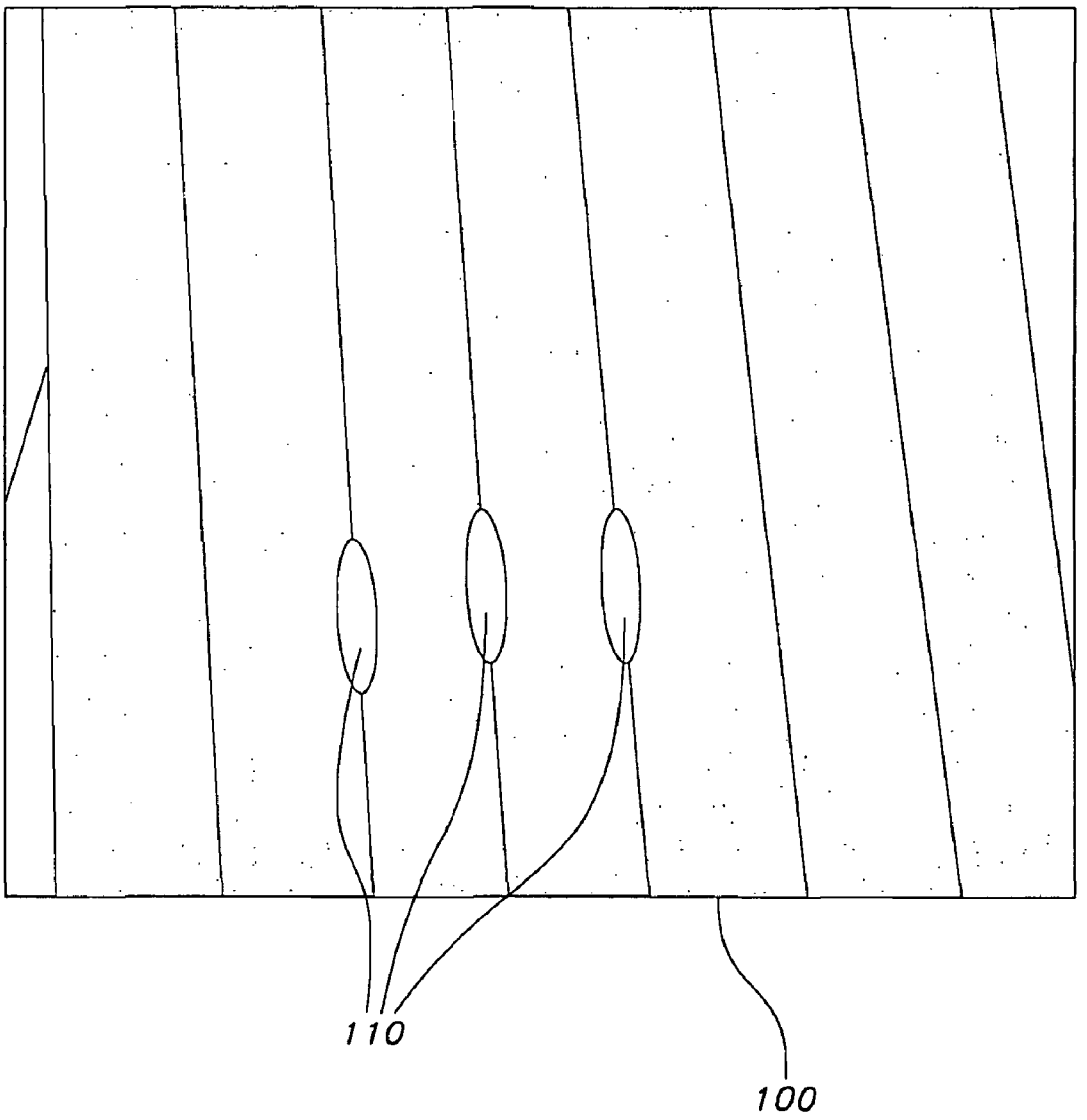


FIG. 16

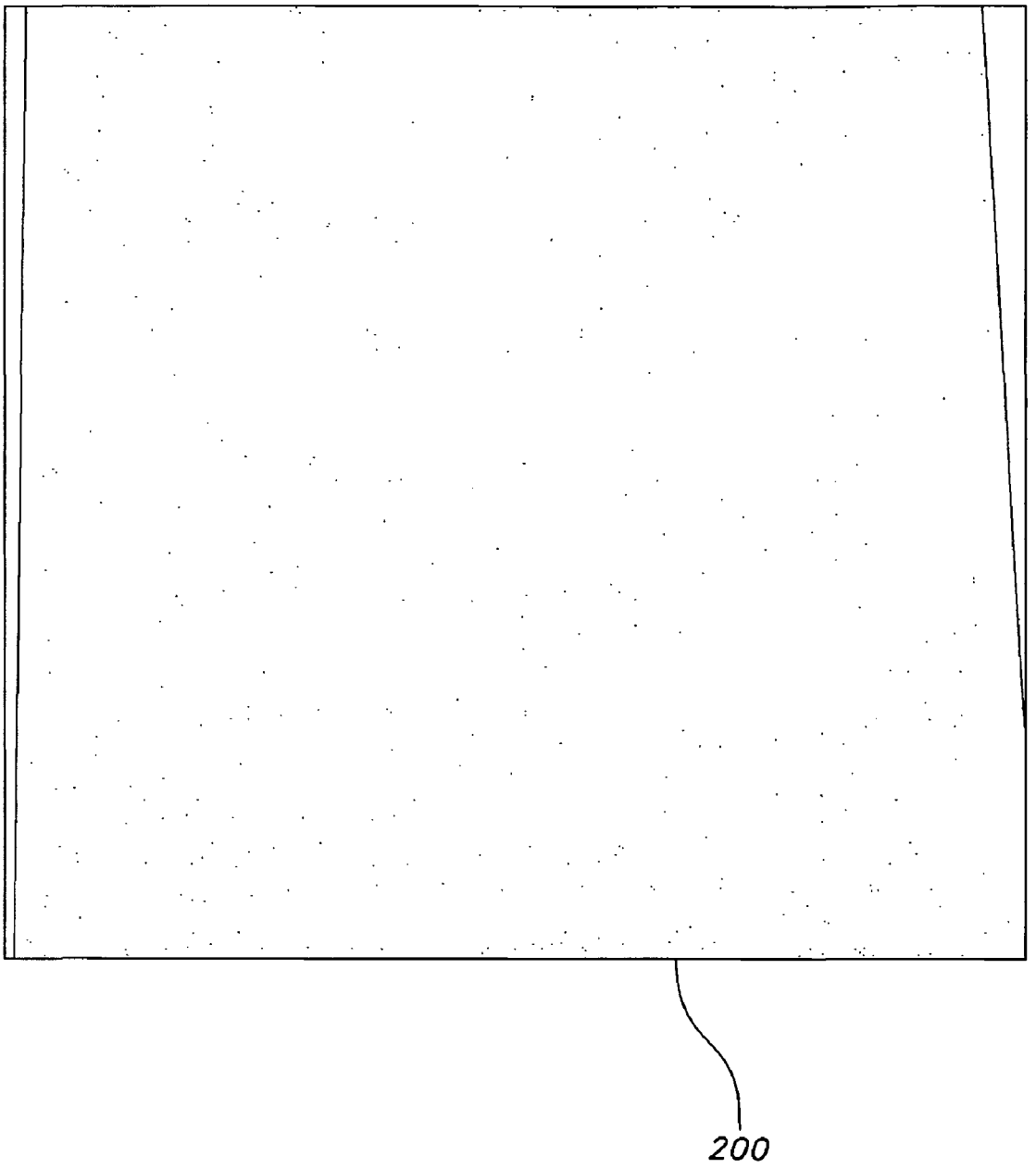


FIG. 17

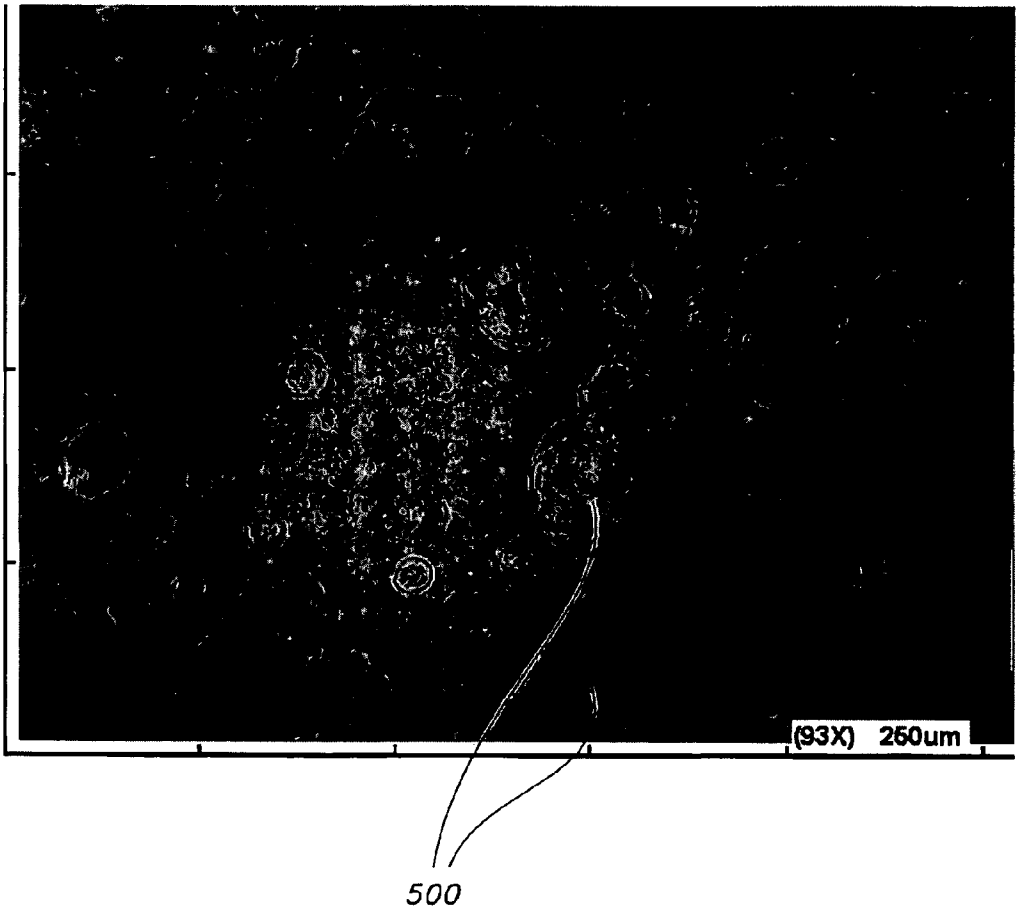


FIG. 18

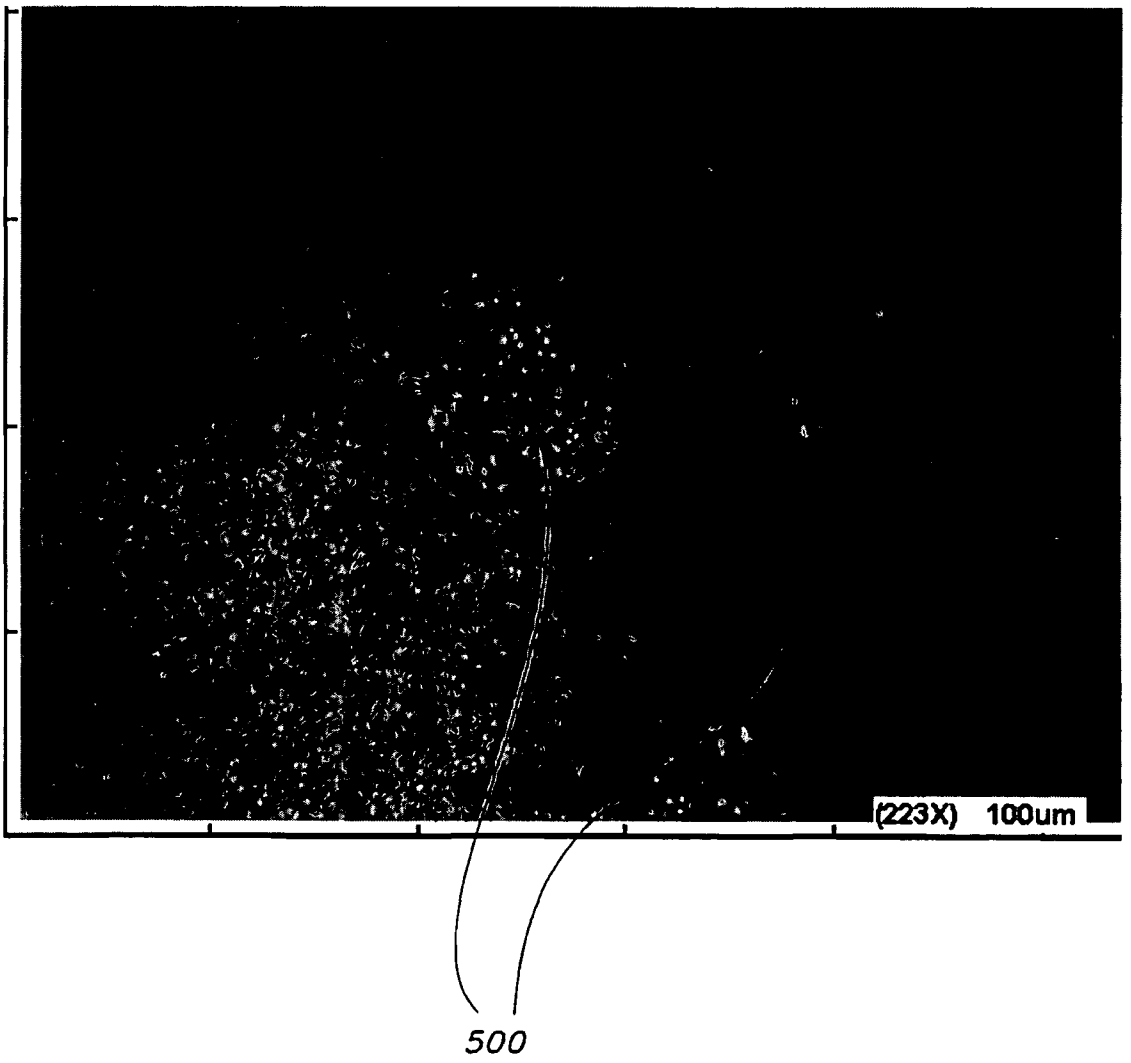


FIG. 19

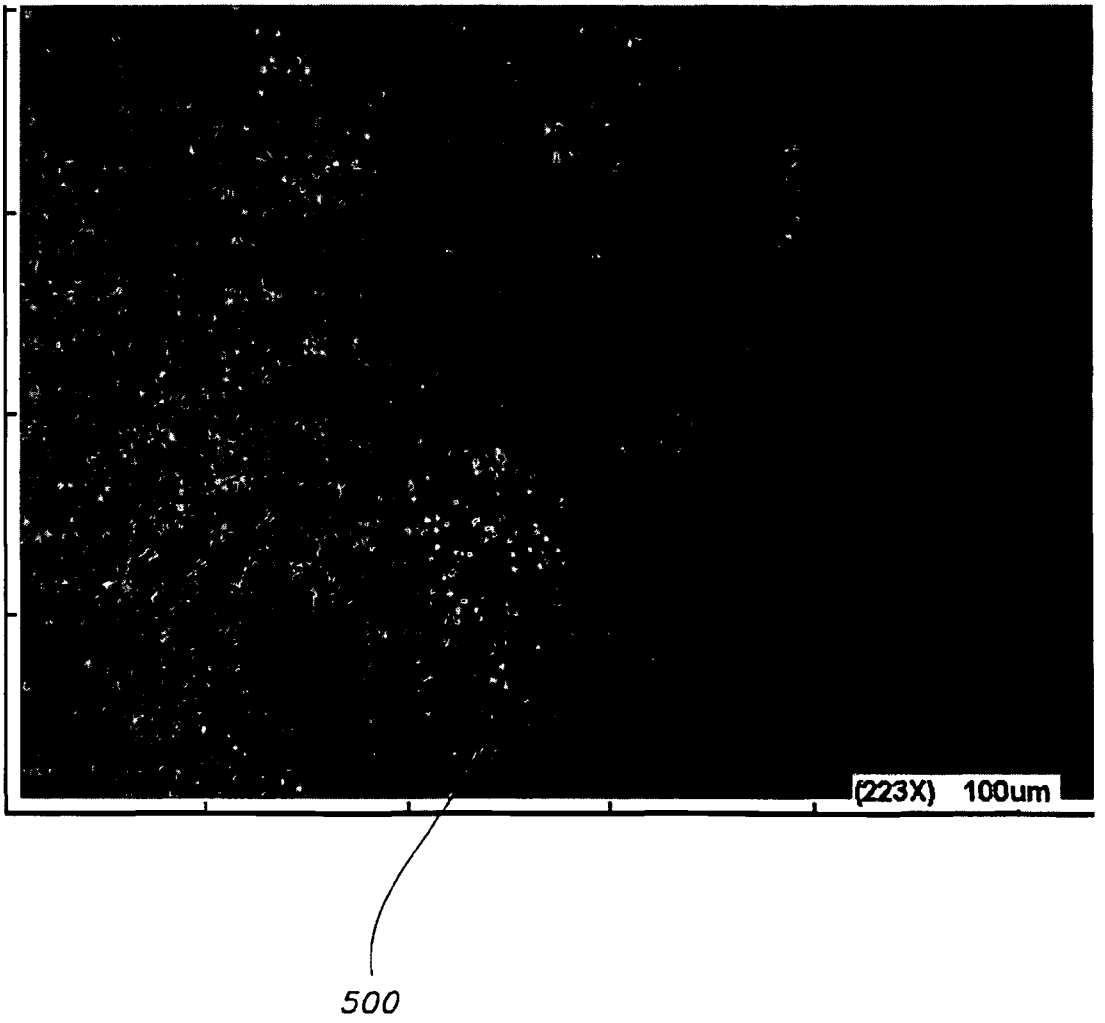


FIG. 20

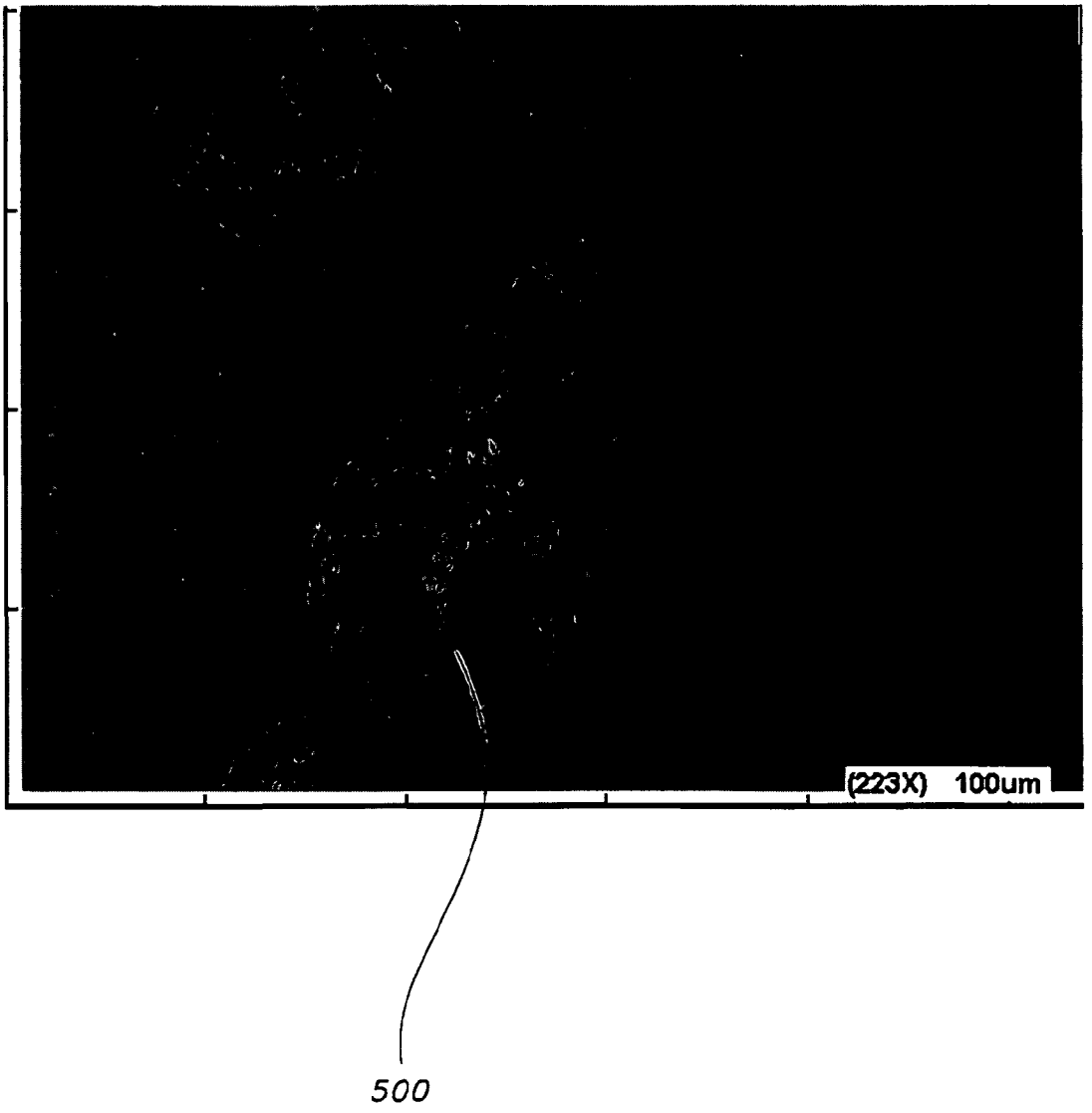


FIG. 21

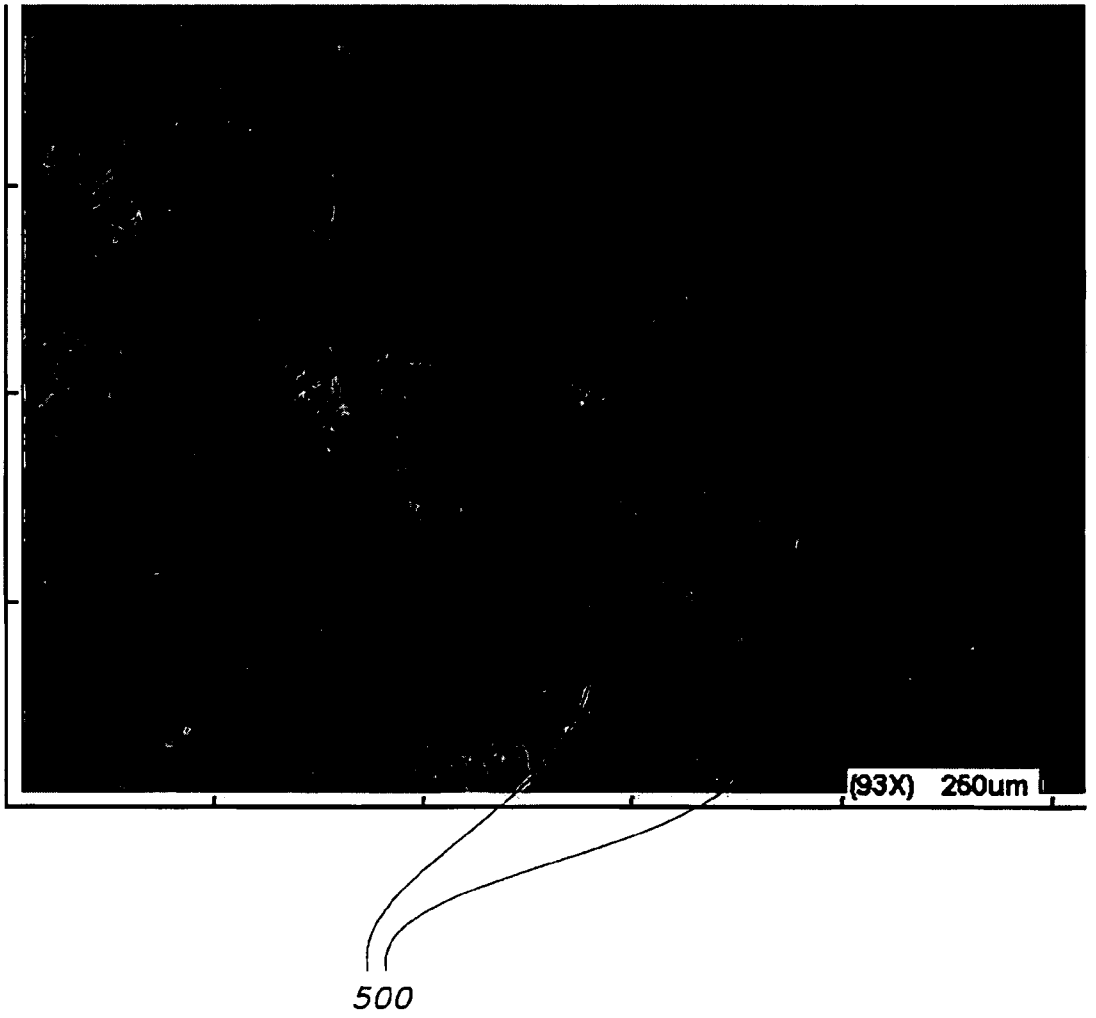


FIG. 22

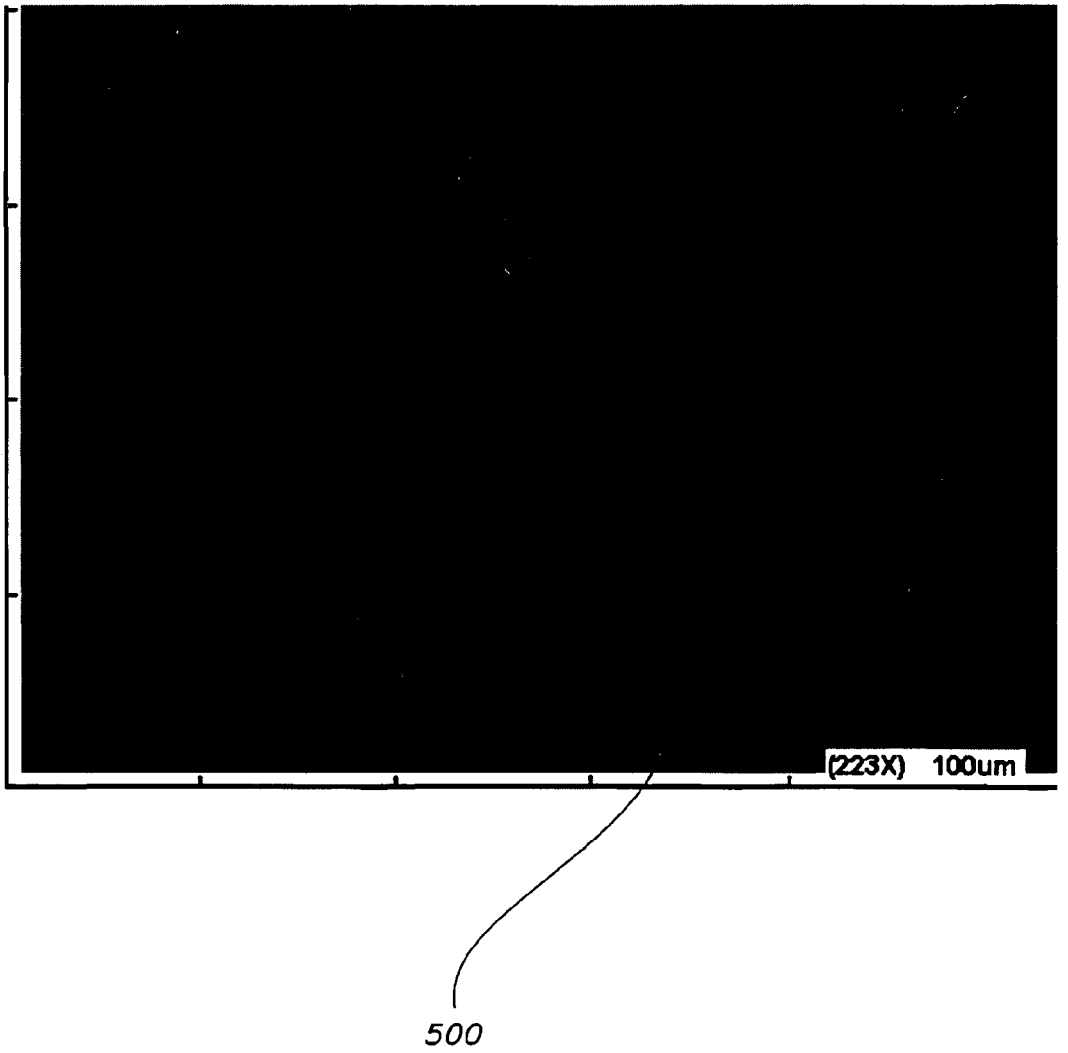


FIG. 23

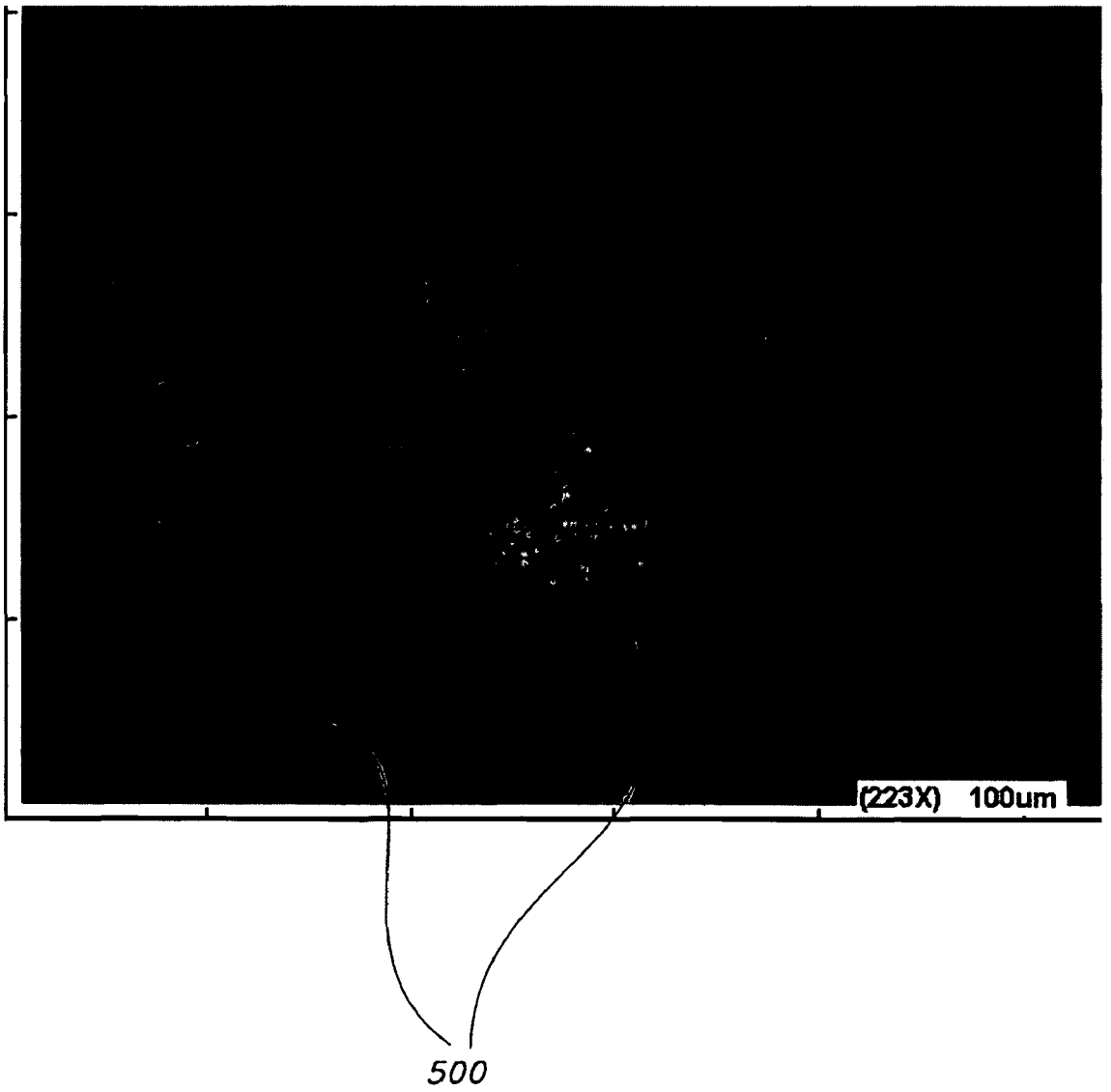


FIG. 24

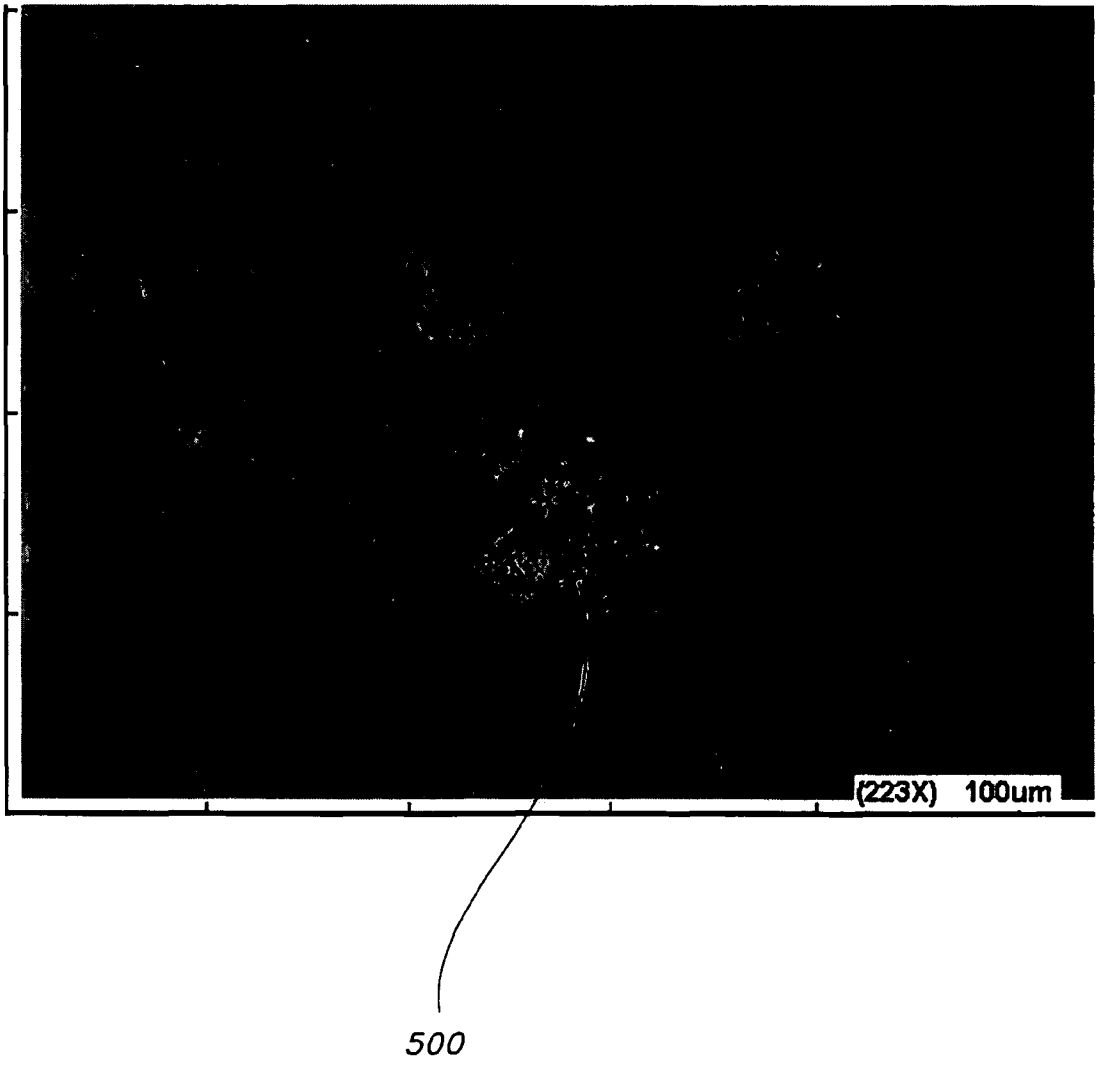


FIG. 25

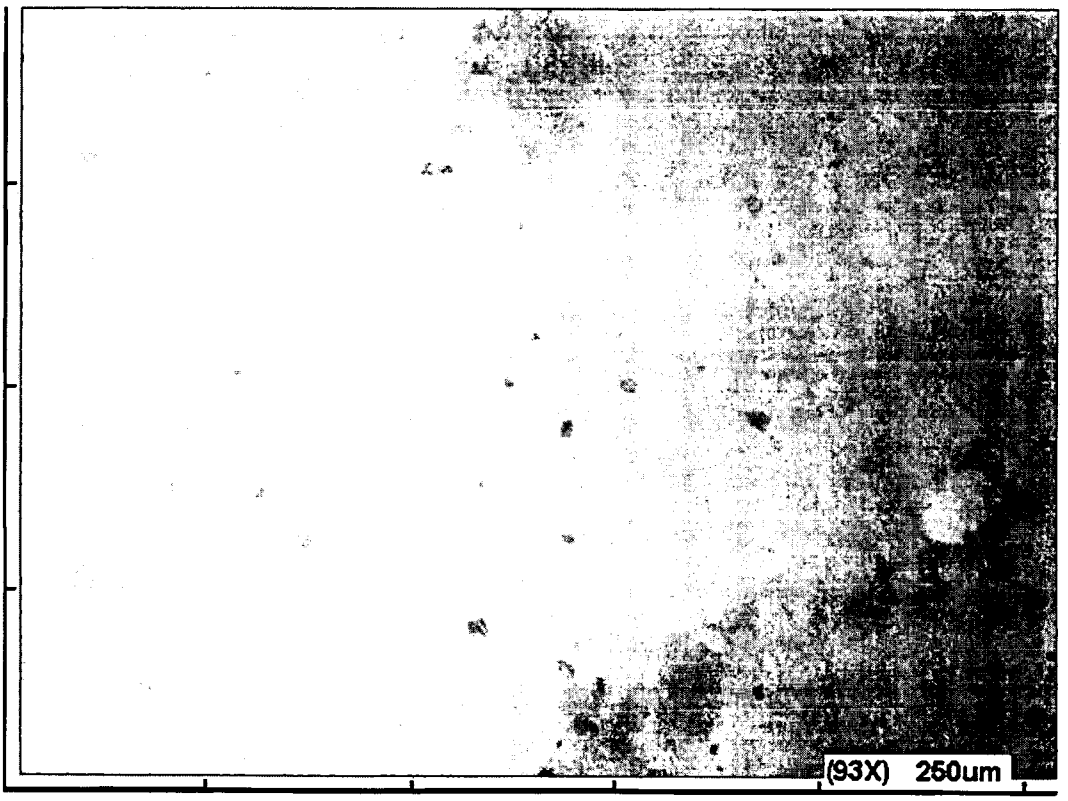


FIG. 26

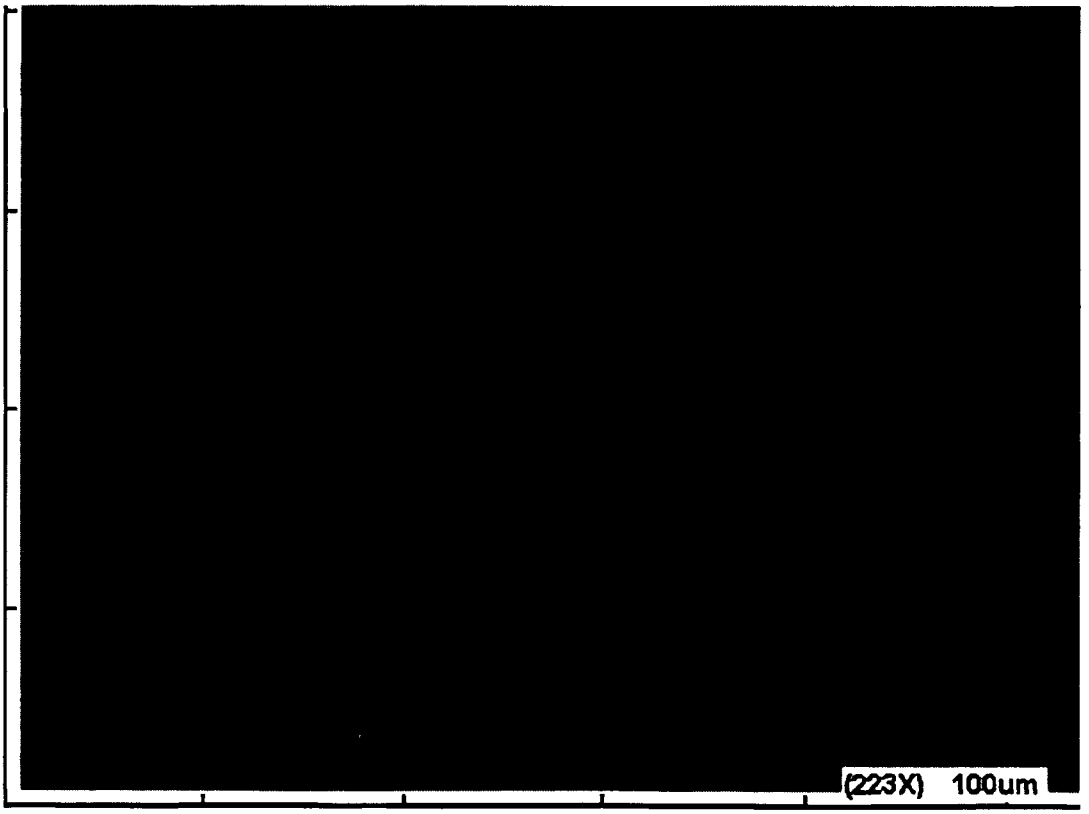


FIG. 27

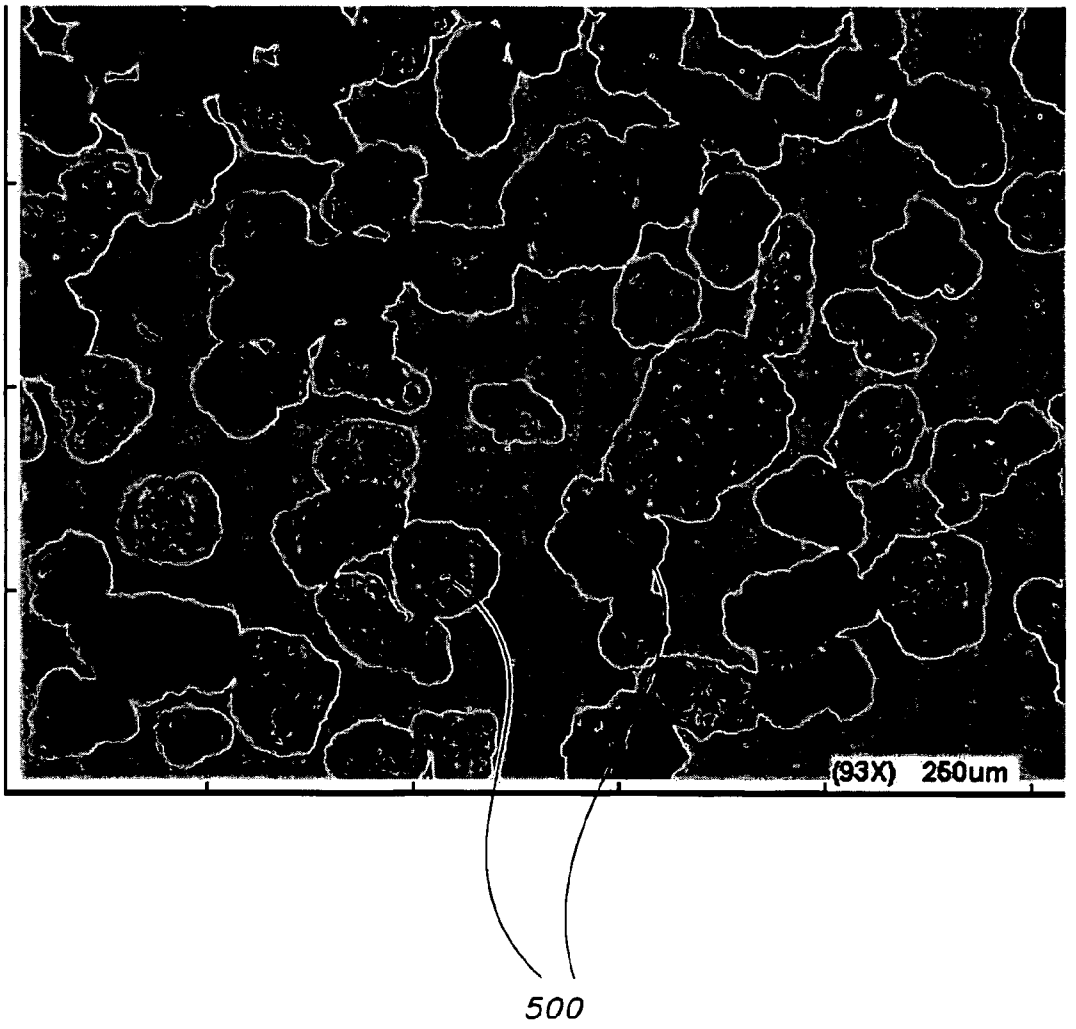


FIG. 28

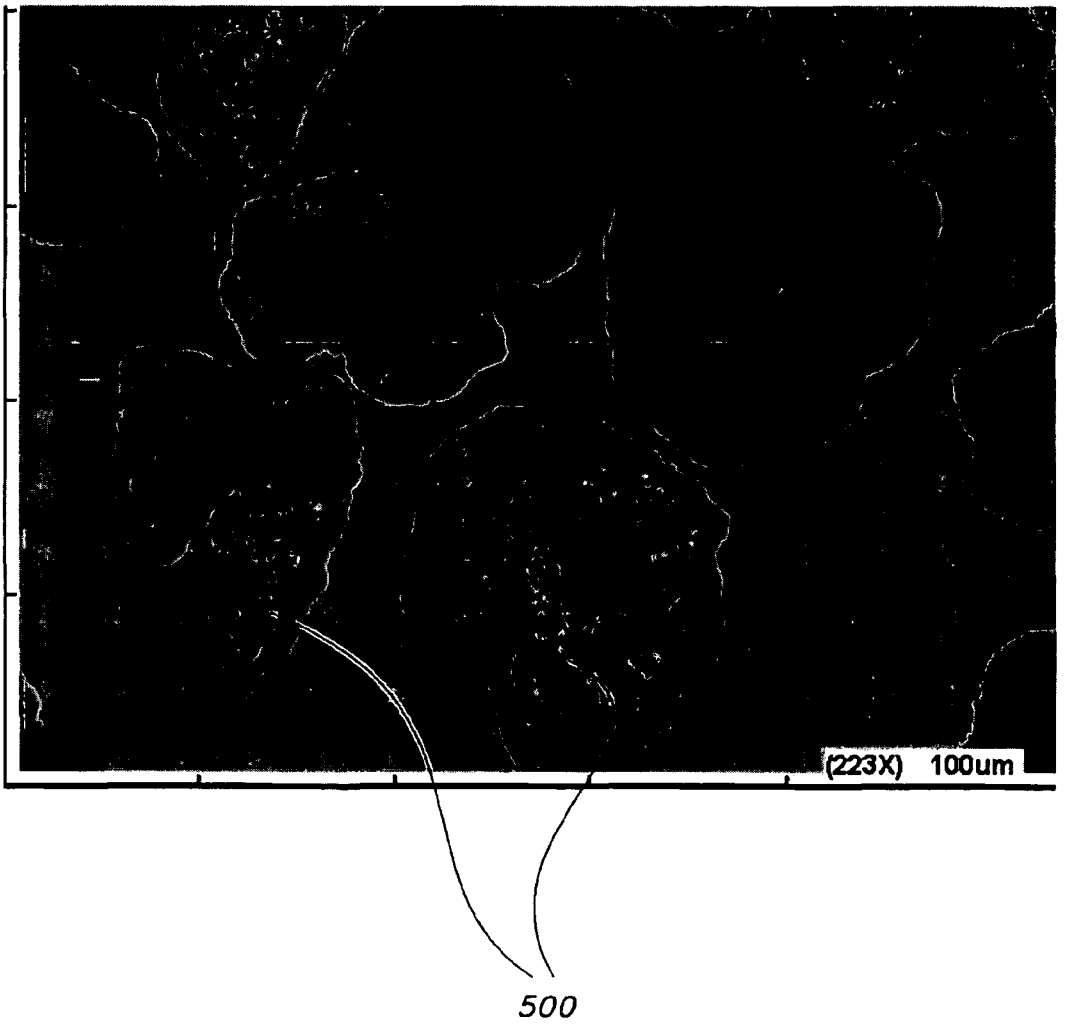


FIG. 29

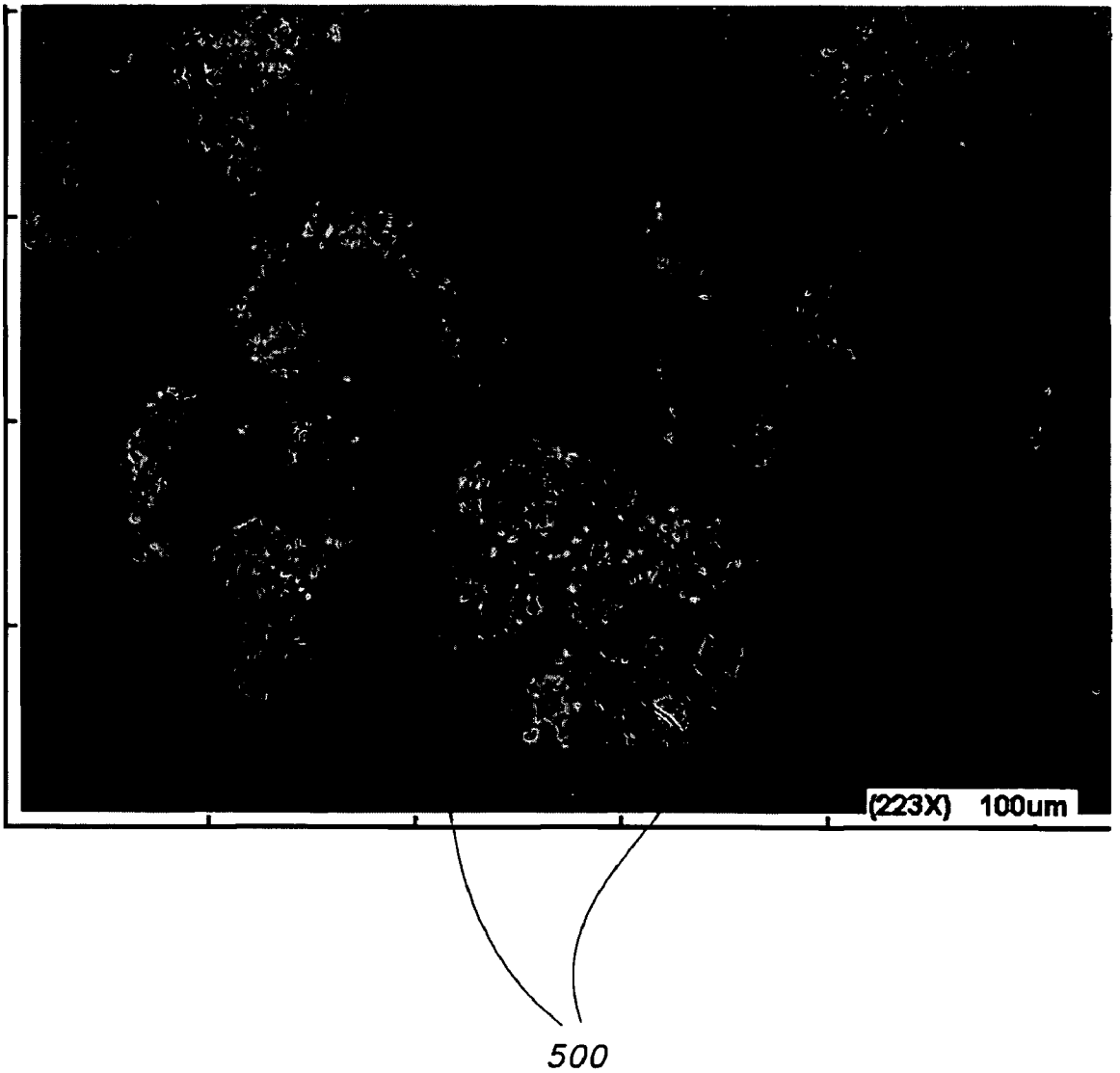


FIG. 30

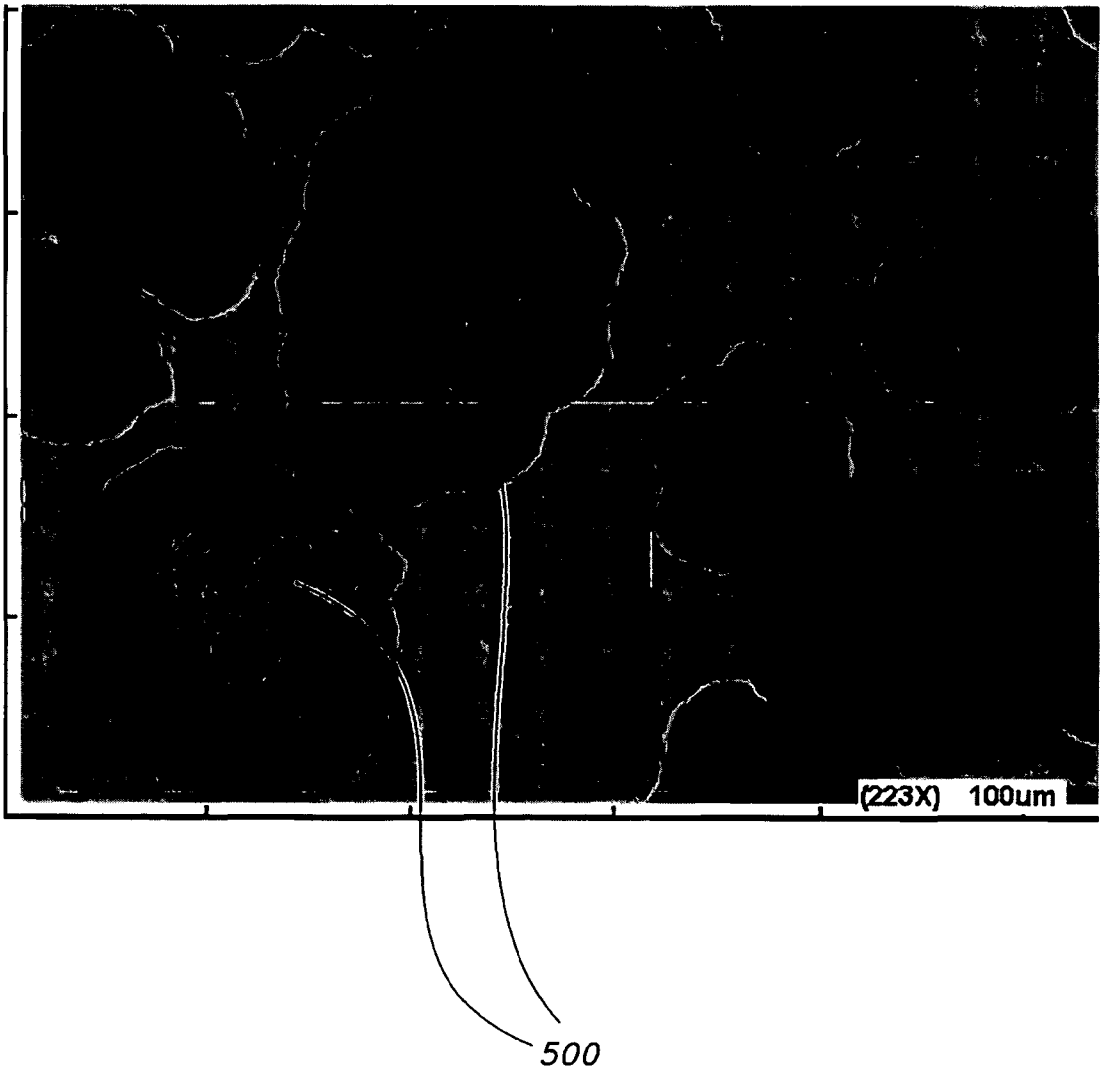
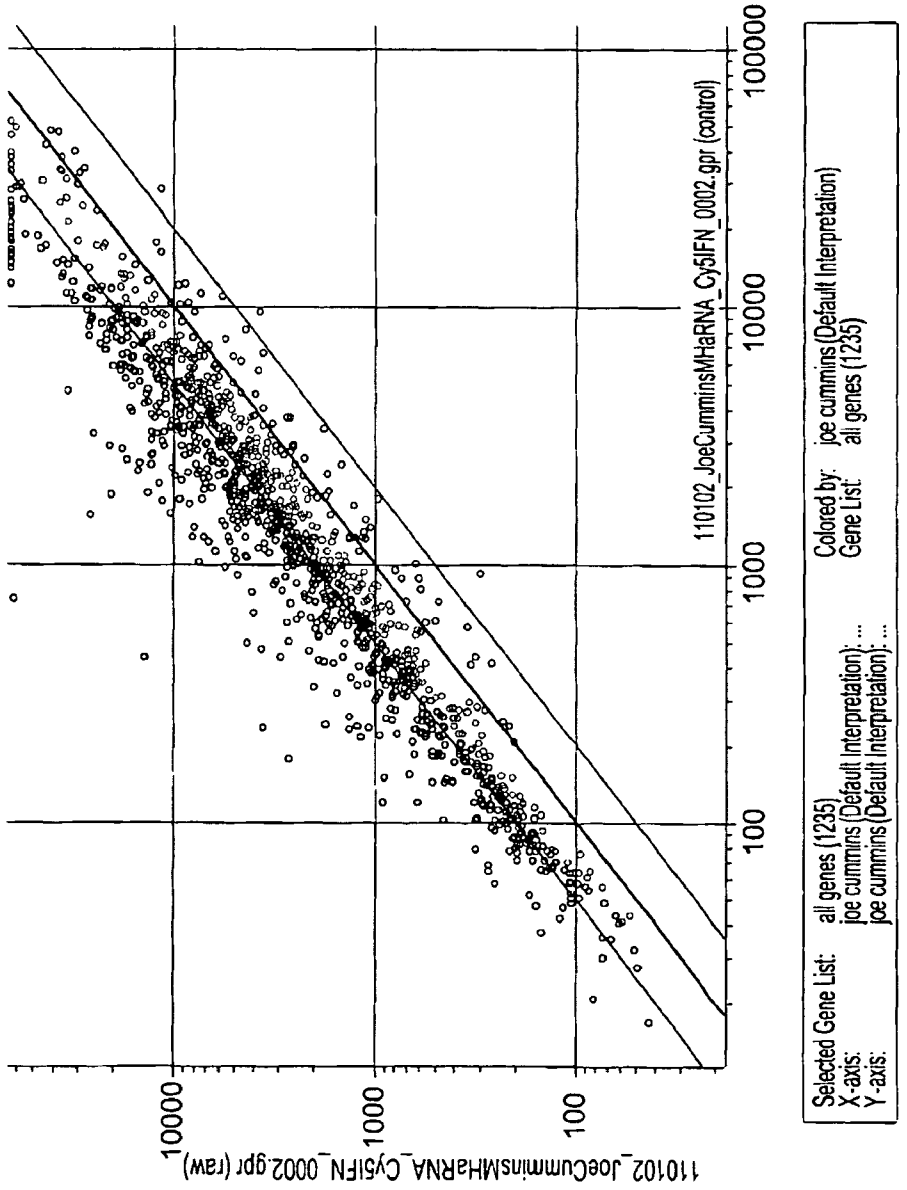


FIG. 31



Normalized to GAPDH, most of the ISGs are induced.

FIG. 32

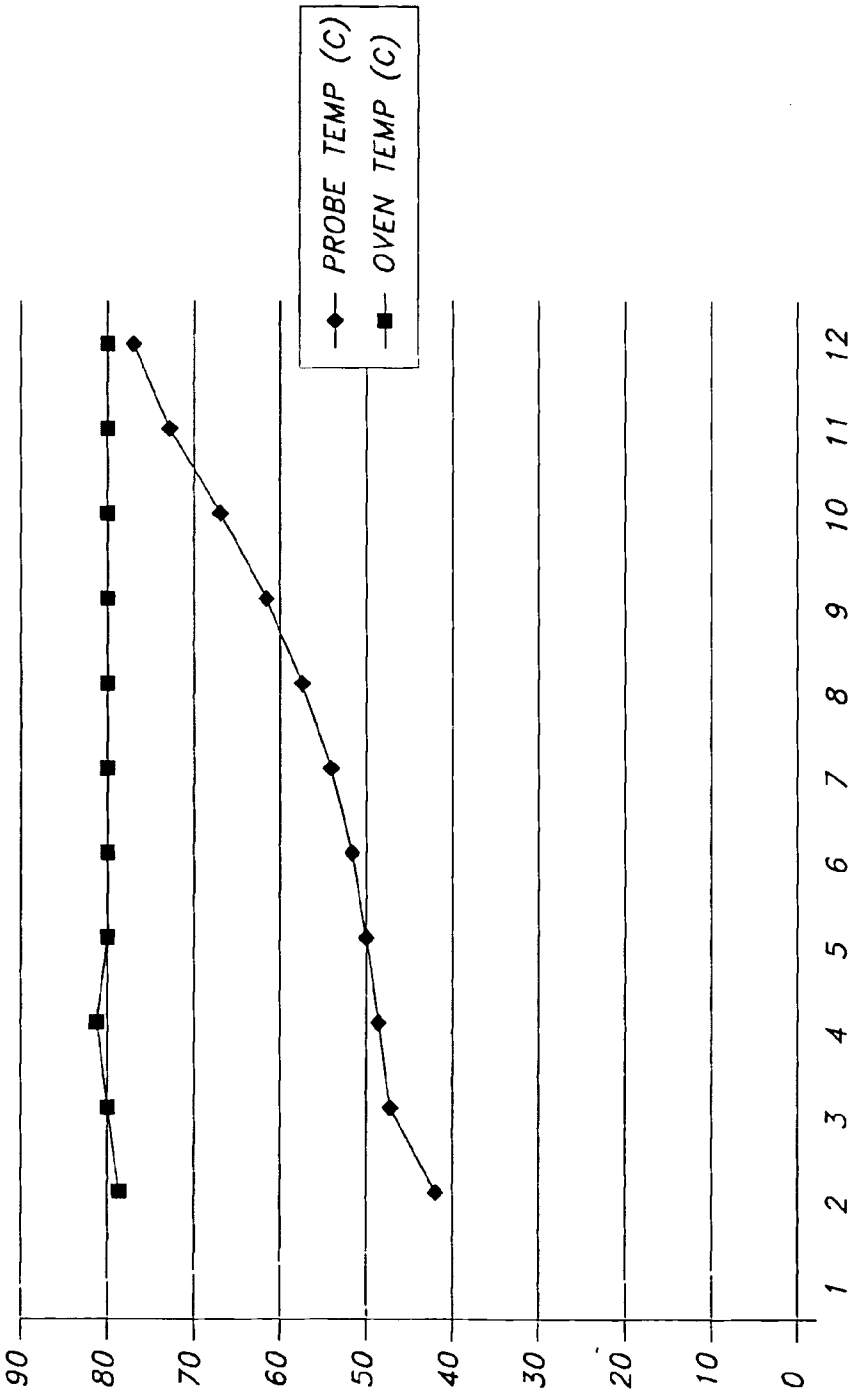

PROBE TEMP (C)
OVEN TEMP (C)
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 33

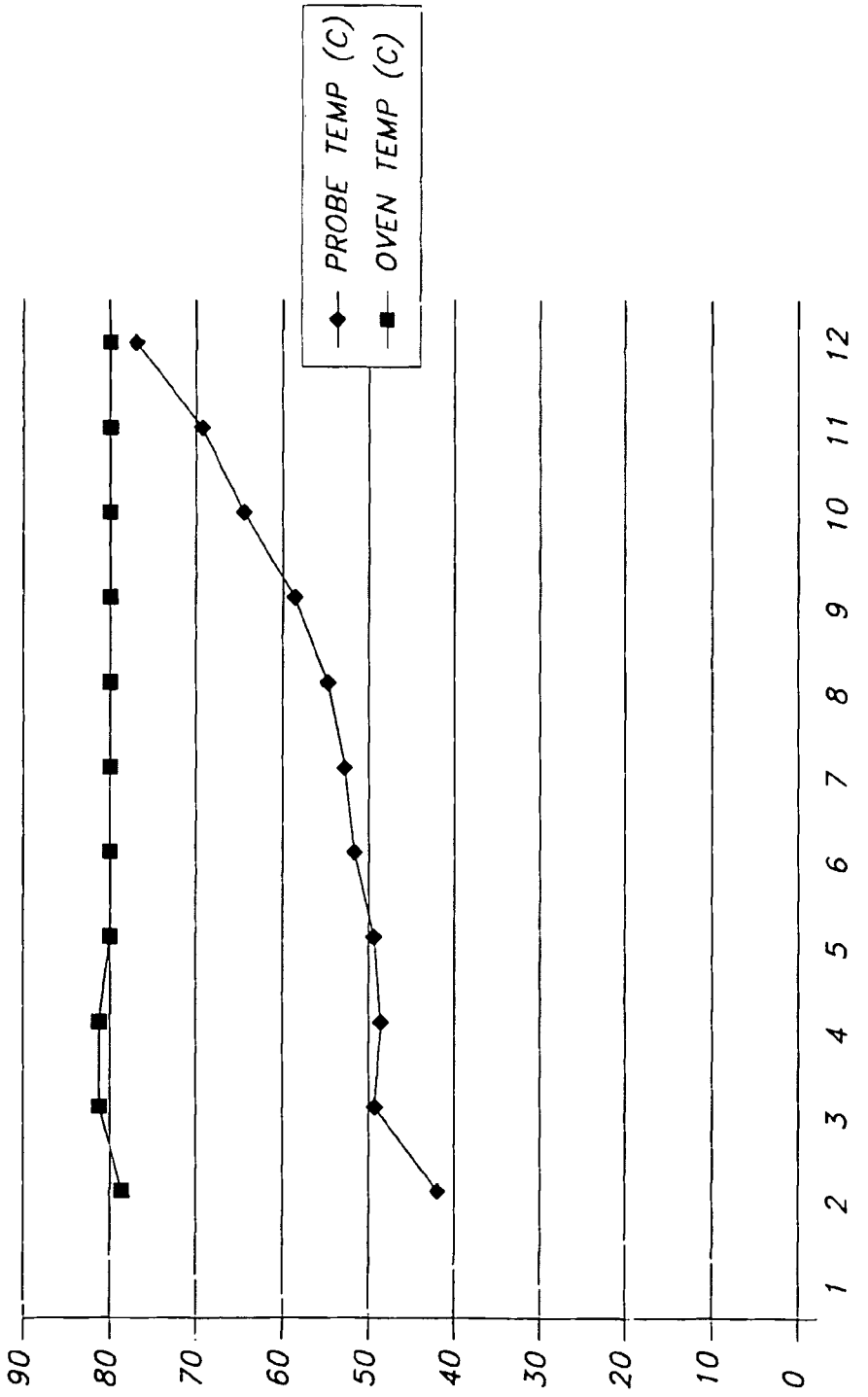

PROBE TEMP (C)
OVEN TEMP (C)
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 34

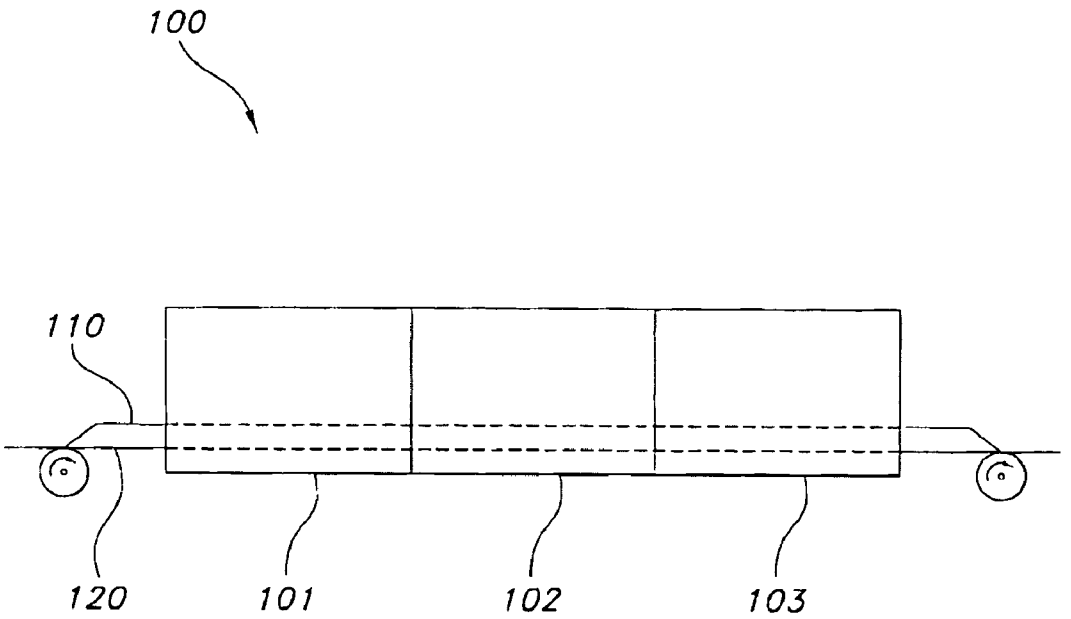


FIG. 35

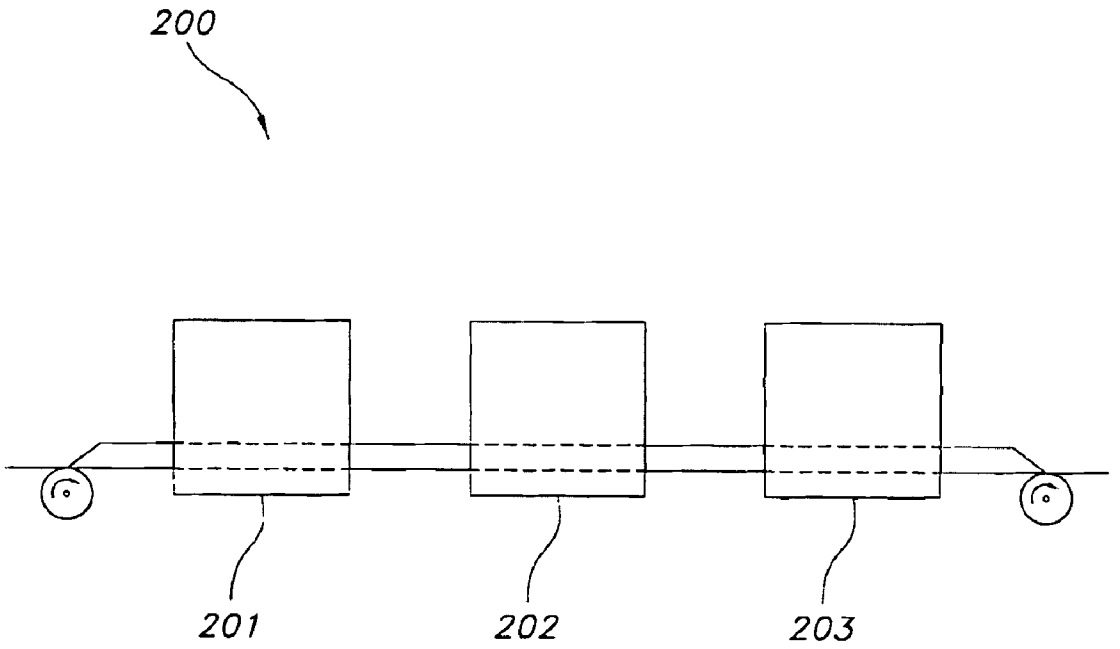


FIG. 36

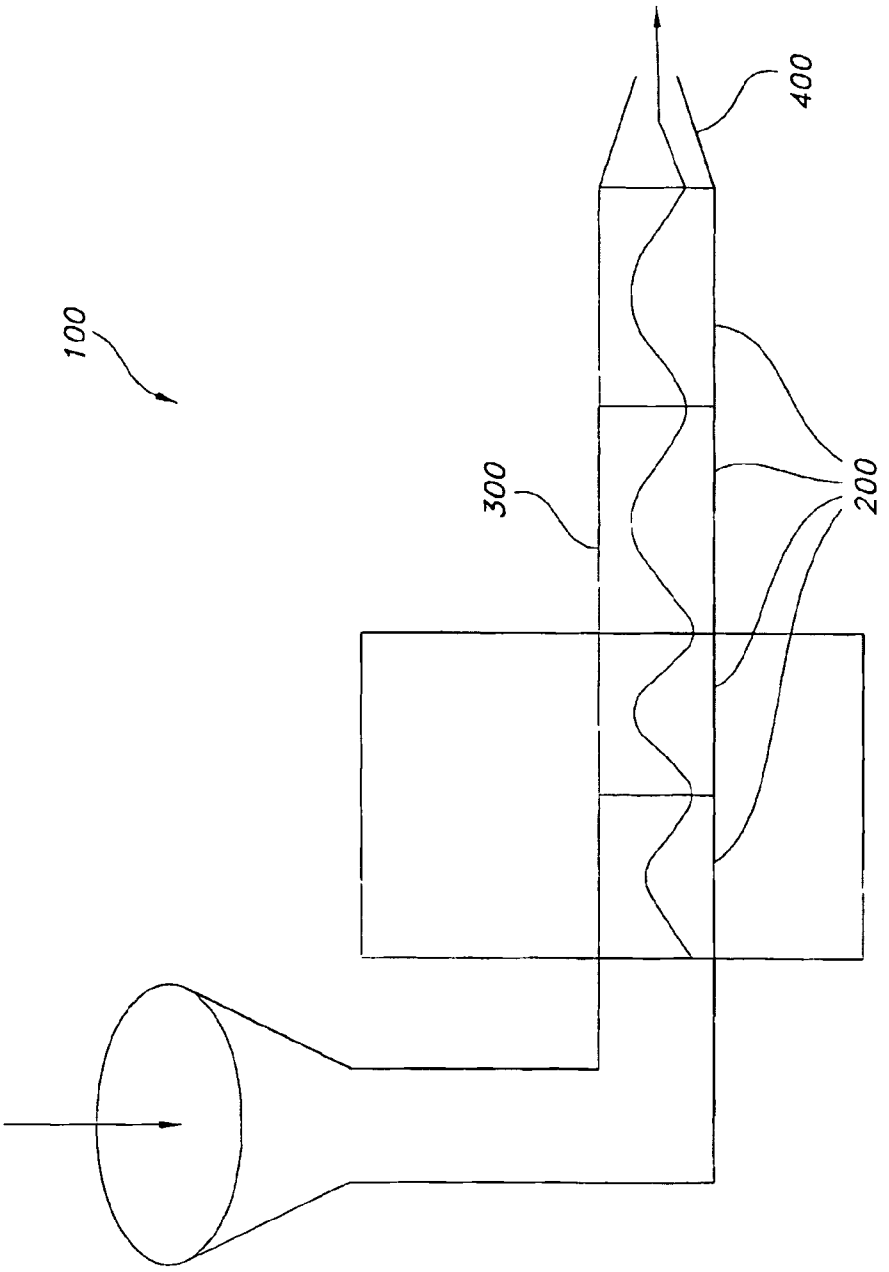


FIG. 37

Ex.	Polymer Component Reference	% Solids of solution	Viscosity (cp) at 5 rpm	% moisture	Film thickness (mils)	Film strength	Tear Resistance	Tendency to go to roof of mouth	180° bend test	Film molding	Dis-solution (sec)	Rating of dissolution in mouth	Time in oven (min)
EI	PEO/PVP (60/40)	45.0	14800	2.21	3.8	Adequate	Excellent	Low	Passed	No	3	Fast to Moderate	9
EJ	PEO/PVP (40/60)	50.0	6600	2.86	4	Weak	Low to moderate	High	Passed	No	3	Fast	8
EK	PEO/Starch (80/20)	40.0	3440	2.27	4.5	Adequate to good	Excellent	High	Passed	No	3	Fast to Moderate	8
EL	PEO/CMC (80/20)	37.5	121,200	1.96	4.1	Good	Excellent	High	Passed	No	5	Slow	9
EM	PEO/CMC (60/40)	30.0	82,000	4.21	3.45	Weak	Good	High	Passed	No	3	Slow to Moderate	9
EN	PEO/CMC (40/60)	30.0	185,000	3.07	3.5	Adequate	Very low	High	Failed	No	4	Slow	9
EO	PEO/HPC (80/20)	37.5	21,200	1.65	4	Good	Excellent	High	Passed	No	4	Fast	8
EP	PEO/HPC (60/40)	37.5	17,000	2.84	3.8	Adequate	Excellent	High	Passed	No	4	Fast	9
EQ	PEO/HPC (40/60)	42.5	43,400	2.83	4.5	Poor to adequate	Poor to good	High	Passed	No	7	Fast to Moderate	7
ER	PEO/HPC (20/80)	42.5	46,400	2.33	4.4	Adequate to good	Poor	Low	Passed	No	14-15	Slow	9
ES	PEO/HPMC (80/20)	37.5	29,000	2.14	4.4	Adequate	Good	High	Passed	Yes	4	Fast to Moderate	8
ET	PEO/HPMC (60/40)	37.5	47,000	2.37	3.9	Poor to adequate	Slight	High	Passed	Yes	3	Fast to Moderate	9
EU	PEO/HPMC (40/60)	35.0	54,800	3.55	4.5	Adequate to good	Low	Low	Passed	Yes	8	Slow	8
EV	PEO/HPMC (20/80)	35.0	96,600	4.43	4.5	Good	Low	Low	Passed	No	22	Slow	10
EW	PEO/PVA (80/20)	37.5	41,600	2.92	9	Weak	Moderate	High	Passed	No	3	Moderate	10

FIG. 38

POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U.S. application Ser. No. 10/856,176, filed May 28, 2004, which claims the benefit of U.S. Provisional Application No. 60/473,902, filed May 28, 2003 and which is a continuation-in-part of PCT/US02/32575 filed Oct. 11, 2002, which claims priority to U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002 which claims priority to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; PCT/US02/32594, filed Oct. 11, 2002, which claims priority to U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002; and PCT/US02/32542, filed Oct. 11, 2002, which claims priority to U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001 and U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002.

FIELD OF THE INVENTION

The invention relates to rapidly dissolving films and methods of their preparation. The films contain a polymer component, which includes polyethylene oxide optionally blended with cellulosic polymers. The films may also contain an active ingredient that is evenly distributed throughout the film. The even or uniform distribution is achieved by controlling one or more parameters, and particularly the elimination of air pockets prior to and during film formation and the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure.

BACKGROUND OF THE RELATED TECHNOLOGY

Active ingredients, such as drugs or pharmaceuticals, may be prepared in a tablet form to allow for accurate and consistent dosing. However, this form of preparing and dispensing medications has many disadvantages including that a large proportion of adjuvants that must be added to obtain a size able to be handled, that a larger medication form requires additional storage space, and that dispensing includes counting the tablets which has a tendency for inaccuracy. In addition, many persons, estimated to be as much as 28% of the population, have difficulty swallowing tablets. While tablets may be broken into smaller pieces or even crushed as a means of overcoming swallowing difficulties, this is not a suitable solution for many tablet or pill forms. For example, crushing or destroying the tablet or pill form to facilitate ingestion, alone or in admixture with food, may also destroy the controlled release properties.

As an alternative to tablets and pills, films may be used to carry active ingredients such as drugs, pharmaceuticals, and the like. However, historically films and the process of making drug delivery systems therefrom have suffered from a number of unfavorable characteristics that have not allowed them to be used in practice.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Pat. No. 4,136,145 to Fuchs, et al. ("Fuchs"). These films may be formed into a sheet, dried and then cut into individual doses. The Fuchs disclosure alleges the fabrication of a uniform film, which includes the combination of water-soluble polymers, surfactants, flavors, sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas.

Examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. This result can be attributed to Fuchs' process parameters, which although not disclosed likely include the use of relatively long drying times, thereby facilitating intermolecular attractive forces, convection forces, air flow and the like to form such agglomeration.

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.

The problems of self-aggregation leading to non-uniformity of a film were addressed in U.S. Pat. No. 4,849,246 to Schmidt ("Schmidt"). Schmidt specifically pointed out that the methods disclosed by Fuchs did not provide a uniform film and recognized that that the creation of a non-uniform film necessarily prevents accurate dosing, which as discussed above is especially important in the pharmaceutical area. Schmidt abandoned the idea that a mono-layer film, such as described by Fuchs, may provide an accurate dosage form and instead attempted to solve this problem by forming a multi-layered film. Moreover, his process is a multi-step process that adds expense and complexity and is not practical for commercial use.

Other U.S. patents directly addressed the problems of particle self-aggregation and non-uniformity inherent in conventional film forming techniques. In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann et al. and U.S. Pat. No. 5,948,430 to Zerbe et al. incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to driving 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. Such processes also run the risk of exposing the active, i.e., a drug, or vitamin C, or other components to prolonged exposure to moisture and elevated temperatures, which may render it ineffective or even harmful.

In addition to the concerns associated with degradation of an active during extended exposure to moisture, the conventional drying methods themselves are unable to provide uniform films. The length of heat exposure during conventional processing, often referred to as the "heat history", and the manner in which such heat is applied, have a direct effect on the formation and morphology of the resultant film product. Uniformity is particularly difficult to achieve via conventional drying methods where a relatively thicker film, which is well-suited for the incorporation of a drug active, is desired. Thicker uniform films are more difficult to achieve because the surfaces of the film and the inner portions of the film do not experience the same external conditions simultaneously during drying. Thus, observation of relatively thick films made from such conventional processing shows a non-uniform structure caused by convection and intermolecular forces and requires greater than 10% moisture to remain flexible. The amount of free moisture can often interfere over time with the drug leading to potency issues and therefore inconsistency in the final product.

Conventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like. The difficulty in achieving a uniform film is directly related to the rheological properties and the process of water evaporation in the film-forming composition. When the surface of an aqueous polymer solution is contacted with a high temperature air current, such as a film-forming composition passing through a hot air oven, the surface water is immediately evaporated forming a polymer film or skin on the surface. This seals the remainder of the aqueous film-forming composition beneath the surface, forming a barrier through which the remaining water must force itself as it is evaporated in order to achieve a dried film. As the temperature outside the film continues to increase, water vapor pressure builds up under the surface of the film, stretching the surface of the film, and ultimately ripping the film surface open allowing the water vapor to escape. As soon as the water vapor has escaped, the polymer film surface reforms, and this process is repeated, until the film is completely dried. The result of the repeated destruction and reformation of the film surface is observed as a "ripple effect" which produces an uneven, and therefore non-uniform film. Frequently, depending on the polymer, a surface will seal so tightly that the remaining water is difficult to remove, leading to very long drying times, higher temperatures, and higher energy costs.

Other factors, such as mixing techniques, also play a role in the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval. Air can be trapped in the composition during the mixing process or later during the film making process, which can leave voids in the film product as the moisture evaporates during the drying stage. The film frequently collapse around the voids resulting in an uneven film surface and therefore, non-uniformity of the final film product. Uniformity is still affected even if the voids in the film caused by air bubbles do not collapse. This situation also provides a non-uniform film in that the spaces, which are not uniformly distributed, are occupying area that would otherwise be occupied by the film composition. None of the above-mentioned patents either addresses or proposes a solution to the problems caused by air that has been introduced to the film.

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, such films are produced through a selection of a polymer or combination of polymers that will provide a desired viscosity, a film-forming process such as reverse roll coating, and a controlled, and desirably rapid, drying process which serves to maintain the uniform distribution of non-self-aggregated components without the necessary addition of gel formers or polyhydric alcohols and the like which appear to be required in the products and for the processes of prior patents, such as the aforementioned Horstmann and Zerbe patents. 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.

SUMMARY OF THE INVENTION

Some embodiments of the present invention provide a mucosally-adhesive water-soluble film product, which includes:

an analgesic opiate pharmaceutical active; and

at least one water-soluble polymer component including polyethylene oxide in combination with a hydrophilic cellulosic polymer;

wherein:

the water-soluble polymer component includes greater than 75% polyethylene oxide and up to 25% hydrophilic cellulosic polymer;

the polyethylene oxide includes one or more low molecular weight polyethylene oxides and one or more higher molecular weight polyethylene oxides, the molecular weight of the low molecular weight polyethylene oxide being in the range 100,000 to 300,000 and the molecular weight of the higher molecular weight polyethylene oxide being in the range 600,000 to 900,000; and

the polyethylene oxide of low molecular weight is about 60% or more in the polymer component.

Another embodiment of the present invention provides a mucosally-adhesive water-soluble film product, which includes:

an analgesic opiate pharmaceutical active; and

at least one water-soluble polymer component including polyethylene oxide in combination with a hydrophilic cellulosic polymer;

wherein:

the water-soluble polymer component includes the hydrophilic cellulosic polymer in a ratio of up to about 4:1 with the polyethylene oxide;

the polyethylene oxide includes one or more low molecular weight polyethylene oxides and one or more higher molecular weight polyethylene oxides, the molecular weight of the low molecular weight polyethylene oxide being in the range 100,000 to 300,000 and the molecular weight of the higher molecular weight polyethylene oxide being in the range 600,000 to 900,000; and

the polyethylene oxide of low molecular weight is about 60% or more in the polymer component.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a side view of a package containing a unit dosage film of the present invention.

FIG. **2** shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

FIG. **3** shows a side view of the adjacently coupled packages of FIG. **2** arranged in a stacked configuration.

FIG. **4** shows a perspective view of a dispenser for dispensing the packaged unit dosage forms, dispenser containing the packaged unit dosage forms in a stacked configuration.

FIG. **5** is a schematic view of a roll of coupled unit dose packages of the present invention.

FIG. **6** is a schematic view of an apparatus suitable for preparation of a pre-mix, addition of an active, and subsequent formation of the film.

FIG. **7** is a schematic view of an apparatus suitable for drying the films of the present invention.

FIG. **8** is a sequential representation of the drying process of the present invention.

FIG. **9** is a photographic representation of a film dried by conventional drying processes.

FIG. **10** is a photographic representation of a film dried by conventional drying processes.

FIG. **11** is a photographic representation of a film dried by conventional drying processes.

FIG. **12** is a photographic representation of a film dried by conventional drying processes.

FIG. **13** is a photographic representation of a film dried by conventional drying processes.

FIG. **14** is a photographic representation of a film dried by conventional drying processes.

FIG. **15** is a photographic representation of a film dried by conventional drying processes.

FIG. **16** is a photographic representation of a film dried by conventional drying processes.

FIG. **17** is a photographic representation of a film dried by the inventive drying process.

FIG. **18** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **19** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **20** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **21** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **22** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **23** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **24** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **25** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **26** is a photomicrographic representation off at coated particles not in film, heated for 9 minutes at 80° C.

FIG. **27** is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80° C.

FIG. **28** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **29** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **30** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **31** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **32** is a graphical representation of a microarray on the blood of a human after ingestion by the human of a film of the present invention containing a bovine derived protein.

FIG. **33** is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

FIG. **34** is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

FIG. **35** is a schematic representation of a continuously-linked zone drying apparatus in accordance with the present invention.

FIG. **36** is a schematic representation of a separate zone drying apparatus in accordance with the present invention.

FIG. **37** is a schematic representation of a extrusion device for use in producing films of the present invention.

FIG. **38** provides a table of various compositions of the invention, as well as certain properties.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention, which are formed from one or more components in addition to a polar solvent, to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity includes the substantial absence of aggregates or conglomerates as is common in conventional mixing and heat drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity of component distribution throughout the area of a given film.

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. 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. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Pat. No. 4,631,837 to Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

The objective of the drying process is to provide a method of drying the films that avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. In conventional oven dry-

ing methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface.

This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the bottom up, such films result.

The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_1) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

$$V_o=(2gr^2)(\rho_p-\rho_1)/9\mu$$

At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

Stokian analyses has shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v, can be expressed as:

$$v/V_o=1/(1+\kappa\phi)$$

where κ=a constant, and ϕ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o=1+2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At higher volume fractions, the viscosity of the dispersion can be expressed as

$\mu/\mu_o=1+2.5\phi+C_1\phi^2+C_2\phi^3+\ldots$

where C is a constant.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The 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. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., <500 μm. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated from the yield stress values. In the case of isolated spherical particles, the maximum shear stress developed in settling through a medium of given viscosity can be given as

$$\tau_{max}=3V\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability 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. For viscoelastic fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt %, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate range. During mixing, pumping, and film casting, shear rates in the range of 10-10^5 $sec.^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelasticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)}=\alpha_o^{(n-1/n)}-((n-1)/(2n-1))(\tau/K)^{1/n}(2\pi/\lambda)^{(3+n)/n}h^{(2n+1)/n}t$$

where α is the surface wave amplitude, α_o is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote thin film formation and uniformity.

Thus, uniformity in the mixture of components depends upon numerous variables. As described herein, viscosity of the components, the mixing techniques and the rheological properties of the resultant mixed composition and wet casted film are important aspects of the present invention. Additionally, control of particle size and particle shape are further considerations. Desirably, the size of the particulate a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

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. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch premix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a premix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

FIG. **6** shows an apparatus **20** suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch **22**, which includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank **24**. The components for pre-mix or master batch **22** are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank **24**. Then a pre-determined amount of the master batch is controllably fed via a first metering pump **26** and control valve **28** to either or both of the first and second mixers, **30**, **30'**. The present invention, however, is not limited to the use of two mixers, **30**, **30'**, and any number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers **30**, **30'**, such as parallel sequencing as depicted in FIG. **6**, and other sequencing or arrangements of mixers, such as series or combination of parallel and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, **32**, **32'**, in each of the mixers, **30**, **30'**. Desirably, the residence time of the pre-mix or master batch **22** is minimized in the mixers **30**, **30'**. While complete dispersion of the drug into the pre-mix or master batch **22** is desirable, excessive residence times may result in leaching or dissolving of the drug, especially in the case for a soluble drug. Thus, the mixers **30**, **30'** are often smaller, i.e. lower residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch **22**. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan **36** through the second metering pumps, **34**, **34'**. The metering roller **38** determines the thickness of the film **42** and applies it to the application roller. The film **42** is finally formed on the substrate **44** and carried away via the support roller **46**.

While the proper viscosity uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the composition and film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry.

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film **48** as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as

the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, 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. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, proteins, or antigens, which may have a low degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

During film preparation, it may be desirable to dry films at high temperatures. High heat drying produces uniform films, and leads to greater efficiencies in film production. Films containing sensitive active components, however, may face degradation problems at high temperatures. Degradation is the "decomposition of a compound . . . exhibiting well-defined intermediate products." The American Heritage Dictionary of the English Language (4^{th} ed. 2000). Degradation of an active component is typically undesirable as it may cause instability, inactivity, and/or decreased potency of the active component. For instance, if the active component is a drug or bioactive material, this may adversely affect the safety or efficacy of the final pharmaceutical product. Additionally, highly volatile materials will tend to be quickly released from this film upon exposure to conventional drying methods.

Degradation of an active component may occur through a variety of processes, such as, hydrolysis, oxidation, and light degradation, depending upon the particular active component. Moreover, temperature has a significant effect on the rate of such reactions. The rate of degradation typically doubles for every 10° C. increase in temperature. Therefore, it is commonly understood that exposing an active component to high temperatures will initiate and/or accelerate undesirable degradation reactions.

Proteins are one category of useful active ingredients that will degrade, denature, or otherwise become inactive when they are exposed to high temperatures for extended periods of time. Proteins serve a variety of functions in the body such as enzymes, structural elements, hormones and immunoglobulins. Examples of proteins include enzymes such as pancreatin, trypsin, pancrelipase, chymotrypsin, hyaluronidase, sutilains, streptokinaw, urokinase, altiplase, papain, bromelainsdiastase, structural elements such as collagen and albumin, hormones such as thyrolibern, gonadoliberin, adrenocorticottropin, corticotrophin, cosyntropin, sometrem, somatropion, prolactin, thyrotropin, somatostatin, vasopressin, felypressin, lypressin, insulin, glucagons, gastrin, pentagastrin, secretin, cholecystokinin-pancreozymin, and immunomodulators which may include polysaccharides in addition to glycoproteins including cytokines which are useful for the inhibition and prevention of malignant cell growth such as tumor growth. A suitable method for the production of some useful glycoproteins is disclosed in U.S. Pat. No. 6,281,337 to Cannon-Carlson, et al., which in incorporated herein in its entirety.

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.

As discussed herein, the flowable mixture is prepared to be uniform in content in accordance with the teachings of the present invention. Uniformity must be maintained as the flowable mass was formed into a film and dried. During the drying process of the present invention, several factors produce uniformity within the film while maintaining the active component at a safe temperature, i.e., below its degradation temperature. First, the films of the present invention have an extremely short heat history, usually only on the order of minutes, so that total temperature exposure is minimized to the extent possible. The films are controllably dried to prevent aggregation and migration of components, as well as preventing heat build up within. Desirably, the films are dried from the bottom. Controlled bottom drying, as described herein, prevents the formation of a polymer film, or skin, on the top surface of the film. As heat is conducted from the film bottom upward, liquid carrier, e.g., water, rises to the film surface. The absence of a surface skin permits rapid evaporation of the liquid carrier as the temperature increases, and thus, concurrent evaporative cooling of the film. Due to the short heat exposure and evaporative cooling, the film components such as drag or volatile actives remain unaffected by high temperatures. In contrast, skinning on the top surface traps liquid carrier molecules of increased energy within the film, thereby causing the temperature within the film to rise and exposing active components to high, potentially deleterious temperatures.

Second, thermal mixing occurs within the film due to bottom heating and absence of surface skinning. Thermal mixing

occurs via convection currents in the film. As heat is applied to the bottom of the film, the liquid near the bottom increases in temperature, expands, and becomes less dense. As such, this hotter liquid rises and cooler liquid takes its place. While rising, the hotter liquid mixes with the cooler liquid and shares thermal energy with it, i.e., transfers heat. As the cycle repeats, thermal energy is spread throughout the film.

Robust thermal mixing achieved by the controlled drying process of the present invention produces uniform heat diffusion throughout the film. In the absence of such thermal mixing, "hot spots" may develop. Pockets of heat in the film result in the formation of particle aggregates or danger areas within the film and subsequent non-uniformity. The formation of such aggregates or agglomerations is undesirable because it leads to non-uniform films in which the active may be randomly distributed. Such uneven distribution may lead to large differences in the amount of active per film, which is problematic from a safety and efficacy perspective.

Furthermore, thermal mixing helps to maintain a lower overall temperature inside the film. Although the film surfaces may be exposed to a temperature above that at which the active component degrades, the film interior may not reach this temperature. Due to this temperature differential, the active does not degrade.

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.

FIG. **8** is a sequential representation of the drying process of the present invention. After mechanical mixing, the film may be placed on a conveyor for continued thermal mixing during the drying process. At the outset of the drying process, depicted in Section A, the film **1** preferably is heated from the bottom **10** as it is travels via conveyor (not shown). Heat may be supplied to the film by a heating mechanism, such as, but not limited to, the dryer depicted in FIG. **7**. As the film is heated, the liquid carrier, or volatile ("V"), begins to evaporate, as shown by upward arrow **50**. Thermal mixing also initiates as hotter liquid, depicted by arrow **30**, rises and cooler liquid, depicted by arrow **40**, takes its place. Because no skin forms on the top surface **20** of the film **1**, as shown in Section B the volatile liquid continues to evaporate **50** and thermal mixing **30**/**40** continues to distribute thermal energy throughout the film. Once a sufficient amount of the volatile liquid has evaporated, thermal mixing has produced uniform heat diffusion throughout the film **1**. 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. Although minor amounts of liquid carrier, i.e., water, may remain subsequent to formation of the visco-elastic, the film may be dried further without movement of the particles, if desired.

Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film **42** prior to the drying of the film **42**. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, hut non-limiting, techniques include the use of an additional roller to place the particles on the film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securably disposed onto the film, such as being embedded into the film. Moreover, such particles are desirably not fully encased or fully embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

The particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof. Desirably, the pharmaceutical agent is a taste-masked or a controlled-release pharmaceutical agent. Useful organoleptic agents include flavors and sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus **50** is depicted in FIG. **7**. Drying apparatus **50** is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film **42** which is disposed on substrate **44**. Hot air enters the entrance end **52** of the drying apparatus and travels vertically upward, as depicted by vectors **54**, towards air deflector **56**. The air deflector **56** redirects the air movement to minimize upward force on the film **42**. As depicted in FIG. **7**, the air is tangentially directed, as indicated by vectors **60** and **60'**, as the air passes by air deflector **56** and enters and travels through chamber portions **58** and **58'** of the drying apparatus **50**. With the hot air flow being substantially tangential to the film **42**, lifting of the film as it is being dried is thereby minimized. While the air deflector **56** is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends **62** and **62'** of the drying apparatus **50** are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors **64** and **64'**, which tend to provide a pulling or drag effect of the film **42** to prevent lifting of the film **42**. Lifting of the film **42** may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film **42** as the film **42** and/or substrate **44** lift away from the processing equipment.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most desirably less than about 2%. The solvent may be water, a

polar organic solvent including but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

In alternative embodiments, the film products of the present invention may be formed by extrusion rather than casting methods. Extrusion is particularly useful for film compositions containing polyethylene oxide-based polymer components, as discussed below. For instance, a single screw extrusion process may be employed in accordance with the present invention. According to such an extrusion process, pressure builds in the polymer melt so that it may be extruded through a die or injected into a mold.

As further explanation, a single screw extruder for use in the process of the present invention may include a barrel **300** containing a number of zones **200**, as shown in the extruder **100** depicted in FIG. **37**. These zones **200** may have varying temperatures and pressures. For instance, it may be desirable for the zones to increase in temperature as the composition proceeds through the barrel **300** to the extrusion die **400**. Any number of zones may be included in accordance with the present invention. In addition, the speed of extrusion may be controlled to produce desired film properties. For example, the extrusion composition may be held for an extended time period in the screw mixing chamber. Although this discussion is directed to single screw extrusion, other forms of extrusion are known to those skilled in the art and are considered well within the scope of the present invention.

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.

Film-Forming Polymers

The polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, polyethylene oxide (PEO), pullulan, hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HPC), hydroxypropyl cellulose, polyvinyl pyrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof.

As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films of the present invention include biodegradable polymers, copolymers, block polymers and combinations thereof. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly (lactic acid) (PLA), polydioxanoes, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of polyurethane and poly(lactic acid), copolymers of α-amino acids, copolymers of α-amino acids and caproic acid, copolymers of α-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Del. and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100 L, believed to be 100% lactide having a melting point within the range of 338°-347° F. (170°-1175° C.); lactide/glycolide 100 L, believed to be 100% glycolide having a melting point within the range of 437°-455° F. (225°-235° C.); lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338-347° F. (170°-175° C.); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.).

The Biodel materials represent a family of various polyanhydrides which differ chemically.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

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.

The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

It has also been observed that certain polymers which when used alone would ordinarily require a plasticizer to achieve a flexible film, can be combined without a plasticizer and yet achieve flexible films. For example, HPMC and HPC when used in combination provide a flexible, strong film with the appropriate plasticity and elasticity for manufacturing and storage. No additional plasticizer or polyalcohol is needed for flexibility.

Additionally, polyethylene oxide (PEO), when used alone or in combination with a hydrophilic cellulosic polymer, achieves flexible, strong films. Additional plasticizers or polyalcohols are not needed for flexibility. Non-limiting examples of suitable cellulosic polymers for combination with PEO include HPC and HPMC. PEO and HPC have essentially no gelation temperature, while HPMC has a gelation temperature of 58-64° C. (Methocel EF available from Dow Chemical Co.). Moreover, these films are sufficiently flexible even when substantially free of organic solvents, which may be removed without compromising film properties. As such, if there is no solvent present, then there is no plasticizer in the films. PEO based films also exhibit good resistance to tearing, little or no curling, and fast dissolution rates when the polymer component contains appropriate levels of PEO.

To achieve the desired film properties, the level and/or molecular weight of PEO in the polymer component may be varied. Modifying the PEO content affects properties such as tear resistance, dissolution rate, and adhesion tendencies. Thus, one method for controlling film properties is to modify the PEO content. For instance, in some embodiments rapid dissolving films are desirable. By modifying the content of the polymer component, the desired dissolution characteristics can be achieved.

In accordance with the present invention, PEO desirably ranges from about 20% to 100% by weight in the polymer component. In some embodiments, the amount of PEO desirably ranges from about 1 mg to about 200 mg. The hydrophilic cellulosic polymer ranges from about 0% to about 80% by weight, or in a ratio of up to about 4:1 with the PEO, and desirably in a ratio of about 1:1.

In some embodiments, it may be desirable to vary the PEO levels to promote certain film properties. To obtain films with high tear resistance and fast dissolution rates, levels of about 50% or greater of PEO in the polymer component are desirable. To achieve adhesion prevention, i.e., preventing the film from adhering to the roof of the mouth, PEO levels of about 20% to 75% are desirable. In some embodiments, however, adhesion to the roof of the mouth may be desired, such as for administration to animals or children. In such cases, higher levels of PEO may be employed. More specifically, structural integrity and dissolution of the film can be controlled such that the film can adhere to mucosa and be readily removed, or adhere more firmly and be difficult to remove, depending on the intended use.

The molecular weight of the PEO may also be varied. High molecular weight PEO, such as about 4 million, may be desired to increase mucoadhesivity of the film. More desirably, the molecular weight may range from about 100,000 to 900,000, more desirably from about 100,000 to 600,000, and most desirably from about 100,000 to 300,000. In some embodiments, it may be desirable to combine high molecular weight (600,000 to 900,000) with low molecular weight (100,000 to 300,000) PEOs in the polymer component.

For instance, certain film properties, such as fast dissolution rates and high tear resistance, may be attained by combining small amounts of high molecular weight PEOs with larger amounts of lower molecular weight PEOs. Desirably, such compositions contain about 60% or greater levels of the lower molecular weight PEO in the PEO-blend polymer component.

To balance the properties of adhesion prevention, fast dissolution rate, and good tear resistance, desirable film compositions may include about 50% to 75% low molecular weight PEO, optionally combined with a small amount of a higher molecular weight PEO, with the remainder of the polymer component containing a hydrophilic cellulosic polymer (HPC or HPMC).

Controlled Release Films

The term "controlled release" is intended to mean the release of active at a pre-selected or desired rate. This rate will vary depending upon the application. Desirable rates include fast or immediate release profiles as well as delayed, sustained or sequential release. Combinations of release patterns, such as initial spiked release followed by lower levels of sustained release of active are contemplated. Pulsed drug releases are also contemplated.

The polymers that are chosen for the films of the present invention may also be chosen to allow for controlled disintegration of the active. This may be achieved by providing a substantially water insoluble film that incorporates an active that will be released from the film over time. This may be accomplished by incorporating a variety of different soluble or insoluble polymers and may also include biodegradable polymers in combination. Alternatively, coated controlled release active particles may be incorporated into a readily soluble film matrix to achieve the controlled release property of the active inside the digestive system upon consumption.

Films that provide a controlled release of the active are particularly useful for buccal, gingival, sublingual and vaginal applications. The films of the present invention are particularly useful where mucosal membranes or mucosal fluid is present due to their ability to readily wet and adhere to these areas.

The convenience of administering a single dose of a medication which releases active ingredients in a controlled fashion over an extended period of time as opposed to the administration of a number of single doses at regular intervals has long been recognized in the pharmaceutical arts. The advantage to the patient and clinician in having consistent and uniform blood levels of medication over an extended period of time are likewise recognized. The advantages of a variety of sustained release dosage forms are well known. However, the preparation of a film that provides the controlled release of an active has advantages in addition to those well-known for controlled release tablets. For example, thin films are difficult to inadvertently aspirate and provide an increased patient

compliance because they need not be swallowed like a tablet. Moreover, certain embodiments of the inventive films are designed to adhere to the buccal cavity and tongue, where they controllably dissolve. Furthermore, thin films may not be crushed in the manner of controlled release tablets which is a problem leading to abuse of drugs such as Oxycontin.

The actives employed in the present invention may be incorporated into the film compositions of the present invention in a controlled release form. For example, particles of drug may be coated with polymers such as ethyl cellulose or polymethacrylate, commercially available under brand names such as Aquacoat ECD and Eudragit E-100, respectively. Solutions of drug may also be absorbed on such polymer materials and incorporated into the inventive film compositions. Other components such as fats and waxes, as well as sweeteners and/or flavors may also be employed in such controlled release compositions.

The actives may be taste-masked prior to incorporation into the film composition, as set forth in co-pending PCT application titled, Uniform Films For Rapid Dissolve Dosage Form Incorporating Taste-Masking Compositions, (based on U.S. Provisional Application No. 60/414,276 Express Mail Label No.: EU552991605 US of the same title, filed Sep. 27, 2003) the entire subject matter of which is incorporated by reference herein.

Actives

When an active is introduced to the film, the amount of active per unit area is determined by the uniform distribution of the film. For example, when the films are cut into individual dosage forms, the amount of the active in the dosage form can be known with a great deal of accuracy. This is achieved because the amount of the active in a given area is substantially identical to the amount of active in an area of the same dimensions in another part of the film. The accuracy in dosage is particularly advantageous when the active is a medicament, i.e. a drug.

The active components that may be incorporated into the films of the present invention include, without limitation pharmaceutical and cosmetic actives, drugs, medicaments, proteins, antigens or allergens such as ragweed pollen, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

A wide variety of medicaments, bioactive active substances and pharmaceutical compositions may be included in the dosage forms of the present invention. Examples of useful drugs include ace-inhibitors, antianginal 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, biological response modifiers, 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, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Examples of medicating active ingredients contemplated for use in the present invention include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in combination with magnesium hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin®), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

Other preferred drugs for other preferred active ingredients for use in the present invention include anti-diarrheals such as immodium AD, anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, chlorpheniramine maleate, dextromethorphan, pseudoephedrine HCl and diphenhydramine may be included in the film compositions of the present invention.

Also contemplated for use herein are anxiolytics such as alprazolam (available as Xanax®); anti-psychotics such as clozopin (available as Clozaril®) and haloperidol (available as Haldol®); non-steroidal anti-inflammatories (NSAID's) such as dicyclofenacs (available as Voltaren®) and etodolac (available as Lodine®), anti-histamines such as loratadine (available as Claritin®), astemizole (available as Hismanal™), nabumetone (available as Relafen®), and Clemastine (available as Tavist®); anti-emetics such as granisetron hydrochloride (available as Kytril®) and nabilone (available as Cesamet™); bronchodilators such as Bentolin®, albuterol sulfate (available as Proventil®); anti-depressants such as fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), and paroxtine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enalaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®); anti-Alzheimer's agents, such as nicergoline; and Ca^H-antagonists such as nifedipine (available as Procardia® and Adalat®), and verapamil hydrochloride (available as Calan®)).

Erectile dysfunction therapies include, but are not limited to, drugs for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful non-limiting drugs include sildenafils, such as Viagra®, tadalafils, such as Cialis®, vard-

enafils, apomorphines, such as Uprima®, yohimbine hydrochlorides such as Aphrodyne®, and alprostadils such as Caverject®.

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidien, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-ordibasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

The pharmaceutically active agents employed in the present invention may include allergens or antigens, such as, but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

An anti-oxidant may also be added to the film to prevent the degradation of an active, especially where the active is photosensitive.

Cosmetic active agents may include breath freshening compounds like menthol, other flavors or fragrances, especially those used for oral hygiene, as well as actives used in dental and oral cleansing such as quaternary ammonium bases. The effect of flavors may be enhanced using flavor enhancers like tartaric acid, citric acid, vanillin, or the like.

Also color additives can be used in preparing the films. Such color additives include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide.

Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides or iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

The films containing flavorings may be added to provide a hot or cold flavored drink or soup. These flavorings include, without limitation, tea and soup flavorings such as beef and chicken.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof; saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; *Stevia Rebaudiana* (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension.

Dosages

The film products of the present invention are capable of accommodating a wide range of amounts of the active ingredient. The films are capable of providing an accurate dosage amount (determined by the size of the film and concentration of the active in the original polymer/water combination) regardless of whether the required dosage is high or extremely low. Therefore, depending on the type of active or pharmaceutical composition that is incorporated into the film, the active amount may be as high as about 300 mg, desirably up to about 150 mg or as low as the microgram range, or any amount therebetween.

The film products and methods of the present invention are well suited for high potency, low dosage drugs. This is accomplished through the high degree of uniformity of the films. Therefore, low dosage drugs, particularly more potent racemic mixtures of actives are desirable.

Anti-Foaming and De-Foaming Compositions

Anti-foaming and/or de-foaming components may also be used with the films of the present invention. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. As described above, such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other anti-foam and/or dc-foaming agents may suitable be used.

As a related matter, simethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser, and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

Simethicone is generally used in the medical field as a treatment for gas or colic in babies. Simethicone is a mixture of fully methylated linear siloxane polymers containing repeating units of polydimethylsiloxane which is stabilized with trimethylsiloxy end-blocking unites, and silicon dioxide. It usually contains 90.5-99% polymethylsiloxane and

4-7% silicon dioxide. The mixture is a gray, translucent, viscous fluid which is insoluble in water.

When dispersed in water, simethicone will spread across the surface, forming a thin film of low surface tension. In this way, simethicone reduces the surface tension of bubbles air located in the solution, such as foam bubbles, causing their collapse. The function of simethicone mimics the dual action of oil and alcohol in water. For example, in an oily solution any trapped air bubbles will ascend to the surface and dissipate more quickly and easily, because an oily liquid has a lighter density compared to a water solution. On the other hand, an alcohol/water mixture is known to lower water density as well as lower the water's surface tension. So, any air bubbles trapped inside this mixture solution will also be easily dissipated. Simethicone solution provides both of these advantages. It lowers the surface energy of any air bubbles that trapped inside the aqueous solution, as well as lowering the surface tension of the aqueous solution. As the result of this unique functionality, simethicone has an excellent anti-foaming property that can be used for physiological processes (anti-gas in stomach) as well as any for external processes that require the removal of air bubbles from a product.

In order to prevent the formation of air bubbles in the films of the present invention, the mixing step can be performed under vacuum. However, as soon as the mixing step is completed, and the film solution is returned to the normal atmosphere condition, air will be re-introduced into or contacted with the mixture. In many cases, tiny air bubbles will be again trapped inside this polymeric viscous solution. The incorporation of simethicone into the film-forming composition either substantially reduces or eliminates the formation of air bubbles.

Simethicone may be added to the film-forming mixture as an anti-foaming agent in an amount from about 0.01 weight percent to about 5.0 weight percent, more desirably from about 0.05 weight percent to about 2.5 weight percent, and most desirably from about 0.1 weight percent to about 1.0 weight percent.

Optional Components

A variety of other components and fillers may also be added to the films of the present invention. These may include, without limitation, surfactants; plasticizers which assist in compatibilizing the components within the mixture; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother film surface by releasing oxygen from the film; thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components; and inclusion compounds, such as cyclodextrins and caged molecules, which improve the solubility and/or stability of certain active components.

The variety of additives that can be incorporated into the inventive compositions may provide a variety of different functions. Examples of classes of additives include excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof. These additives may be added with the active ingredient(s).

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragancanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

Such extenders may optionally be added in any desired amount desirably within the range of up to about 80%, desirably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all components.

Further additives may be inorganic fillers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.02% to about 3% by weight and desirably about 0.02% to about 1% based on the weight of all components.

Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5% to about 30%, and desirably ranging from about 0.5% to about 20% based on the weight of the polymer.

There may further be added compounds to improve the flow properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form, especially those which are solid at room temperature. These fats desirably have a melting point of 50° C. or higher. Preferred are tri-glycerides with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantageously added alone or together with mono- and/or di-glycerides or phosphatides, especially lecithin. The mono- and di-glycerides are desirably derived from the types of fats described above, i.e. with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids.

The total amounts used of the fats, mono-, di-glycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5% to about 2% by weight of the total composition

It is further useful to add silicon dioxide, calcium silicate, or titanium dioxide in a concentration of about 0.02% to about 1% by weight of the total composition. These compounds act as texturing agents.

These additives are to be used in amounts sufficient to achieve their intended purpose. Generally, the combination of

certain of these additives will alter the overall release profile of the active ingredient and can be used to modify, i.e. impede or accelerate the release.

Lecithin is one surface active agent for use in the present invention. Lecithin can be included in the feedstock in an amount of from about 0.25% to about 2.00% by weight. Other surface active agents, i.e. surfactants, include, but are not limited to, cetyl alcohol, sodium lauryl sulfate, the Spans™ and Tweens™ which are commercially available from ICI Americas, Inc. Ethoxylated oils, including ethoxylated castor oils, such as Cremophor® EL which is commercially available from BASF, are also useful. Carbowax™ is yet another modifier which is very useful in the present invention. Tweens™ or combinations of surface active agents may be used to achieve the desired hydrophilic-lipophilic balance ("HLB"). The present invention, however, does not require the use of a surfactant and films or film-forming compositions of the present invention may be essentially free of a surfactant while still providing the desirable uniformity features of the present invention.

As additional modifiers which enhance the procedure and product of the present invention are identified, Applicants intend to include all such additional modifiers within the scope of the invention claimed herein.

Other ingredients include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, pregelatinize starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, and polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or instable actives may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or instable actives to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

Forming the Film

The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

Roll coating, or more specifically reverse roll coating, is particularly desired when forming films in accordance with the present invention. This procedure provides excellent control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common.

The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is 100% solids, the process is termed "Extrusion" and in this case, the line speed is frequently much faster than the speed of the extrusion. This enables coatings to be considerably thinner than the width of the slot.

It may be particularly desirable to employ extrusion methods for forming film compositions containing PEO polymer components. These compositions contain PEO or PEO blends in the polymer component, and may be essentially free of added plasticizers, and/or surfactants, and polyalcohols. The compositions may be extruded as a sheet at processing temperatures of less than about 90° C. Extrusion may proceed by squeezing the film composition through rollers or a die to obtain a uniform matrix. The extruded film composition then is cooled by any mechanism known to those of ordinary skill in the art. For example, chill rollers, air cooling beds, or water cooling beds may be employed. The cooling step is particularly desirable for these film compositions because PEO tends to hold heat.

The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a "gap" between a "knife" and a support roller. As the coating and substrate pass through, the excess is scraped off.

Air knife coating is where the coating is applied to the substrate and the excess is "blown off" by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Drying the Film

The drying step is also a contributing factor with regard to maintaining the uniformity of the film composition. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate. An alternative method of forming a film with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.

Desirably, the film is dried from the bottom of the film to the top of the film. Desirably, substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, e.g. about the first 0.5 to about 4.0 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides. Then, heat is initially applied to the bottom side of the film to provide the necessary energy to evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

The temperature at which the films are dried is about 100° C. or less, desirably about 90° C. or less, and most desirably about 80° C. or less.

Another method of controlling the drying process, which may be used alone or in combination with other controlled methods as disclosed above includes controlling and modifying the humidity within the drying apparatus where the film is being dried. In this manner, the premature drying of the top surface of the film is avoided.

Additionally, it has also been discovered that the length of drying time can be properly controlled, i.e. balanced with the heat sensitivity and volatility of the components, and particularly the flavor oils and drugs. The amount of energy, temperature and length and speed of the conveyor can be balanced to accommodate such actives and to minimize loss, degradation or ineffectiveness in the final film.

A specific example of an appropriate drying method is that disclosed by Magoon. Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an interesting property of water. Although water transmits energy by conduction and convection both within and to its surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this creates a "refractance window." This means that infrared energy is permitted to radiate through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the film.

Another method of controlling the drying process involves a zone drying procedure. A zone drying apparatus may include a continuous belt drying tunnel having one or more drying zones located within. The conditions of each drying zone may vary, for example, temperature and humidity may be selectively chosen. It may be desirable to sequentially order the zones to provide a stepped up drying effect.

The speed of the zone drying conveyor desirably is continuous. Alternatively, the speed may be altered at a particular stage of the drying procedure to increase or decrease exposure of the film to the conditions of the desired zone. Whether continuous or modified, the zone drying dries the film without surface skinning.

According to an embodiment of the zone drying apparatus **100**, shown in FIG. **35**, the film **110** may be fed onto the continuous belt **120**, which carries the film through the different drying zones. The first drying zone that the film travels through **101** may be a warm and humid zone. The second zone **102** may be hotter and drier, and the third zone **103** may also be hot and dry. These different zones may be continuous, or alternatively, they may be separated, as depicted by the zone drying apparatus **200** in FIG. **36**. The zone drying apparatus, in accordance with the present invention, is not limited to three drying zones. The film may travel through lesser or additional drying zones of varying heat and humidity levels, if desired, to produce the controlled drying effect of the present invention.

To further control temperature and humidity, the drying zones may include additional atmospheric conditions, such as inert gases. The zone drying apparatus further may be adapted to include additional processes during the zone drying procedure, such as, for example, spraying and laminating processes, so long as controlled drying is maintained in accordance with the invention.

The films may initially have a thickness of about 500 μm to about 1,500 μm, or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm, or about 0.1 mils to about 10 mils. Desirably, the dried films will have a thickness of about 2 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

Testing Films for Uniformity

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.

A method for testing uniformity in accordance with the present invention includes conveying a film through a manufacturing process. This process may include subjecting the film to drying processes, dividing the film into individual dosage units, and/or packaging the dosages, among others. As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus, it is cut widthwise into at least one portion. The at least one portion has opposing ends that are separate from any other film portion. For instance, if the film is a roll, it may be cut into separate sub-rolls. Cutting the film may be accomplished by a variety of methods, such as with a knife, razor, laser, or any other suitable means for cutting a film.

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). Leaving the middle section intact permits the predominant portion of the film to proceed through the manufacturing process without interrupting the conformity of the film and creating sample-inducted gaps in the film. Accordingly, the concern of missing doses is alleviated as the film is further processed, e.g., packaged. Moreover, maintaining the completeness of cut portions or sub-rolls throughout the process will help to alleviate the possibility of interruptions in further film processing or packaging due to guilty control issues, for example, alarm stoppage due to notice of missing pieces.

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.

Moreover, it may be desirable to repeat the steps of sampling and testing throughout the manufacturing process. Testing at multiple intervals may ensure that uniform film dosages are continuously produced. Alterations to the process can be implemented at any stage to minimize non-uniformity between samples.

Uses of Thin Films

The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate that the active is released, which may allow for a sustained release delivery system. In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal, opthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. If an adhesive is used, it will desirably be a food grade adhesive that is ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives themselves.

The films may be applied under or to the tongue of the mammal. When this is desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

Another use for the films of the present invention takes advantage of the films' tendency to dissolve quickly when introduce to a liquid. An active may be introduced to a liquid by preparing a film in accordance with the present invention, introducing it to a liquid, and allowing it to dissolve. This may be used either to prepare a liquid dosage form of an active, or to flavor a beverage.

The films of the present invention are desirably packaged in sealed, air and moisture resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to FIG. **1**, a packaged pharmaceutical dosage unit **10**, includes each film **12** individually wrapped in a pouch or between foil and/or plastic laminate sheets **14**. As depicted in FIG. **2**, the pouches **10**, **10'** can be linked together with tearable or perforated joints **16**. The pouches **10**, **10'** may be packaged in a roll as depicted in FIG. **5** or stacked as shown in FIG. **3** and sold in a dispenser **18** as shown in FIG. **4**. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

The features and advantages of the present invention are more fully shown by the following examples which are provided for purposes of illustration, and are not to be construed as limiting the invention in any way.

EXAMPLES

Examples A-I

Water soluble thin film compositions of the present invention are prepared using the amounts described in Table 1.

TABLE 1

	Weight (g)								
Component	A	B	C	D	E	F	G	H	I
Hydroxypropylmethyl cellulose		1.76		1.63	32.00		3.67		32.00
Peppermint oil		0.90	1.0	1.05		8.0	2.67		
Sweetener	0.15	0.15	0.22	0.10		4.6	1.53	0.15	
Polyvinylpyrrolidone		0.94		1.05		7.0	2.33		
Tween 80[1]	0.5	0.5	2.0	0.65	11.80		1.35	0.5	11.80
Simethicone[2]	0.2	0.2	0.15	0.30	1.80		0.21	0.2	1.80
Listerine[3]	83.35							83.35	
Methylcellulose	6.0								
Cornstarch[4]			1.75						
Agar			1.25						
Water		42.24	93.63	39.22	768.0	280.0	88.24		768.0
Loratadine[5]					19.2				19.2
Pullulan[6]								6.0	
Ibuprofen									38.4

[1]Available from ICI Americas

[2]Available from OSI

[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color

[4]Available from Grain Processing Corporation as Pure Cote B792

[5]Available from Schering Corporation as Claritin

[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

The ingredients of inventive compositions A-I were combined by mixing until a uniform mixture was achieved. The compositions were then formed into a film by reverse roll coating. These films were then dried on the top side of an infrared transparent surface, the bottom side of which was in contact with a heated water bath at approximately 99° C. No external thermal air currents were present above the film. The films were dried to less than about 6% by weight water in about 4 to 6 minutes. The films were flexible, self-supporting and provided a uniform distribution of the components within the film.

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.

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 2

	Additive Weight (g)	
Sample	Trial 1	Trial 2
1	0.04	0.04
2	0.08	0.08
3	0.12	0.12
4	0.16	0.16
5	0.20	0.20
6	0.24	0.24
7	0.28	0.28
8	0.32	0.32

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.

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.

When the films formed from inventive compositions A-H are placed on the tongue, they rapidly dissolve, releasing the active ingredient. Similarly, when they are placed in water, the films rapidly dissolve which provides a flavored drink when the active is chosen to be a flavoring.

Examples J-L

Thin films that have a controlled degradation time and include combinations of water soluble and water insoluble

polymers and water soluble films that allow controlled release of an active are prepared using approximately the amounts described in Table 3.

TABLE 3

Component	Weight (g) J	K	L
Hydroxypropylmethyl cellulose		1.0	1.0
Tween 80[1]	0.7	0.7	0.7
Water			5.0
Aquacoat ECD[2]	17.0	17.0	17.5
Peppermint oil	1.0	0.4	1.1

[1]Available from ICI Americas
[2]A 30% by weight aqueous dispersion of ethyl cellulose available from FMC

The components of inventive compositions J-L were combined and formed into films using the methods for preparing inventive compositions A-I above. These films were also flexible, self-supporting and provided a uniform distribution of active which permits accuracy in dosing.

The uniformity of the films prepared from inventive compositions J-L may also be tested by either visual means measuring the weights of individual dosage films, or by dissolving the films and testing for the amount of active as described above.

Examples M-O

An alternative method of preparing films which provides an accurate dosing may be used for any of inventive compositions A-I. The method begins with first combining the ingredients with mixing. The combination of ingredients is then divided among individual wells or molds. In such a method, aggregation of the components during drying is prevented by the individual wells.

TABLE 4

Component	Weight % M	N	O
5% Methylcellulose Solution[1]	73.22	44.22	74.22
Raspberry Flavor	3.28	3.28	3.28
Sweetener Blends	1.07	1.07	1.07
Tween-80[2]	2.47	2.47	2.47
Polyvinylpyrrolidone	3.30	3.30	3.30
Ethanol 95%	8.24	8.24	8.24
Propylene Glycol	1.65	1.65	1.65
Calcium Carbonate	4.12	4.12	4.12
Cornstarch[3]	1.65	1.65	1.65
Red Dye[4]	1.00		
Corn Syrup[5]		30.00	

[1]Available from Dow Chemical Co. as Methocel K35
[2]Available from ICI Americas
[3]Available from Grain Processing Corporation as Pure Cote B792
[4]Available from McCormick
[5]Available from Bestfoods, Inc. as Karo Syrup

The ingredients in the above Table 4 were combined and formed into a film by casting the combination of ingredients onto the glass surface and applying heat to the bottom side of the glass. This provided inventive compositions M-O.

The film of composition M was examined both prior to and after drying for variations in the shading provided by the red dye. The film was examined both under sunlight and by incandescent bulb light. No variations in shade or intensity of color were observed.

Further testing of the films of composition M included testing of absorption which is directly related to concentration. The film was cut into segments each measuring 1.0 in. by 0.75 in., which were consecutively assigned numbers. Approximately 40 mg of the scrap material from which the segments were cut was dissolved in about 10 ml of distilled water and then quantitatively transferred to a 25 ml volumetric flask and brought to volume. The solution was centrifuged and scanned at 3 nm intervals from 203-1200 nm. The frequency of maximum absorption was found to be 530 nm. The solution was then re-centrifuged at a higher RPM (for the same length of time) and re-scanned, which demonstrated no change in the % transmission or frequency.

Each of the segments were weighed to 0.1 mg and then dissolved in 10 ml distilled water and transferred quantitatively to a 25 ml volumetric flask and brought to volume with distilled water. Each segment solution was then centrifuged as above, and then scanned, at first from 203-1200 nm and later from only 500 nm to 550 nm at a 1 nm scanning speed. The value recorded was the % transmission at the lowest wave length, which was most frequently 530 nm.

The absorption values are shown in Table 5 below:

TABLE 5

Segment	mg/% A
1-2	1.717
3-4	1.700
5-6	1.774
7*	1.701
9-10	1.721
11-12	1.729
13-14	1.725
15-16	1.713

*segment 8 was lost

The overall average absorption was 1.724. Of the 15 segments tested, the difference between the highest and lowest values was 0.073 units, or 4% based on the average. This shows excellent control over the uniformity of the dye within the composition because the absorption is directly proportional to the concentration of the dye within each segment.

The film of inventive composition N provided a very flexible film. This film was able to be stretched and exhibited a very high tensile strength.

After forming the film of inventive composition O, the film was removed from the glass by very rapidly stripping the length of the glass with a razor. This provided very tightly wound "toothpick-like" dosage forms. Each dosage form consistently weighed 0.02 g. This demonstrates the uniformity of the dosage forms as well as the superior self-supporting properties of the films.

Examples P-W

Compositions P-W were prepared to demonstrate the interaction among various conditions in production of films as they relate to the present invention. The ingredients in the below Table 6 were combined and formed into a film using the process parameters listed in Table 7 below, prepared in a 6 m drying tunnel designed to incorporate bottom drying of the films. Each of the examples shows the effect of different ingredient formulations and processing techniques on the resultant film products.

TABLE 6

Component	Weight (g) P	Q	R	S	T	U	V	W
Hydroxypropyl-methyl cellulose	320	320	320	320	320	320	345	345
Water	1440	1440	1440	1440		1440	999	999
Sweetener						60	60	45
Mint Flavor						80	80	
Propylene Glycol	50	50	50	100	100	100	100	69.3
Xanthan	22		11	11.23	10	10	10	6.9
Water/Ethanol (60/40)					1440			
Orange Flavor								42

TABLE 7

	Film Thickness (Micron)	Top[1] v (m/sec)	Bot.[1] v (m/sec)	T[1] (° C.)	Top[2] v (m/sec)
P1	100	0	22	75	0
P2	350	0	22	75	0
P3	350	0	40	75	0
P4	350	0	40	75	0
P5	350	10	40	75	10
Q	350	0	40	75	10
R	350	0	40	85	10
S1	250	0	40	100	0
S2	300	0	40	100	0
S3	350	0	40	100	0
T1	250	0	40	100	0
T2	350	0	40	100	0
U1	300	0	40	100	0
U2	250	0	40	100	0
U3	300	0	40	100	0
V1	300	0	40	100	0
V2	300	0	40	100	0
V3	300	0	40	100	0
W1	300	0	40	93	0
W2	250	0	40	90	0
W3	200	0	40	90	0

	Bot.[2] v (m/sec)	T[2] (° C.)	Film Weight (g)	Coater Speed m/min	% Moisture
P1	23	60	109	5	>20
P2	23	60	n/a	5	>20
P3	40	60	161	3	>20
P4	40	75	191	3	>20
P5	40	75	253	3	>20
Q	40	75	n/a	3	>20
R	0	85		2.5	>20
S1	40	90	163	1.5	<5
S2	40	90	193	1.5	<5
S3	40	90	225	1.5	<5
T1	40	90	64	1.5	<5
T2	40	90	83	1.5	<5
U1	40	90	208	1.5	20
U2	40	90	177	1.5	20
U3	40	90	212	1.3	20
V1	40	90	237	1.3	20
V2	40	100	242	1.3	20
V3	40	100	221	1	6
W1	40	90	220	1.3	5
W2	40	90	199	1.3	5
W3	40	90	169	1.3	5

[1]First Heater Section (3 m)
[2]Second Heater Section (3 m)

In Table 7, each of the process parameters contributes to different properties of the films. Film thickness refers to the distance between the blade and the roller in the reverse roll coating apparatus. Bottom velocity and top velocity refer to the speed of air current on the bottom and top sides of the film, respectively. The film weight is a measure of the weight of a circular section of the substrate and the film of 100 cm^2.

Compositions P-R show the effects of visco-elastic properties on the ability to coat the film composition mixture onto the substrate for film formation. Composition P displayed a stringy elastic property. The wet film would not stay level, the coating was uneven, and the film did not dry. In Composition Q, substantially the same formulation as P was used however the xanthan was not included. This product coated the substrate but would not stay level due to the change in the visco-elastic properties of the wet foam. Composition R was prepared using substantially the same formulation, but incorporated one-half of the amount of xanthan of Composition P. This formulation provided a composition that could be evenly coated. Compositions P-Q demonstrate the importance of proper formulation on the ability of the film matrix to conform to a particular coating technique.

The films produced from Composition S contained a large amount of air in the films. This is shown by the dried film thickness which was the same despite that variation in the coated thickness as in Table 7. Microscopic examination of the film revealed a large number of air bubbles in the film. In order to correct for the addition of air in the films, care must be taken in the mixing process to avoid air inclusion.

Composition T included a change in the solvent to 60/40 water ethanol. Composition T was stirred slowly for 45 min. to deaerate the mixture. The dried weight film products T1 and T2 were consistent with the increase in solids from T1 to T2. The films dried much faster with less than 5% moisture. With the particular combination of ingredients in Composition T, the substitution of part ethanol for part water allowed the film to dry more quickly. The elimination of air from the film as a result of the slow stirring also contributed to the uniformity of the final film product and the faster drying time.

Only water was used as a solvent in Composition U. The dried weight of the U1-U3 changed consistently in accordance with the change in coating thickness indicating that no air bubbles were present. However, these films contained 20% moisture upon exit from the oven, unlike the films of Composition T, which included part ethanol and dried completely.

The amount of solids was increased and the amount of water was decreased in Compositions V1 and V2. The dried weight was greater than U1-U3 due to the increase in solids, however the films still contained 20% moisture upon exit from the oven, similar to Composition U.

The coating line speed was reduced for Composition V3, to prevent premature drying of the exposed top film surface. This film product dried to 6% moisture.

While increasing the amount of solids improved the film weight, longer drying times were required. This was due to the surface of the film sealing preventing easy removal of the water. Therefore, for Compositions W1-W3, the temperature in the first 3 m section of the dryer was decreased. This prevented the premature drying of the top surface of the films.

Even at greater film thicknesses, the films were dried to 5% moisture even at faster coater line speeds.

Examples X-AA

TABLE 8

Component	Weight (g) X	Y	Z	AA
Loratadine	104.69			
Zomig		52.35		
Paxil			104.69	
Hydroxypropyl methylcellulose	320	320	320	150
Sweetener blend	60	60	60	0.4
Simethicone	1.5	1.5	1.5	1.5
Propylene glycol	100	100	100	
Water	1440	1440	1440	790
Cream essence				0.4
Polyvinyl pyrrolidinone				4
Ethanol				40
Cocoa				55.2
Polyoxyl-40-stearate				7

Compositions X, Y and Z of Table 8 were taste mask coated using a Glatt coater and Eudragit E-100 polymethacrylate polymer as the coating. The coating was spray coated at a 20% level. Therefore 10 mg of drug 12.5 mg of the final dry product must be weighed.

The base formula which excluded the drug additive was mixed with care to not incorporate air. After initial mixing the formula was slowly mixed to deaerate over 30 min. During this time the drug was weighed and prepared for addition to the base mix.

For Composition X, the Loratadine (80% drug) was added slowly to the mix with stirring. After 5 min. of stirring, the total mix was added to the pan of a three roll coater set (reverse roll coater) at 30 micron coating thickness.

The process bottom temperature was set at 90° C. with no top heat or air, the bottom air velocity was set at 40 m/sec., and the line speed was set at 1.3 m/min. Total drying time for the film was 4.6 min.

The liquid was coated at 30 microns and dried in the oven in less than 5 min. The film was flexible and a 1"×0.75" piece weighed 70 mg and contained 10 mg of Loratadine.

The experiment was repeated for Compositions Y and Z, Zomig and Paxil, respectively. Both produced flexible films with the target weight of 70 mg containing 5 mg of Zomig and 70 mg containing 10 mg of Paxil, respectively.

The products were sweet without any noticeable drug aftertaste.

The ingredients of Composition AA were mixed in order to reduce air captured in the fluid matrix. After mixing 45 g of loratadine coated at a 80% active level and 20% coating using Eudragit E-100, this mixture was added slowing with mixing until the drug was evenly dispersed, approximately 5 min. The liquid was then deposited into the 3 roll coater (reverse roll coater) and coated at 30 microns at a line speed of 1.3 m/min. The oven temperature was set at 90° C. to apply air and heat to the bottom only, with an air velocity set at 40 m/sec. The dried film was 0.005 inch. thick (5 mil) and was cut into 1 in.×0.75 in. pieces weighing 70 mg+/−0.7 mg, demonstrating the uniformity of the composition of the film. The film was flexible with 5% moisture, free of air bubbles, and had uniform drug distribution as seen under the light microscope, as well as shown by the substantially identical weight measurements of the film pieces.

Examples BA-BI

The incorporation of the anti-foaming/de-foaming agent (i.e., simethicone) provided a film that not only provided a uniform film that substantially reduced or eliminated air bubbles in the film product, but also provided other benefits. The films displayed more desirable organoleptic properties. The films had an improved texture that was less "paper-like" provided a better mouth-feel to the consumer.

The compositions in Table 9 were prepared (including the addition of simethicone in inventive compositions BA-BG) and mixed under vacuum to remove air bubbles.

The resultant uncut films of inventive compositions BA-BG exhibited uniformity in content particularly with respect to the insoluble active, as well as unit doses of ¾" by 1" by 5 mils cut therefrom. The inventive compositions also were observed to have a smooth surface, absent of air bubbles. The significantly higher amounts of simethicone present in inventive compositions BF-BG also provided a very uniform film, but not significantly improved from that of inventive compositions BA-BE.

By contrast, comparative examples BH-BI were observed to have a rougher surface, exhibiting the inclusion of air bubbles in the resultant film which provided a less uniform texture and distribution of the ingredients.

TABLE 9

Component	BA	BB	BC	BD	BE	BF	BG	BH	BI
Hydroxypropylmethyl cellulose	0	3.77	3.70	3.84	0	3.67	0	0	3.84
Peppermint oil	2.94	1.93	2.39	0	0	2.67	2.94	2.67	0
Sweetener	2.20	0.32	0.23	0	0.17	1.53	2.20	1.54	0
Polyvinylpyrrolidone	2.68	2.01	2.39	0	0	2.33	2.68	2.34	0
Tween 80[1]	2.24	1.07	1.48	1.42	0.55	1.35	2.24	0	1.42
Simethicone[2]	0.66	0.42	0.68	0.22	0.22	5.00	2.00	0	0
Listerine[3]	0	0	0	0	92.41	0	0	0	0
Methylcellulose	4.03	0	0	0	0	0	4.03	0	0
Cornstarch[4]	2.68	0	0	0	0	0	2.68	0	0
Water	73.53	90.47	89.14	92.22	0	83.45	72.19	93.46	92.44
Loratadine[5]	4.29	0	0	2.31	0	0	4.29	0	2.31
Pullulan[6]	0	0	0	0	6.65	0	0	0	0
Calcium Carbonate	1.43	0	0	0	0	0	1.43	0	0

TABLE 9-continued

Component	BA	BB	BC	BD	BE	BF	BG	BH	BI
Xanthan Gum	0.30	0	0	0	0	0	0.30	0	0
Propylene Glycol	3.02	0	0	0	0	0	3.02	0	0

[1]Available from ICI Americas
[2]Available from OSI
[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color
[4]Available from Grain Processing Corporation as Pure Cote B792
[5]Available from Schering Corporation as Claritin
[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

Examples CA-CC

The following examples of the present invention describe films and film-forming compositions that use an ethoxylated caster oil as a surfactant, or alternatively are free of surfactants, plasticizers and/or polyalcohols. Desirably, the films or film-forming compositions of the present invention are essentially free of surfactants. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of plasticizers. Still furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of polyalcohols. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants and plasticizers. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants, plasticizers and polyalcohols.

TABLE 10

Component	(parts by wt.) CA
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
Xanthan Gum	1.14
SURFACTANT[2]:	2.0
PLASTICIZER[3]:	11.67
ANTI-FOAM AGENT[4]	2.44
OTHER	
Spearmint Flavor	10.43
Loratadine (drug)	16.62
Calcium Carbonate	5.54
Sweetener	9.36

[1]Available from Grain Processing Corporation as Pure Cote B792
[2]Ethoxylated caster oil, Cremophor ® EL available from BASF
[3]Propylene Glycol
[4]Silicone Emulsion

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 45 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over 45 min.

After release of the vacuum, 6 grams of the liquid was added to a coating paper using a 200 micron spiral wound rod and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. until about 5% moisture remained. The formula coated and dried to a film thickness of approx. 60 microns and quickly dissolved in the mouth.

TABLE 11

Component	(parts by wt.) CB
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
PLASTICIZER/SOLVENT[2]:	22.1
ANTI-FOAM AGENT[3]	2.44
OTHER	
Raspberry Flavor	0.3
Calcium Carbonate[4]	30.38
Sweetener	8.36

[1]Available from Grain Processing Corporation as Pure Cote B792
[2]Propylene Glycol
[3]Polydimethyl Siloxane Emulsion
[4]Functioned to mimic drug loading

The above ingredients were added to water at 40% until a homogeneous suspension was made. Vacuum was added over 20 min. starting at 500 mm Hg, and ending at 660 mm Hg. until all air was removed from suspension. Film was made as described in prior experiments. The liquid coated the silicone release substrate and dried to a uniform flexible film. The film passed the 180° bend test without cracking and dissolved in the mouth.

TABLE 12

Component	(parts by wt.) CC
POLYMERS:	
Hydroxypropylmethyl cellulose	7.8
Hydroxypropyl cellulose	7.8
ANTI-FOAM AGENT[1]	0.75
OTHER	
Peppermint & Bittermint Flavor	2.25
Tastemasking Flavor[2]	0.3
Calcium Carbonate[3]	15.2
Sweeteners	0.9

[1]Polydimethyl Siloxane Emulsion
[2]Prosweet from Virginia Dare
[3]Functioned to mimic drug loading

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 20 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner up to 760 mm over 35 min.

After release of the vacuum, the liquid was added to a coating paper using a 350 micron smooth bar and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone

coated paper. The coated paper was then dried at 90° C. until about 4% moisture remained. The formula coated and dried to a film. The film had an acceptable taste and quickly dissolved in the mouth. The taste-masking flavor is an ingredient that affects the taste receptors to mask the receptors from registering a different, typical undesirable, taste. The film passed the 180° bend test without cracking and dissolved in the mouth.

Example CD

The following example of the present invention describes films and film-forming compositions that use a taste-masked, pharmaceutically active agent which also contains flavors and taste-masking aids. A taste-masking flavor is an ingredient that effects taste receptors to mask the receptors from registering a different, typically undesirable, taste.

TABLE 13

Component	(grams) CD
Hydroxypropylmethyl cellulose	4.26
Hydroxypropyl cellulose	1.42
Precipitated calcium Carbonate	1.22
Sweetner[1]	0.6
Taste-Masking flavor[2]	0.08
Taste-masked Acetaminophen[3]	5.86
Cinnamon Flavor	0.9
Spearmint Flavor	0.43
Polydimethylsiloxane emulsion	0.23

[1]Sucralose, available from McNeil Nutritionals
[2]Magna Sweet, available from Mafco Worldwide Corp.
[3]Gutte Enteric, coated acetaminophen, Gatte, LLC

The above ingredients, except for the pharmaceutically active agent and flavors, were added at 35 grams water and stirred until polymers were fully hydrated which took about 20 min. Food coloring (7 drops of red food coloring and 1 drop of yellow fool coloring) was also added. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over about 10 to 20 minutes. The taste-masked Acetaminophen was added to the mix in about 4 minutes was stirring under vacuum. The flavors were then added to the mix in about 4 minutes was stirring under vacuum.

After release of the vacuum, the liquid solution was added to a coating paper using a 350 micron smooth bar. The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. for about 11 minutes until about 3% moisture remained.

The formula coated and dried to a film. The film had an acceptable taste and moderately quickly dissolved in the mouth. The film did not curl on standing. The film passed the 180° bend test without cracking and dissolved in the mouth.

Examples CE-CF

Thin film compositions of the present invention were prepared using the amounts described in Table 14.

TABLE 14

Component	Weight (g)
Hydroxypropylmethyl cellulose	3.92
Pullulan	3.92
Trehalose[1]	3.5
Precipitated Calcium Carbonate	3.85
Propylene Glycol	1.96
Simethicone[2]	0.35
Bovine Extract[3]	32.5
Water	q.s.

[1]Available from Cargill Inc.
[2]Available from Sentry
[3]Available from Amarillo Biosciences Inc.

The above ingredients were combined by mixing until a uniform mixture was achieved. A sufficient amount of water was present in the film compositions prior to drying, i.e., q.s., which may range between about 200 g to about 1000 g. The bovine extract protein contained in the compositions is a heat sensitive protein. After mixing, the compositions were cast into films on release paper using a K-Control Coater with a 250 micron smooth bar.

In Example CE, the films subsequently were dried in an oven at approximately 80° C. for about 6 minutes. The films were dried to about 4.3 percent moisture. In Example CF, the films were dried in an oven at approximately 60° C. for about 10 minutes. The films were dried to about 5.06 percent moisture. After drying, the protein derived from bovine extract, which was contained in the films, was tested to determine whether or not it remained substantially active. To test the activity, a film dosage unit of this example was administered to a human. After ingesting the dosage, a microarray on the human's blood was conducted. The results, listed in Appendix A which is incorporated by reference herein, and graphically represented in FIG. **32**, demonstrate that the protein was approximately 100 percent active in the final, dried film products of both Examples CE and CF. Therefore, the heat sensitive active did not substantially degrade or denaturize during the drying process.

Example CG

Thin film compositions of the present invention were prepared using the amounts described in Table 15.

TABLE 15

	Weight (g unless otherwise indicated)	
Component	CG	CH
Hydroxypropylmethyl cellulose	4.59	9.18
Hydroxypropyl cellulose	1.53	3.06
Sucralose[1]	0.7	1.4
Magna Sweet[2]	0.09	0.18
Precipitated calcium carbonate	2.0	4
Fat-coated dextromethorphan hydrobromide	5.96	11.93
Orange concentrate flavor	1.05	2.1
Prosweet MM24[3]	0.18	0.35
Propylene glycol	1.22	2.45
Simethicone[4]	0.18	0.35
Water	32.5	65
Red food color		4 drops
Yellow food color		6 drops

[1]Available from McNeil Nutritional
[2]Taste-masking flavor, available from Mafco Worldwide Corp.
[3]Taste-masking flavor, available from Virginia Dare
[4]Available from Sentry

The above ingredients in the amounts listed for CG were combined by mixing, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth

bar. The films were subsequently dried according to conventional drying techniques, rather than via the uniform drying process of the present invention. One film was dried in an oven at 80° C. for 9 minutes on a wire rack. The second film was dried in an oven at 80° C. for 9 minutes on a wire screen. Both films were dried to about 2.4 percent moisture.

The resulting dried films showed imprints of the wire rack and screen after drying. These configurations comprise imprints of wire supports typically used in the drying process. Without uniform heat diffusion, the wire supports conducted heat more intensely at the points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The result is increased particle density seen as aggregations at the contact points.

The solution was cast into two more films on release paper using the K-Control Coater with a 350 micron smooth bar. These films were dried by the process of the present invention, under the same time and temperature conditions as above. In particular, the films were dried in an 80° C. air oven for 9 minutes on trays lined with furnace filters, which uniformly disperse heat. The films were dried to about 1.89 percent moisture. The resulting films had no streaks, and were homogenous. Due to uniform heat diffusion throughout the film, no particle aggregations developed.

Example CH

The ingredients in Table 15, in the amounts listed for CH, were combined by mixing, and then cast into three films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for 9 minutes in an 80° C. air oven on trays lined with furnace filters, which uniformly distribute heat. The films were dried to about 2.20 percent moisture. As depicted in FIG. **17**, the dried films **200** had no streaks, and were homogenous, i.e., no particle aggregations developed. The active particles appeared intact in the dried films. The films exhibited adequate strength and passed the 180° bend test without cracking, in which the films are bent in half with pressure.

The mixed solution was cast into three more films on release paper using a K-Control Coater with a 350 micron smooth bar. These films similarly were dried for 9 minutes in an 80° C. air oven, but by conventional top and bottom drying means. Two of the films were dried on wire racks, while the third was dried on a wire screen. All three films were dried to about 2.65 percent moisture. The dried films showed the imprints of the wire racks and screen, for the reasons described above in Example CG.

More particularly, the dried films **100** exhibited aggregations **110** of particles in both line and diamond configurations, as shown in FIGS. **9-16**. These configurations comprise imprints of wire supports used in the drying process to display the disuniformity in heat transfer which occurs in conventional top and bottom drying. As discussed above, the wire supports conducted heat more intensely at the points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The resulting increased particle density at the contact points is depicted in FIGS. **9-16**.

Moreover, the fat-coated dextromethorphan particles contained within the films of this example were not destroyed by the drying processes. FIGS. **28-31** depict fat-coated dextromethorphan particles **500** prior to any processing, and particularly, their substantially spherical shape. After exposure to drying conditions of 80° C. for 9 minutes, the fat-coated drug particles **500** were found to have remained intact within the films, i.e., maintained their spherical shape, as shown in FIGS. **18-25**. Although the active particles were exposed to potentially deleterious temperatures, they did not degrade. In contrast, fat-coated dextromethorphan particles placed in an evaporating dish and heated in an air oven at 80° C. for 9 minutes substantially degrade. As seen in FIGS. **26** and **27**, the fat-coated dextromethorphan particles appear completely melted after the exposure.

Example CI

Thin film compositions of the present invention were prepared using the amounts described in Table 16.

TABLE 16

Component	Weight (g unless otherwise indicated)
Hydroxypropylcellulose	6.00
Polyethylene oxide	2.00
Sucralose[1]	0.84
Magna sweet[2]	0.09
Mixture of microcrystalline cellulose and sodium carboxymethylcellulose[3]	0.18
Precipitated calcium carbonate	1.55
Sildenafil[4]	2.91
Peppermint & bittermint flavor	1.75
Prosweet[5]	0.44
Masking flavor[6]	1.31
N,2,3-trimethyl-2-isopropylbutanamide[7]	0.075
Simethicone[8]	0.035
Water	32.5
Blue food coloring	3 drops

[1]Available from McNeil Nutritional
[2]Taste-masking flavor, available from Mafco Worldwide Corp.
[3]Avicel CL-611, available from FMC Biopolymer
[4]Available from Pfizer, Inc. as Viagra ®
[5]Taste-masking flavor, available from Virginia Dare
[6]Available from Ungerer and Co.
[7]Cooling agent
[8]Available from Sentry

The above ingredients were combined by mixing until a uniform mixture was achieved, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth bar. One film was dried for 10 minutes in an 80° C. air oven to a moisture level of 3.52%, while the second film was dried for 10 minutes in an 80° C. air oven to a moisture level of 3.95%. The dried films had adequate strength and tear resistance. The films passed the 180° bend test without breaking. The films also dissolved at a moderately fast rate in the mouth and exhibited an acceptable flavor.

As mentioned above, 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. One of the additional advantages of the present invention is that the film composition reaches its viscoelastic state, and even the fully dried state, without exposing the components of the composition to temperatures which will cause them to be altered or unusable for their intended purpose. For example, heat sensitive drugs, proteins, flavors, sweeteners, volatile components, antigens, antibodies and the like, readily decompose at certain temperatures become inactive or denature, making them ineffective for their intended use. In the present invention, due to the combination of a short heat history required to dry, and the controlled non-top-skinning drying process, the

film composition never need to attain the oven temperature (or other heat source) to reach the dried state. To demonstrate this, films were made in accordance with the present invention and dried as discussed below. A first thermocouple was placed within the film and a second thermocouple was suspended in the oven in order to measure the temperature differential between the oven environment and the film composition during the drying process.

To measure the temperature differentials, a thermocouple, which was connected to a Microtherma 1 thermometer, was placed within the films, and another thermocouple was suspended in the drying oven. Temperature readings in the films and oven were recorded every 30 seconds during the drying of the films.

The thermocouple results for the first film are listed in Table 17 below, and graphically represented in FIG. **33**. The results for the second film are listed in Table 18 below, and graphically represented in FIG. **34**. The results show that even after 10 minutes of drying, the temperatures of the film were substantially below (at least about 5° C.) the oven environment. Films dried for less than 10 minutes may experience significantly greater temperature differentials. For example, drying for 4 to 6 minutes, which is a particularly desirable time frame for many films of the present invention, produces differentials of about 25° C. to about 30° C. Accordingly, films may be dried at high, potentially deleterious temperatures without harming heat sensitive actives contained within the films.

TABLE 17

Time (Min.)	Probe Temp (° C.)	Oven Temp (° C.)
0	42.7	78
1	48.1	80
2	48.8	81
3	50	80
4	51.6	80
5	53.6	80
6	56.8	80
7	61.4	80
8	66.8	80
9	72.7	80
10	76.1	80

TABLE 18

Time (Min.)	Probe Temp (° C.)	Oven Temp (° C.)
0	44.4	77
1	49.8	81
2	49.2	81
3	49.4	80
4	51	80
5	52	80
6	55	80
7	58.9	80
8	64.5	80
9	69.8	80
10	74.4	80

Examples CJ-DB

The following examples describe film compositions of the present invention, which contain water-soluble polymers including polyethylene oxide (PEO) alone or in combination with hydroxypropyl cellulose (HPC) or hydroxypropylmethyl cellulose (HPMC). Thin film compositions were prepared using the polymer amounts listed in Table 19.

TABLE 19

Composition	PEO (g)	HPC (g)	HPMC (g)
CJ		32	8
CK		24	16
CL		16	24
CM		8	32
CN			40
CO	8		32
CP	16		24
CQ	24		16
CR	32		8
CS	40		
CT	4		36
CV	6		34
CV	32	8	
CW	24	16	
CX	16	24	
CY	8	32	
CZ		40	
DA	4	36	
DB	6	34	

The above polymer components were combined with equal amounts of precipitated calcium carbonate (mimics drug loading), simethicone emulsion, and water to form the film compositions. The components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films then were dried for about 9 minutes at 80° C. in accordance with the present invention. The film compositions were tested for various properties, the results of which are described in Table 20 below.

TABLE 20

Composition	Composition of Polymer in Film	Solution Coating Rating	Solution Leveling Rating	% Moisture in Film	180° Bend Test	Dissolution Test (seconds)	Curl Test
CJ	20% HPMC/ 80% HPC	well	well	2.9	Failed at crease	12, 15	Curl
CK	40% HPMC/ 60% HPC	well	well	1.70	Failed at crease	21, 22	Curl
CL	60% HPMC/ 40% HPC	well	well	2.40	Failed at crease	24, 27	Curl
CM	80% HPMC/ 20% HPC	well	well	2.76	Failed at crease	31, 31	Curl
CN	100% HPMC	reasonably well	well	2.66	Failed at crease	35, 38	Curl

TABLE 20-continued

Composition	Composition of Polymer in Film	Solution Coating Rating	Solution Leveling Rating	% Moisture in Film	180° Bend Test	Dissolution Test (seconds)	Curl Test
CO	10% PEO/ 90% HPMC	some streaking	well	2.27	Failed at crease	31, 32	Curl
CP	15% PEO/ 85% HPMC	well	well	3.31	Failed	24, 27	Curl
CQ	20% PEO/ 80% HPMC	well	well	2.06	Passed	22, 31	Slight curl
CR	40% PEO/ 60% HPMC	well	well	2.01	Passed	13, 12	Slight curl
CS	60% PEO/ 40% HPMC	well	well	1.40	Passed	5, 6	Very slight curl
CT	80% PEO/ 20% HPMC	well	well	1.35	Passed	5, 6	Very slight curl
CU	100% PEO	well	well	0.98	Passed	5, 5	No curl
CV	20% HPC/ 80% PEO	well	well	1.01	Passed	5, 5	No curl
CW	40% HPC/ 60% PEO	well	well	2.00	Passed	6, 6	No curl
CX	60% HPC/ 40% PEO	well	well	0.97	Passed	7, 7	Slight curl
CY	80% HPC/ 20% PEO	well	well	1.41	Passed	12, 12	Very slight curl
CZ	85% HPC/ 15% PEO	well	well	1.86	Failed at crease	13, 14	Curl
DA	90% HPC/ 10% PEO	well	well	1.62	Failed at crease	14, 13	Curl
DB	100% HPC	well	well	2.01	Failed at crease	16, 17	Curl

The solution coating rating and solution leveling rating were both based upon panel observations made during casting of the film compositions.

For the 180° bend test, the dried films were placed in a moisture analyzer (HR73 Moisture Analyzer from Mettler Toledo) to obtain percent moisture and to remove any solvent (e.g. water) remaining in the films after drying at 80° C. in accordance with the present invention. The films then were creased to about 180° and observed for break. Films that broke during creasing were considered a failure. If the film did not break during creasing, a 200 g weight was dropped onto the creased film from a height of about 8.5 mm. Films that broke were considered a failure, and those that did not break were considered a pass. It should be noted, however, that this flexibility test is an extreme test. Films that failed this test are still considered operable within the scope of the present invention. More specifically, there may be certain applications that do not require such extreme flexibility properties.

The films also were tested for dissolution rate. An approximately 20 mm by 100 mm piece of film, having a 2.85 g weight attached, was lowered into a 32.5° C. water bath to a depth of about 50 mm. The time required for the film to dissolve and separate into two pieces was determined (in seconds).

For the curl test, samples of film (about 35 mm by 35 mm) were placed on a glass plate in a laboratory window ledge. The film samples were allowed to stand in the window ledge at room conditions for two to three days and then were observed for curling.

In accordance with the present invention, desirable film compositions are flexible, fast dissolving, and not likely to substantially curl. As indicated by the results in Table 20, Compositions CQ-CY performed best, exhibiting good flexibility, dissolution, and curling properties. In particular, Compositions CQ-CY passed the 180° bend test and dissolved at moderate to fast rates. These compositions also exhibited no or only slight curl. Accordingly, it may be desirable to employ polymer components as in Compositions CQ-CY, particularly about 20% to 100% PEO in the polymer component optionally combined with about 0% to 80% HPC or HPMC.

Examples DC-DG

The following examples of the present invention describe films that include PEO or PEO-polymeric blends and an active component. Thin film compositions with these components were prepared using the amounts described in Table 21.

TABLE 21

	Weight (g unless otherwise indicated)				
Component	DC	DD	DE	DF	DG
PEO[1]	8.75	7	1.75	7	1.75
Sucralose	0.7	0.7	0.7	0.7	0.7
Precipitated calcium carbonate	3.65	3.65	3.65	3.65	3.65
Orange concentrate flavor	1.05	1.05	1.05	1.05	1.05
Vanilla	0.5	0.5	0.5	0.5	0.5
HPMC		1.75	7.0		
HPC				1.75	7.0
Simethicone[2]	0.35	0.35	0.35	0.35	0.35
Water	32.5	32.5	32.5	32.5	32.5
Loratadine[3]	2.5	2.5	2.5	2.5	2.5
Yellow food coloring	3 drops	3 drops	3 drops	3 drops	3 drops
Red food coloring	2 drops	2 drops	2 drops	2 drops	2 drops

[1]Available from the Dow Chemical Company
[2]Available from Sentry
[3]Available from Schering Corporation as Claritin

The above components for each of Compositions DC through DG were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for about 9 minutes at 80° C. in accordance with the method of the present invention to varying moisture levels.

After drying, the films were tested for various properties, including the 180° bend test, dissolution test, and curl test, as described above in Examples CJ-DB. The films also were tested for resistance to tearing. Tear resistance was measured by a panel test in which members tried to tear the film apart by pulling on opposing ends of the film. Films that tore cleanly received a low grade. Films that stretched a little and began to break received a moderate grade, and films that stretched and were difficult to tear received a high grade.

Composition DC, which included a 100% PEO film base, was dried in accordance with the method of the present invention to about 1.30 percent moisture. The dried film had good strength, and passed the 180° bend test. The film also exhibited good resistance to tearing (high grade). The film dissolved at a fast rate on the tongue, and had a dissolution testing rate of about 3.5 to 4 seconds. The film exhibited no curling.

Composition DD, which included an 80%/20% PEO/HPMC film base, was dried in accordance with the method of the present invention to about 2.30 percent moisture. The dried film exhibited adequate strength, and passed the 180° bend test. The film also exhibited good resistance to tearing. It dissolved at a moderate to fast rate on the tongue, and had a dissolution testing rate of about 5 seconds. The film exhibited slight curling.

Composition DE, which included a 20%/80% PEO/HPMC film base, was dried in accordance with the method of the present invention to about 3.0 percent moisture. The film had good strength, and passed the 180° bend test. The film exhibited moderate tear resistance, dissolved on the tongue at a slow rate, and had a dissolution testing rate of 16 seconds. The film exhibited some curling.

Composition DF, which included an 80%/20% PEO/HPC film base, was dried in accordance with the method of the present invention to about 2.52 percent moisture. The film exhibited good strength, passed the 180° bend test, and exhibited high tear resistance. The film also dissolved at a fast rate on the tongue, and had a dissolution rating of 4 seconds. The film exhibited very slight curling.

Composition DG, which included a 20%/80% PEO/HPC film base, was dried in accordance with the method of the present invention to about 2.81 percent moisture. The film had adequate strength, passed the 180° bend test, and exhibited moderate tear resistance. The film dissolved on the tongue at a fast rate, and had a 10 second dissolution testing rate. The film exhibited no curling.

As indicated above, each of Compositions DC-DG contained about 20% to 100% PEO in the polymer component, optionally in combination with varying levels of HPC or HPMC. The results indicate that varying the polymer component achieved different film properties.

Examples DH-DZ

The following examples of the present invention describe films that include PEO or PEO-HPC polymer blends. The film compositions include PEO of varying molecular weights. Thin film compositions with these components were prepared using the amounts described in Table 22 (listed by weight percent of the polymer component).

TABLE 22

Composition	100,000 PEO (wt. %)	200,000 PEO (wt. %)	300,000 PEO (wt. %)	900,000 PEO (wt. %)	HPC (wt. %)
DH			20		80
DI			50		50
DJ			80		20
DK		50			50
DL		67.5			32.5
DM		70			30
DN		75			25
DO		100			
DP	50				50
DQ	100				
DR				10	90
DS				20	80
DT		40		10	50
DU	25			15	60
DV	20	80			
DW		80		20	
DX		80	20		
DY		50	50		
DZ		20	80		

The above polymer components were combined with sucralose, precipitated calcium carbonate (mimics drug loading), orange concentrate flavor, Tween 80 (available from ICI Americas), vanilla flavor, simethicone emulsion, water, and yellow and red food coloring to form the film compositions. The components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The solution coating and leveling properties were observed. The films then were dried for about 9 minutes at 80° C. in accordance with the method of the present invention. The film compositions were tested for various properties to determine the effect of varying the PEO molecular weight and level in the polymer component, the results of which are described in Table 23 below.

TABLE 23

Composition	Film thickness (mils)	% Moisture	Roof of Mouth Tendency	180° Bend Test	Dissolution Test (seconds)	Tear Resistance
DH	3.5	2.5	low	passed	8	poor
DI	3.8	2.01	low	passed	7	moderate
DJ	2.6	2.63	high	passed	3	excellent
DK	3.4	2.35	low	passed	4	poor
DL	3.5	1.74	low	passed	4	good to excellent
DM	3.5	1.68	low	passed	4	good to excellent
DN	3.3	2.33	moderate	passed	3	good to excellent
DO	3.1	2.14	high	passed	4	excellent
DP	4.1	1.33	high	passed	3.5	poor
DQ	3.2	2.07	high	passed	4	good
DR	3.4	1.90	low	passed	10	poor
DS	3.5	2.04	low	passed	10	poor

TABLE 23-continued

Composition	Film thickness (mils)	% Moisture	Roof of Mouth Tendency	180° Bend Test	Dissolution Test (seconds)	Tear Resistance
DT	3.3	2.25	moderate	passed	5	good
DU	3.6	2.84	low to moderate	passed	6	moderate
DV	2.5	3.45	high	passed	2	excellent
DW	2.5	2.83/1.68	high	passed	3-4	excellent
DX	3.5	2.08	high	passed	5	excellent
DY	2.8	1.67	high	passed	3	excellent
DZ	2.5	1.89/0.93	high	passed	3	excellent

The films were tested for various properties, including the 180° bend test, dissolution test, and tear resistance, as described above. The films also were tested for adhesion, i.e., tendency to go to the roof of the mouth. Adhesion was rated by a panel test in which films that did not stick to the roof of the mouth received a low grade, films that stuck somewhat received a moderate grade, and films that stuck completely received a high grade.

As indicated above, the level and molecular weight of PEO in the polymer component were varied to achieve different film properties. In general, the higher the level of PEO in the polymer component, the greater the adhesiveness and tear resistance exhibited by the film. Film compositions containing about 50% or greater levels of PEO attained higher tear resistance ratings than those with less than 50% PEO. The tear resistance of lower levels of PEO, however, was shown to be improved by combining small amounts of higher molecular weight PEOs with the lower molecular weight PEOs (e.g. Compositions DT and DU).

Compositions containing about 20% to 75% PEO performed best with respect to adhesion prevention (lower tendencies to go to the roof of the mouth). Compositions containing higher levels of PEO performed well when adhesion was desired.

As regards dissolution rate, polymer components containing about 50% or higher levels of PEO performed best, providing faster dissolving film compositions. In those films containing combinations of varying molecular weight PEOs, those with about 60% or higher of the lower molecular weight PEOs (100,000 to 300,000) in the PEO combination dissolved faster.

Example EA

The following example of the present invention describes films that include PEO and polyvinyl pyrrolidone (PVP) polymeric blends. Thin film compositions with these components were prepared using the amounts described in Table 24. In particular, the polymer component of the films contained about 80% PEO and 20% PVP, or a ratio of 4:1 PEO to PVP.

TABLE 24

Component	Weight (g unless otherwise noted)
PVP	3.75
PEO	15
Sucralose[1]	1.5
Precipitated calcium carbonate	14.57
Orange concentrate flavor	2.25
Tween 80[2]	0.056
Simethicone[3]	0.38
Water	62.5
Yellow food color	6 drops
Red food color	4 drops

[1]Available from McNeil Nutritionals
[2]Available from Fisher
[3]Available from Sentry

The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for about 9 minutes at 80° C. in accordance with the method of the present invention to a moisture level of about 2.19%. The films exhibited good strength, dissolved in the mouth at a moderate to fast rate, had high tear resistance, a thickness of about 4 mils, good flavor, low tendency to adhere to the roof of the mouth, and passed the 180° bend test. The film had a dissolution rate of 4 seconds, according to the test described above. In addition, the film easily released from the release paper.

Example EB-ED

The following examples of the present invention describe extruded films that include PEO-based polymer components. Film compositions were prepared using the amounts described in Table 25 for Example EC and Table 26 for Example ED.

TABLE 25

COMPONENT	WEIGHT (g unless otherwise noted)
HPC	73.78
Polyethylene oxide	153.22
Sucralose	18.16
Precipitated calcium carbonate	176.38
Orange concentrated flavor	27.24
Tween 80	0.68
Simethicone	4.54
Yellow food coloring	27 drops
Red food coloring	18 drops

TABLE 26

COMPONENT	WEIGHT (g unless otherwise noted)
Polyethylene oxide	227
Sucralose	18.16
Precipitated calcium carbonate	176.38
Orange concentrated flavor	27.24

TABLE 26-continued

COMPONENT	WEIGHT (g unless otherwise noted)
Tween 80	0.68
Simethicone	4.54
Yellow food coloring	27 drops
Red food coloring	18 drops

The films of Examples EB-ED were extruded using a single screw extruder in accordance with the specifications provided in Table 27 below (temperatures are in ° F.).

TABLE 27

Composition	RPM	Temp. Barrel Zn. 1	Temp. Barrel Zn. 2	Temp. Barrel Zn. 3	Temp. Zn. 4	Temp. Die	Temp. Melt	PSI Pressure P1	PSI Pressure P2	Amps
EB	73	175	181	185	190	190	194	600	1250	12
EB	153	177	181	199	211	210	217	175	1070	7.8
ED	253	175	181	200	211	210	222	0	761	6.3
ED	109	175	181	200	211	210	207	0	1000	6.0
EC	109	175	181	200	211	210	217	0	875	12.1
EC	149	175	200	226	248	239	258	0	583	7.3

More specifically, for Example EB, two pounds of PEO having a molecular weight of about 200,000 were weighed and placed in a polyethylene plastic bag. This PEO flush was then extruded according to the specifications in Table 27.

For Example EC, a blend of the components listed in Table 25 was prepared. The HPC, PEO, sucralose, and precipitated calcium carbonate were placed in a large electric blender and allowed to mix. A solution of orange concentrate flavor and Tween 80 was added to the blender while mixing, after which a solution of simethicone and the food colors was added to the blender while mixing. The blended composition was extruded in accordance with the specifications in Table 27.

For Example ED, a blend of the components listed in Table 26 was prepared. The PEO, sucralose, and precipitated calcium carbonate were placed in a large electric blender and allowed to mix. A solution of orange concentrate flavor and Tween 80 was added to the blender while mixing, after which a solution of simethicone and the food colors was added to the blender while mixing. The blended composition was extruded in accordance with the specifications in Table 27.

The extruded films did not exhibit stickiness to each other during processing. As such, the resulting film could be rolled or wound onto itself without the need for a backing material.

Examples EE-EH

The following examples of the present invention describe films that include a densifying agent. A thin film composition including PEO-polymeric blends and a densifying agent (simethicone) were prepared using the amounts described in Table 28.

TABLE 28

Component	Weight (g unless otherwise indicated) EE	EF	EG	EH
Hydroxypropylcellulose	3.05	3.05	3.05	3.05
Polyethylene oxide	6.33	6.33	6.33	6.33
Sucralose	0.75	0.75	0.75	0.75
Precipitated calcium carbonate	7.47	7.47	7.09	7.09

TABLE 28-continued

Component	Weight (g unless otherwise indicated) EE	EF	EG	EH
Orange concentrate flavor	1.12	1.12	1.12	1.12
Tween 80	0.028	0.028	0.028	0.028
Simethicone	0	0	0.38	0.38
Water	31.25	31.25	31.25	31.25
Yellow food coloring	3 drops	3 drops	3 drops	3 drops
Red food coloring	2 drops	2 drops	2 drops	2 drops

The densities of these thin film compositions were measured, the results of which are shown in Table 29.

TABLE 29

Composition	Average Weight of Film/Density
EE	146.5 mg/1.123
EF	126.5 mg/0.969
EG	137 mg/1.057
EH	146 mg/1.119

Vacuum conditions were added to two of the film compositions (EE and EH). Composition EE contained 0% simethicone and vacuum was applied. Composition EF contained 0% simethicone and no vacuum applied. As shown in Table 29 above, the density increased with the addition of vacuum conditions from 0.969 (EF) to 1.123 (EE). Composition EG contained 2% simethicone and no vacuum applied. Composition EH contained 2% simethicone and vacuum was applied. Again, density increased from 1.057 (EG) to 1.119 (EH). Overall, the density of the films increased from 0.969 (EF: no simethicone and no vacuum) to 1.057 (EG: simethicone but no vacuum) to 1.119 (EH: simethicone and vacuum).

Examples EI-EW

The following examples of the present invention describe films that include PEO or PEO-polymeric blends. In particular, PEO was combined with polyvinylpyrrolidone (PVP), starch (pregelatinized modified corn starch), sodium carboxymethyl cellulose (CMC), hydroxypropylcellulose (HPC), hydroxypropylmethyl cellulose (HPMC) or polyvinyl alcohol (PVA) to form the polymer components of the films. Thin film compositions with these components were prepared in accordance with the method of the present invention using the amounts described in FIG. **38**.

In addition to the polymer components listed in FIG. **38**, each of these film compositions included: about 4% sucralose, about 38.85% calcium carbonate, about 6% orange flavor, about 0.15% Tween 80, about 1% simethicone, and food

coloring. The PEO included in the polymer component of these examples had a molecular weight of about 200,000.

FIG. **38** also displays certain properties of these films, including: percent solids of solution; viscosity; percent moisture; film thickness; film strength; tear resistance of the film; tendency of the film to go to the roof of the mouth; the 180° bend test; whether molding, or aggregations, are present in the film; dissolution times of the film; rating of dissolution in the mouth; and time in drying oven. Each of these film property tests is described in detail above. The results of these various tests are indicated in FIG. **38**.

Examples EX-FK

The following examples of the present invention describe films that include PEO or PEO-polymeric blends (with HPC) and different active components. Thin film compositions with these components were prepared in accordance with the method of the present invention using the amounts described in Tables 30 and 31.

TABLE 30

	Weight (in g, unless otherwise indicated)						
Component	EX	EY	EZ	FA	FB	FC	FD
HPC	5.68	5.64	6	6.73	6.22	6.22	
PEO	1.89	1.88	2	2.25	1.78	1.78	9.04
Sucralose	0.84	0.84	0.44	0.66	0.84	0.84	0.44
Magna Sweet	0.08	0.08	0.09	0.10	0.09	0.09	
Avicel CL 611[1]	0.18	0.18	0.18	0.20	0.18	0.18	
Precipitated calcium carbonate	0.67		2.2		0.71	3.07	
Dextromethorphan	5.83	6.94					
Caffeine			3.28				
Tadalafil[2]				4.92			
Sildenafil[3]					4.38		
Loperamide[4]						2.8	
Prosweet	0.18	0.18		0.20	0.61	0.18	
Taste Masking Flavor			0.87		1.31	0.89	
Peppermint			0.87				
Peppermint Bittermask flavor			1.07				
Vanilla flavor				0.56			
Watermelon artificial flavor	1.23	1.23			1.22		
Orange flavor				1.18			
Hawaiian punch flavor						1.22	
Strawberry & cream flavor							1.11
WS-23[5]	0.075	0.075	0.075	0.084	0.075	0.075	
WS-3[6]							0.025
Simethicone	0.08	0.08	0.18	0.39	0.09	0.18	46.43
Propylene glycol	0.76	0.38	0.25	0.22			
Water	32.5	32.5	32.5	32.5	32.5	32.5	
Green color	5 drop	5 drop			5 drop		
Red color				2 drop		5 drop	7 drop
Blue color			3 drop				
Yellow color				3 drop			

[1]Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer
[2]Available from Lilly ICOS, LLC, as Cialis ®
[3]Available from Pfizer, Inc. as Viagra ®
[4]Available as Imodium
[5]N-2,3-trimethyl-2-isopropyl butanamide
[6]N-Ethyl-p-menthane-3-carboxamide

TABLE 31

	Weight (in g, unless otherwise indicated)						
Component	FE	FF	FG	FH	FI	FJ	FK
HPC	1.28	3.05	4.5	3.29	2.6	2.92	3.29
PEO	2.66	6.33	3	6.83	5.4	6.08	6.83
Sucralose	0.31	0.9	0.6		0.64		
Magna Sweet		0.09					
Avicel CL 611[1]		0.56	0.45				
Precipitated calcium carbonate	1.07	2.02	0.99	6.05	0.90	2.67	1.39
Meloxicam[2]	1.97						
Risperidone[3]		0.62					
Zyrtec ®[4]			3.75				
Five Grass Powder[5]				2.207			
Tea Tree Oil[6]					4		
Antibacterial concentrate[7]						6.12	
Mite extract[8]							6.87
Prosweet		0.66					
Taste Masking Flavor		1.41					
Peppermint Bittermask flavor		2.81			2.24		
Orange flavor	0.47						

TABLE 31-continued

Component	Weight (in g, unless otherwise indicated)						
	FE	FF	FG	FH	FI	FJ	FK
Strawberry & cream flavor			1.5				
WS-3[9]	0.020	0.081	0.038		0.04		
Tween 80	0.012	0.028	0.022		0.024	0.027	
Simethicone	0.08	0.19	0.15	0.37	0.16	0.18	0.37
Water	14.63	31.25	25	31.25	24	22	31.25
Red color	2 drop		5 drop				
Blue color		3 drop			3 drop		
Yellow color	3 drop						

[1]Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer
[2]Available as Mobic ®
[3]Available as Risperdal ®
[4]Available from Pfizer, Inc.
[5]Allergy treatment
[6]Antibiotic
[7]MegaBac ™, available from Nicrosol Technologies
[8]Allergy treatment
[9]N-Ethyl-p-menthane-3-carboxamide

The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 250 or 350 micron smooth bar. The films were dried for about 9 to 10 minutes at 80° C. in accordance with the method of the present invention resulting in dried films having adequate to good strength.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

What is claimed is:

1. A mucosally-adhesive water-soluble film product comprising:
an analgesic opiate pharmaceutical active; and
at least one water-soluble polymer component consisting of polyethylene oxide in combination with a hydrophilic cellulosic polymer;
wherein:
the water-soluble polymer component comprises greater than 75% polyethylene oxide and up to 25% hydrophilic cellulosic polymer;
the polyethylene oxide comprises one or more low molecular weight polyethylene oxides and one or more higher molecular weight polyethylene oxides, the molecular weight of the low molecular weight polyethylene oxide being in the range 100,000 to 300,000 and the molecular weight of the higher molecular weight polyethylene oxide being in the range 600,000 to 900,000; and
the polyethylene oxide of low molecular weight comprises about 60% or more in the polymer component.

2. The film product according to claim **1**, wherein said film product has a viscosity of about 1,000 cps to about 40,000 cps.

3. The film product according to claim **1**, wherein said film product has a thickness of about 3 mils to about 6 mils.

4. The film product according to claim **1**, further comprising an additional pharmaceutical active.

5. The film product according to claim **1**, further comprising one or more sweeteners.

6. The film product according to claim **5**, wherein said one or more sweeteners comprise a hydrogenated starch hydrolysate.

7. The film product according to claim **5**, wherein said one or more sweeteners comprise the potassium salt of 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide.

8. The film product according to claim **1**, further comprising one or more flavors.

9. The film product according to claim **1**, further comprising one or more buffers.

10. A mucosally-adhesive water-soluble film product comprising:
an analgesic opiate pharmaceutical active; and
at least one water-soluble polymer component consisting of polyethylene oxide in combination with a hydrophilic cellulosic polymer;
wherein:
the water-soluble polymer component comprises the hydrophilic cellulosic polymer in a ratio of up to about 4:1 with the polyethylene oxide;
the polyethylene oxide comprises one or more low molecular weight polyethylene oxides and one or more higher molecular weight polyethylene oxides, the molecular weight of the low molecular weight polyethylene oxide being in the range 100,000 to 300,000 and the molecular weight of the higher molecular weight polyethylene oxide being in the range 600,000 to 900,000; and
the polyethylene oxide of low molecular weight comprises about 60% or more in the polymer component.

11. The film product according to claim **10**, wherein said film product has a viscosity of about 1,000 cps to about 40,000 cps.

12. The film product according to claim **10**, wherein said film product has a thickness of about 3 mils to about 6 mils.

13. The film product according to claim **10**, further comprising an additional pharmaceutical active.

14. The film product according to claim **10**, further comprising one or more sweeteners.

15. The film product according to claim **14**, wherein said one or more sweeteners comprise a hydrogenated starch hydrolysate.

16. The film product according to claim **14**, wherein said one or more sweeteners comprise the potassium salt of 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide.

17. The film product according to claim **10**, further comprising one or more flavors.

18. The film product according to claim **10**, further comprising one or more buffers.

* * * * *

EXHIBIT C

(12) **United States Patent**
Myers et al.

(10) **Patent No.: US 8,475,832 B2**
(45) **Date of Patent: Jul. 2, 2013**

(54) **SUBLINGUAL AND BUCCAL FILM COMPOSITIONS**

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(58) **Field of Classification Search**
None
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(57) **ABSTRACT**

The present invention relates to products and methods for treatment of narcotic dependence in a user. The invention more particularly relates to self-supporting dosage forms which provide an active agent for treating narcotic dependence while providing sufficient buccal adhesion of the dosage form.

19 Claims, No Drawings

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SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to compositions, methods of manufacture, products and methods of use relating to films containing therapeutic actives. The invention more particularly relates to self-supporting film dosage forms which provide a therapeutically effective dosage, essentially matching that of currently-marketed tablets containing the same active. Such compositions are particularly useful for treating narcotic dependence while providing sufficient buccal adhesion of the dosage form.

BACKGROUND OF THE RELATED TECHNOLOGY

Oral administration of two therapeutic actives in a single dosage form can be complex if the intention is to have one active absorbed into the body and the other active remain substantially unabsorbed. For example, one active may be relatively soluble in the mouth at one pH, and the other active may be relatively insoluble at the same pH. Moreover, the absorption kinetics of each therapeutic agent may be substantially different due to differing absorption of the charged and uncharged species. These factors represent some of the challenges in appropriately co-administering therapeutic agents.

Co-administration of therapeutic agents has many applications. Among such areas of treatment include treating individuals who suffer from narcotic dependence. Such individuals have a tendency to suffer from serious physical dependence on the narcotic, resulting in potentially dangerous withdrawal effects when the narcotic is not administered to the individual. In order to help individuals addicted to narcotics, it is known to provide a reduced level of a drug, which provides an effect of satisfying the body's urge for the narcotic, but does not provide the "high" that is provided by the misuse of the narcotic. The drug provided may be an agonist or a partial agonist, which provides a reduced sensation and may help lower dependence on the drug. However, even though these drugs provide only a low level of euphoric effect, they are capable of being abused by the individuals parenterally. In such cases, it is desirable to provide a combination of the drug with a second drug, which may decrease the likelihood of diversion and abuse of the first drug. For example, it is known to provide a dosage of an antagonist in combination with the agonist or partial agonist. The narcotic antagonist binds to a receptor in the brain to block the receptor, thus reducing the effect of the agonist.

One such combination of drugs has been marketed under the trade name Suboxone® as an orally ingestible tablet. However, such combinations in tablet form have the potential for abuse. In some instances, the patient who has been provided the drug may store the tablet in his mouth without swallowing the tablet, then later extract the agonist from the tablet and inject the drug into an individual's body. Although certain antagonists (such as highly water-soluble antagonists) may be used to help reduce the ability to separate the agonist, the potential for abuse still exists. It is desired to provide a dosage that cannot be easily removed from the mouth once it has been administered.

There is currently a need for an orally dissolvable film dosage form that provides the desired absorption levels of the agonist and antagonist, while providing an adhesive effect in the mouth, rendering it difficult to remove once placed in the mouth, thereby making abuse of the agonist difficult.

SUMMARY OF THE INVENTION

In one embodiment of the present invention, there is provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof, a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine.

In another embodiment of the present invention, there is provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof, a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffer in an amount sufficient to inhibit the absorption of the naloxone when administered orally.

In still other embodiments, there may be provided a film dosage composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof, a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and a buffering system; where the buffering system includes a buffer capacity sufficient to maintain the ionization of naloxone during the time which the composition is in the oral cavity of a user.

In another embodiment of the invention, there is provided a method of treating narcotic dependence of a user, including the steps of: providing a composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof, a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof, and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine; and administering the composition to the oral cavity of a user.

In still another embodiment of the invention, there is provided a process of forming a film dosage composition including the steps of: casting a film-forming composition, the film-forming composition including: a polymeric carrier matrix; a therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof, a therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof, and a buffer in an amount to provide a pH of the composition of a value sufficient to optimize absorption of the buprenorphine and drying the film-forming composition to form a self-supporting film dosage composition.

In another embodiment, there is provided a film dosage composition including a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, the film dosage composition having a bioequivalent release profile as compared to a Suboxone® tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof.

Still other embodiments of the present invention provide an orally dissolving film formulation including buprenorphine and naloxone, where the formulation provides an in-vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in-vivo

plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

As used herein, the term Cmax refers to the mean maximum plasma concentration after administration of the composition to a human subject. As also used herein, the term AUC refers to the mean area under the plasma concentration-time curve value after administration of the compositions formed herein. As will be set forth in more detail below, the term "optimizing the absorption" does not refer to reaching the maximum absorption of the composition, and rather refers to reaching the optimum level of absorption at a pH of about 2 to about 4. The "optimum" absorption may be, for example, a level that provides a bioequivalent absorption as administration of the currently available Suboxone® tablet. An "optimum" Cmax of buprenorphine is about 0.67 to about 5.36 mg/ml at dosages of from 2-16 mg buprenorphine at a given pH. Similarly, an "optimum" AUC of buprenorphine may be about 7.43 to about 59.46 hr*ng/ml at dosages of from 2-16 mg buprenorphine at a given pH. As will be described in more detail below, it has been surprisingly discovered that the absorption of one particular agonist, buprenorphine, can provide an optimum absorption at a pH of about 2-4 as well as about 5.5-6.5. Thus, one may "optimize" the absorption of buprenorphine by providing a pH of about 2-4 or about 5.5-6.5.

"Maximizing the absorption" refers to the maximum in vivo absorption values achieved at a pH of about 4 to about 9.

The term "local pH" refers to the pH of the region of the carrier matrix immediately surrounding the active agent as the matrix hydrates and/or dissolves, for example, in the mouth of the user.

By "inhibiting" the absorption of an active, it is meant achieving as complete an ionization state of the active as possible, such that little to none of the active is measurably absorbable. For example, at a pH of 3-3.5, the Cmax of an active such as naloxone for dosage of 0.5 mg to 4.0 mg ranges from 32.5 to 260 pg/ml, and an AUC of naloxone for dosage of 0.5 mg to 4.0 mg ranges from 90.55 to 724.4 hr*pg/ml. It is understood that at a pH lower than 3.0, further ionization would be expected and thus result in lower absorption.

The term "bioequivalent" means obtaining 80% to 125% of the Cmax and AUC values for a given active in a different product. For example, assuming Cmax and AUC values of buprenorphine for a commercially-available Suboxone® tablet (containing 2 mg buprenorphine and 0.5 mg naloxone) are 0.780 ng/ml and 6.789 hr*ng/ml, respectively, a bioequivalent product would have a Cmax of buprenorphine in the range of 0.624-0.975 ng/ml, and an AUC value of buprenorphine of 5.431-8.486 hr*ng/ml.

It will be understood that the term "film" includes thin films and sheets, in any shape, including rectangular, square, or other desired shape. The films described herein may be any desired thickness and size such that it may be placed into the oral cavity of the user. For example, the films may have a relatively thin thickness of from about 0.1 to about 10 mils, or they may have a somewhat thicker thickness of from about 10 to about 30 mils. For some films, the thickness may be even larger, i.e., greater than about 30 mils. Films may be in a single layer or they may be multi-layered, including laminated films.

Oral dissolving films generally fall into three main classes: fast dissolving, moderate dissolving and slow dissolving. Fast dissolving films generally dissolve in about 1 second to about 30 seconds in the mouth. Moderate dissolving films generally dissolve in about 1 to about 30 minutes in the mouth, and slow dissolving films generally dissolve in more than 30 minutes in the mouth. Fast dissolving films may consist of low molecular weight hydrophilic polymers (i.e., polymers having a molecular weight between about 1,000 to 9,000, or polymers having a molecular weight up to 200,000). In contrast, slow dissolving films generally have high molecular weight polymers (i.e., having a molecular weight in the millions).

Moderate dissolving films tend to fall in between the fast and slow dissolving films. Moderate dissolving films dissolve rather quickly, but also have a good level of mucoadhesion. Moderate dissolving films are also flexible, quickly wettable, and are typically non-irritating to the user. For the instant invention, it is preferable to use films that fall between the categories of fast dissolving and moderate dissolving. Such moderate dissolving films provide a quick enough dissolution rate, most desirably between about 1 minute and about 20 minutes, while providing an acceptable mucoadhesion level such that the film is not easily removable once it is placed in the oral cavity of the user.

Inventive films described herein may include one or more agonists or partial agonists used for the treatment of drug addiction. As used herein, the term "agonist" refers to a chemical substance that is capable of providing a physiological response or activity in the body of the user. The films described herein may further include one or more antagonists. As used herein, the term "antagonist" refers to any chemical substance that acts within the body of the user to reduce the physiological activity of another chemical substance. In some embodiments, an antagonist used herein may act to reduce and/or block the physiological activity of the agonist. The actives may be water-soluble, or they may be water-insoluble. As used herein, the term "water-soluble" refers to substances that are at least partially dissolvable in a solvent, including but not limited to water. The term "water-soluble" does not necessarily mean that the substance is 100% dissolvable in the solvent. The term "water-insoluble" refers to substances that are not dissolvable in a solvent, including but not limited to water. Solvents may include water, or alternatively may include other polar solvents by themselves or in combination with water.

Inventive Films

The present invention relates to methods of treating narcotic dependence in an individual. More desirably, the invention relates to the treatment of opioid dependence in an individual, while using a formulation and delivery that hinders misuse of the narcotic. Currently, treatment of opioid dependence is aided by administration of Suboxone®, which is an orally dissolvable tablet. This tablet which provides a combination of buprenorphine (an opioid agonist) and naloxone (an opioid antagonist). Therefore, the present invention provides a method of treating narcotic dependence by providing an orally dissolvable film dosage, which provides a bioequivalent effect to Suboxone®. The film dosage preferably provides buccal adhesion while it is in the user's mouth, rendering it difficult to remove after placement.

The film dosage composition preferably includes a polymeric carrier matrix. Any desired polymeric carrier matrix may be used, provided that it is orally dissolvable. Desirably, the dosage should have enough bioadhesion to not be easily removed and it should form a gel like structure when administered. The orally consumable films are preferably moderate-dissolving in the oral cavity and particularly suitable for

delivery of actives, although both fast and sustained release compositions are also among the various embodiments contemplated.

The films used in the pharmaceutical products may be produced by a combination of at least one polymer and a solvent, optionally including other fillers known in the art. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, or any combination thereof. In some embodiments, the solvent may be a non-polar organic solvent, such as methylene chloride. The film may be prepared by utilizing a selected casting or deposition method and a controlled drying process. For example, the film may be prepared through controlled drying processes, which include application of heat and/or radiation energy to the wet film matrix to form a visco-elastic structure, thereby controlling the uniformity of content of the film. Such processes are described in more detail in commonly assigned U.S. application Ser. No. 10/074,272, filed on Feb. 14, 2002, and published as U.S. Patent Publication No. 2003/0107149 A1, the contents of which are incorporated herein by reference in their entirety. Alternatively, the films may be extruded as described in commonly assigned U.S. application Ser. No. 10/856,176, filed on May 28, 2004, and published as U.S. Patent Publication No. 2005/0037055 A1, the contents of which are incorporated herein by reference in their entirety.

The polymer included in the films may be water-soluble, water-swellable, water-insoluble, or a combination of one or more either water-soluble, water-swellable or water-insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water-soluble polymers include, but are not limited to, polyethylene oxide, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water-insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof. For higher dosages, it may be desirable to incorporate a polymer that provides a high level of viscosity as compared to lower dosages.

As used herein the phrase "water-soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water-swellable polymers. The materials useful with the present invention may be water-soluble or water-swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water-soluble or water-swellable at pressures less than atmospheric pressure. Desirably, the water-soluble polymers are water-soluble or water-swellable having at least 20 percent by weight water uptake. Water-swellable polymers having a 25 or greater percent by weight water uptake are also useful. In some embodiments, films formed from such water-soluble polymers may be sufficiently water-soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films include biodegradable polymers, copolymers, block polymers and combinations thereof. It is understood that the term "biodegradable" is intended to include materials that chemically degrade, as opposed to materials that physically break apart (i.e., bioerodable materials). Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanes, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy)propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly (lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of polyurethane and poly(lactic acid), copolymers of α-amino acids, copolymers of α-amino acids and caproic acid, copolymers of α-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Del. and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100 L, believed to be 100% lactide having a melting point within the range of 338°-347° F. (170°-175° C.); lactide/glycolide 100 L, believed to be 100% glycolide having a melting point within the range of 437°-455° F. (225°-235° C.); lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.).

The Biodel materials represent a family of various polyanhydrides which differ chemically.

Although a variety of different polymers may be used, it is desired to select polymers that provide mucoadhesive properties to the film, as well as a desired dissolution and/or disintegration rate. In particular, the time period for which it is desired to maintain the film in contact with the mucosal tissue depends on the type of active contained in the composition. Some actives may only require a few minutes for delivery through the mucosal tissue, whereas other actives may require up to several hours or even longer. Accordingly, in some embodiments, one or more water-soluble polymers, as described above, may be used to form the film. In other embodiments, however, it may be desirable to use combinations of water-soluble polymers and polymers that are water-swellable, water-insoluble and/or biodegradable, as provided above. The inclusion of one or more polymers that are water-swellable, water-insoluble and/or biodegradable may provide films with slower dissolution or disintegration rates than films formed from water-soluble polymers alone. As such, the film may adhere to the mucosal tissue for longer periods or time, such as up to several hours, which may be desirable for delivery of certain active components.

Desirably, the individual film dosage has a small size, which is between about 0.5-1 inch by about 0.5-1 inch. Most preferably, the film dosage is about 0.75 inches×0.5 inches. The film dosage should have good adhesion when placed in the buccal cavity or in the sublingual region of the user. Further, the film dosage should disperse and dissolve at a moderate rate, most desirably dispersing within about 1 minute and dissolving within about 3 minutes. In some

embodiments the film dosage may be capable of dispersing and dissolving at a rate of between about 1 to about 1.5 minutes.

For instance, in some embodiments, the films may include polyethylene oxide alone or in combination with a second polymer component. The second polymer may be another water-soluble polymer, a water-swellable polymer, a water-insoluble polymer, a biodegradable polymer or any combination thereof. Suitable water-soluble polymers include, without limitation, any of those provided above. In some embodiments, the water-soluble polymer may include hydrophilic cellulosic polymers, such as hydroxypropyl cellulose and/or hydroxypropylmethyl cellulose. In accordance with some embodiments, polyethylene oxide may range from about 20% to 100% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight. In some embodiments, one or more water-swellable, water-insoluble and/or biodegradable polymers also may be included in the polyethylene oxide-based film. Any of the water-swellable, water-insoluble or biodegradable polymers provided above may be employed. The second polymer component may be employed in amounts of about 0% to about 80% by weight in the polymer component, more specifically about 30% to about 70% by weight, and even more specifically about 40% to about 60% by weight.

The molecular weight of the polyethylene oxide also may be varied. In some embodiments, high molecular weight polyethylene oxide, such as about 4 million, may be desired to increase mucoadhesivity of the film. In some other embodiments, the molecular weight may range from about 100,000 to 900,000, more specifically from about 100,000 to 600,000, and even more specifically from about 100,000 to 300,000. In some embodiments, it may be desirable to combine high molecular weight (600,000 to 900,000) with low molecular weight (100,000 to 300,000) polyethylene oxide in the polymer component.

A variety of optional components and fillers also may be added to the films. These may include, without limitation: surfactants; plasticizers; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother film surface by releasing oxygen from the film; thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components; inclusion compounds, such as cyclodextrins and caged molecules; coloring agents; and flavors. In some embodiments, more than one active components may be included in the film.

Additives may be included in the films. Examples of classes of additives include excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof. These additives may be added with the active ingredient(s).

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragancanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcelulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water-soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

Such extenders may optionally be added in any desired amount desirably within the range of up to about 80%, desirably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all film components.

Further additives may flow agents and opacifiers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.02% to about 3% by weight and desirably about 0.02% to about 1% based on the weight of all film components.

Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5% to about 30%, and desirably ranging from about 0.5% to about 20% based on the weight of the polymer.

There may further be added compounds to improve the texture properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form, especially those which are solid at room temperature. These fats desirably have a melting point of 50° C. or higher. Preferred are tri-glycerides with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantageously added alone or together with mono- and/or di-glycerides or phosphatides, especially lecithin. The mono- and di-glycerides are desirably derived from the types of fats described above, i.e. with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids.

The total amounts used of the fats, mono-, di-glycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5% to about 2% by weight of the total film composition.

It further may be useful to add silicon dioxide, calcium silicate, or titanium dioxide in a concentration of about 0.02% to about 1% by weight of the total composition. These compounds act as flow agents and opacifiers.

Lecithin is one surface active agent for use in the films described herein. Lecithin may be included in the feedstock in an amount of from about 0.25% to about 2.00% by weight. Other surface active agents, i.e. surfactants, include, but are not limited to, cetyl alcohol, sodium lauryl sulfate, the Spans™ and Tweens™ which are commercially available from ICI Americas, Inc. Ethoxylated oils, including ethoxylated castor oils, such as Cremophor EL which is commer-

cially available from BASF, are also useful. Carbowax™ is yet another modifier which is very useful in the present invention. Tweens™ or combinations of surface active agents may be used to achieve the desired hydrophilic-lipophilic balance ("HLB"). The present invention, however, does not require the use of a surfactant and films or film-forming compositions of the present invention may be essentially free of a surfactant while still providing the desirable uniformity features of the present invention.

Other ingredients include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, pregelatinize starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, and polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or instable actives may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or instable actives to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

Suitable coloring agents include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide.

Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides or iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof, saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

Anti-foaming and/or de-foaming components may also be used with the films. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. Such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other anti-foam and/or de-foaming agents may suitable be used.

As a related matter, simethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser, and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

Simethicone is generally used in the medical field as a treatment for gas or colic in babies. Simethicone is a mixture of fully methylated linear siloxane polymers containing repeating units of polydimethylsiloxane which is stabilized with trimethylsiloxy end-blocking unites, and silicon dioxide. It usually contains 90.5-99% polymethylsiloxane and 4-7% silicon dioxide. The mixture is a gray, translucent, viscous fluid which is insoluble in water.

When dispersed in water, simethicone will spread across the surface, forming a thin film of low surface tension. In this way, simethicone reduces the surface tension of bubbles air located in the solution, such as foam bubbles, causing their collapse. The function of simethicone mimics the dual action of oil and alcohol in water. For example, in an oily solution any trapped air bubbles will ascend to the surface and dissipate more quickly and easily, because an oily liquid has a lighter density compared to a water solution. On the other hand, an alcohol/water mixture is known to lower water density as well as lower the water's surface tension. So, any air bubbles trapped inside this mixture solution will also be easily dissipated. Simethicone solution provides both of these advantages. It lowers the surface energy of any air bubbles that trapped inside the aqueous solution, as well as lowering the surface tension of the aqueous solution. As the result of this unique functionality, simethicone has an excellent anti-foaming property that can be used for physiological processes (anti-gas in stomach) as well as any for external processes that require the removal of air bubbles from a product.

In order to prevent the formation of air bubbles in the films, the mixing step can be performed under vacuum. However, as soon as the mixing step is completed, and the film solution is returned to the normal atmosphere condition, air will be re-introduced into or contacted with the mixture. In many cases, tiny air bubbles will be again trapped inside this polymeric viscous solution. The incorporation of simethicone into the film-forming composition either substantially reduces or eliminates the formation of air bubbles.

Simethicone may be added to the film-forming mixture as an anti-foaming agent in an amount from about 0.01 weight percent to about 5.0 weight percent, more desirably from about 0.05 weight percent to about 2.5 weight percent, and most desirably from about 0.1 weight percent to about 1.0 weight percent.

Any other optional components described in commonly assigned U.S. Pat. No. 7,425,292 and U.S. application Ser. No. 10/856,176, referred to above, also may be included in the films described herein.

When the dosage form includes at least one antagonist, it may be desired to control the release of the antagonist, so as to delay or wholly prevent the release of the antagonist from the dosage when taken orally. Desirably, the dosage form is a self-supporting film composition, which is placed into the oral cavity of the user. In a dosage form that is to be placed in the oral cavity, it is desired to absorb the agonist buccally, so as to provide rapid integration of the agonist into the body of the user. At the same time, it may be desired to prevent or reduce absorption of any antagonist buccally, thereby allowing the antagonist to be swallowed and destroyed in the stomach. Reducing the absorption of an antagonist may be achieved via physical means, such as by encapsulating the antagonist in a material that blocks absorption. It is desired, however, to reduce the absorption of the antagonist by chemical means, such as by controlling the local pH of the dosage.

It has been found that by controlling the local pH of the dosage form, the release and/or absorption of the actives therein may be controlled. For example, in a dosage that includes an amount of an agonist, the local pH may be controlled to a level that maximizes its release and/or absorption into the oral cavity of the user. In dosages incorporating an amount of an agonist and an amount of an antagonist, the local pH may be controlled to a level that maximizes the release and/or absorption of the agonist while simultaneously minimizing the release and/or absorption of the antagonist.

The dosage form preferably includes a combination of a partial agonist and an antagonist, while the dosage has a controlled pH. In one embodiment, the partial agonist may include buprenorphine or a pharmaceutically acceptable salt thereof, while the antagonist includes naloxone or a therapeutically acceptable salt thereof. It should be understood that the present invention is not limited to the use of buprenorphine and naloxone, and any agonist (or partial agonist) and any antagonist may be incorporated into the present invention for use in treatment of drug addiction. The agonist and optional antagonist should be selected from those agonists and antagonists that are useful in treating the particular narcotic dependence being treated.

As discussed above, the local pH of the dosage is preferably controlled to provide the desired release and/or absorption of the agonist and antagonist. Buprenorphine is known to have a pKa of about 8.42, while naloxone has a pKa of about 7.94. According to pH partition theory, one would expect that saliva (which has a pH of about 6.5) would maximize the absorption of both actives. However, it has been surprisingly discovered by the Applicants that by buffering the dosage to a particular pH level, the optimum levels of absorption of the agonist and antagonist may be achieved. Desirably, the local pH of a composition including an agonist and an antagonist is between about 2 to about 4, and most desirably is from 3 to 4. At this local pH level, the optimum absorption of the agonist and the antagonist is achieved. As will be described in more detail in the Examples below, controlling the local pH of the film compositions of the present invention provides a system in which the desired release and/or absorption of the components is bioequivalent to that of a similar Suboxone® tablet.

In one embodiment, the dosage form is a self-supporting film. In this embodiment, the film dosage includes a polymer carrier matrix, a therapeutically effective amount of buprenorphine, an agonist. The buffer is preferably capable of providing a local pH of the composition within a range that provides the desired level of absorption of the buprenorphine. The resulting dosage is a film composition that allows for a rapid and effective release of buprenorphine into the oral cavity of the user. At the same time, the film composition preferably has a sufficient adhesion profile, such that the film cannot easily be removed from the oral cavity of the user once it has been placed into the cavity. Full release of the buprenorphine preferably takes place within less than about thirty minutes, and preferably remains in the oral cavity for at least 1 minute.

As explained above, while providing a pharmaceutically acceptable level of an agonist is helpful in treating those with narcotic addiction, it may be desirable to provide the buprenorphine in combination with naloxone (an antagonist) so as to reduce the effect of the agonist and therefore aid in reducing dependency of the narcotic. Therefore, it may be desirable to combine the opioid agonist (or partial agonist) in the film composition with an opioid antagonist or a pharmaceutically acceptable salt thereof. The actives may be dispersed throughout the dosage separately or they may be combined together and dispersed into the dosage. Most desirably the antagonist includes naloxone, but any suitable basic antagonist may be selected as desired. The antagonist may optionally be water-soluble, so as to render separation of the antagonist and agonist difficult, thereby lessening the potential for abuse of the agonist.

As with a film including an agonist, the film including an agonist and an antagonist is desirably pH-controlled through the inclusion of a buffer. In such combination films, it has been discovered that the local pH of the film composition should preferably be in the range of about 2 to about 4, and more preferably about 3 to about 4 so as to provide a bioequivalent product as the commercially-available Suboxone® tablet. Most preferably the local pH of the film composition is about 3.5. At this local pH level, absorption of the buprenorphine is optimized while the absorption of the naloxone is inhibited.

The film may contain any desired level of self-supporting film forming polymer, such that a self-supporting film composition is provided. In one embodiment, the film composition contains a film forming polymer in an amount of at least 25% by weight of the composition. The film forming polymer may alternatively be present in an amount of at least 50% by weight of the composition. As explained above, any film forming polymers that impart the desired mucoadhesion and rate of film dissolution may be used as desired.

Any desired level of agonist and optional antagonist may be included in the dosage, so as to provide the desired effect. In one particular embodiment, the film composition includes about 2 mg to about 16 mg of agonist per dosage. More desirably, the film composition includes about 4 mg to about 12 mg of agonist per dosage. If desired, the film composition may include about 0.5 mg to about 5 mg of antagonist per dosage. More desirably, the film composition includes about 1 mg to about 3 mg of antagonist per dosage. If an antagonist is incorporated into the film, the film composition may include the antagonist in a ratio of about 6:1-2:1 agonist to antagonist. Most desirably, the film composition contains about 4:1 agonist to antagonist per dosage. For example, in one embodiment, the dosage includes an agonist in an amount of about 12 mg, and includes an antagonist in an amount of about 3 mg.

The film compositions further desirably contains a buffer so as to control the local pH of the film composition. Any desired level of buffer may be incorporated into the film composition so as to provide the desired local pH level. The buffer is preferably provided in an amount sufficient to control the release from the film and/or the absorption into the

body of the agonist and the optional antagonist. In a desired embodiment, the film composition includes buffer in a ratio of buffer to agonist in an amount of from about 2:1 to about 1:5 (buffer:agonist). The buffer may alternatively be provided in a 1:1 ratio of buffer to agonist. As stated above, the film composition preferably has a local pH of about 2 to about 4, and most preferably has a local pH of about 3.5. Any buffer system may be used as desired. In some embodiments, the buffer may include sodium citrate, citric acid, and combinations thereof.

In this embodiment, the resulting film composition includes a polymer matrix, an agonist, and an optional antagonist, while the film composition has a controlled local pH to the level desired. The buffer is preferably present in an amount to provide a therapeutically adequate absorption of the agonist, while simultaneously limiting the absorption of the antagonist. Controlling of the local pH allows for the desired release and/or absorption of the components, and thus provides a more useful and effective dosage.

The film dosage composition may include a polymer carrier matrix, a therapeutically effective amount of agonist, a therapeutically effective amount of antagonist, and a buffering system. The buffering system may include a buffer in addition to a solvent. The buffering system desirably includes a sufficient level of buffer so as to provide a desired local pH level of the film dosage composition.

In addition to a desired local pH level, the buffer preferably has a buffer capacity sufficient to maintain the ionization of the optional antagonist during the time that the composition is in the oral cavity of a user. Maintaining the ionization of the antagonist serves to limit the absorption of the antagonist, and thus provide the desired control of the antagonist. While the ionization of the antagonist is limited, the ionization of the agonist may not be so limited. As such, the resulting dosage form provides absorption of the agonist to the user, while sufficiently reducing and/or preventing absorption of the antagonist. By keeping the antagonist ionized and the local pH at the optimum pH, the antagonist has limited if any absorption, but is still present should the product be abused or taken via a different route of administration. However, when taken as administered, the antagonist has little to no effect in blocking the agonist.

The film dosage composition including an agonist may be configured to provide an in vivo plasma profile having a mean maximum plasma concentration (Cmax) in a desired range. It has been discovered by the Applicants that controlling the Cmax of the film composition allows one to control the absorption of the active (such as an agonist) into the user. The resulting film composition is more effective and suitable for delivery to a user.

As explained, the film dosage composition provides a bioequivalent result to a commercially available Suboxone® product. As will be explained more in the Examples below, commercially available Suboxone® provides different absorption levels depending on the amount of buprenorphine and naloxone administered. The present invention desirably provides a film product providing bioequivalent release as that of the Suboxone® product. As with the Suboxone® product, the buprenorphine may be present in an amount of from about 2 mg to about 16 mg per dosage, or, if desired about 4 mg to about 12 mg per dosage. Additionally, the naloxone may be present in any desired amount, preferably at about 25% the level of buprenorphine. For example, an inventive film product may have 2 mg buprenorphine and 0.5 mg naloxone, 4 mg buprenorphine and 1 mg naloxone, 8 mg buprenorphine and 2 mg naloxone, 12 mg buprenorphine and 3 mg naloxone, 16 mg buprenorphine and 4 mg naloxone, or any similar amounts.

It has further been discovered that, by controlling the mean area under the curve (AUC) value of the film composition, a more effective dosage form may be provided. As is described in more detail in the Examples below, the inventive film composition preferably provides an AUC value so as to provide a bioequivalent result as that provided by the commercially available Suboxone® tablet. In one embodiment, the film composition may include a mean AUCinf value of about 6.8 hr·ng/ml or greater. Alternatively, the film composition may include a mean AUCinf value of from about 6.8 hr·ng/ml to about 66 hr·ng/ml.

As explained above, the film compositions may include naloxone, an antagonist. When the film composition includes a combination of agonist and antagonist, the film composition may be configured to provide a particular Cmax and/or AUCinf for the antagonist. For example, when a buprenorphine agonist and a naloxone antagonist are incorporated into the film composition, the naloxone may be configured to provide a Cmax of less than about 400 pg/ml, less than about 318 pg/ml, less than about 235 pg/ml, less than about 92 pg/ml or less than about 64 pg/ml. In such films, the naloxone may provide a mean AUCinf value of less than about 1030 hr·ng/ml.

In formulations which include an agonist in combination with an antagonist, the film composition may be prepared to provide a desired Cmax and/or AUCinf value for each of the agonist and antagonist. In one embodiment, the film composition provides an in vivo plasma profile having a Cmax of less than about 6.4 ng/ml for the agonist and an in vivo plasma profile having a Cmax of less than about 400 pg/ml for the antagonist. In such embodiments, the formulation may provide an AUCinf value of more than about 6.8 hr·ng/ml for the agonist. If desired, the formulation may provide an AUCinf value of less than about 1030 hr·pg/ml for the antagonist. Such compositions may include the agonist and the antagonist in any desired amount, and in a preferred embodiment, the composition includes about 2 mg to about 16 mg of the agonist per dosage and about 0.5 mg to about 4 mg of the antagonist per dosage.

The present invention provides a method of treating narcotic dependence in a patient. In one embodiment, the patient is dependent on opioid narcotics, but the patient may have a dependence on non-opioid narcotics. Desirably, the patient is treated by providing a dosage to the patient, which provides an effective release of actives but simultaneously provides a suitable adhesion so that the dosage cannot be easily removed. In one method of treatment, an orally dissolvable film composition is provided to a patient.

Depending on the particular narcotic that the patient experiences dependence upon, the film composition may include one or more particular active components. In one embodiment, the film composition includes a polymer carrier matrix and a therapeutically effective amount of an agonist. Desirably the agonist is a partial agonist. For opioid dependency, the agonist may be an opioid agonist, such as buprenorphine or a pharmaceutically acceptable salt thereof. The film composition preferably includes a buffer in an amount sufficient to control the local pH of the film composition. Any buffer system may be used, including sodium citrate, citric acid, and combinations thereof. In compositions solely including an agonist, the local pH of the film composition is desirably about 5 to about 6.5, and most desirably the local pH is about 5.5. At this level, the absorption of the agonist is most effec-

tive. To treat the dependency, the film composition is administered to the patient, most desirably into the oral cavity of the patient.

If desired, the composition may include a therapeutically effective amount of an antagonist, to prevent abuse of the agonist. A "therapeutically effective amount" of an antagonist is intended to refer to an amount of the antagonist that may be useful in diverting abuse of the agonist by a user. The antagonist may be any desired antagonist, and in one embodiment includes naloxone or a pharmaceutically acceptable salt thereof. The film composition is preferably administered to a patient through the oral cavity of the patient, but may be administered in any desired means. The orally dissolvable film composition is then allowed to dissolve in the oral cavity of the patient for a sufficient time so as to release the active(s) therein. In some embodiments, the film composition may remain in the oral cavity for at least 30 seconds, and in some embodiments may remain in the oral cavity for at least 1 minute. After the film composition is placed into the oral cavity of the patient, the film preferably becomes sufficiently adhered so as to render its removal difficult. After the film composition has been administered to the patient, the active(s) are sufficiently released from the composition and allowed to take effect on the patient.

The film compositions of the present invention may be formed via any desired process. Suitable processes are set forth in U.S. Pat. Nos. 7,425,292 and 7,357,891, the entire contents of which are incorporated by reference herein. In one embodiment, the film dosage composition is formed by first preparing a wet composition, the wet composition including a polymeric carrier matrix, a therapeutically effective amount of an agonist, and a buffer in an amount sufficient to control the local pH of the composition to a desired level. The wet composition is cast into a film and then sufficiently dried to form a self-supporting film composition. The wet composition may be cast into individual dosages, or it may be cast into a sheet, where the sheet is then cut into individual dosages. The agonist may be a partial agonist. If desired, the wet composition may include a therapeutically effective amount of an antagonist.

The agonist and the optional antagonist are preferably selected to treat a particular narcotic dependency. For opioid dependency, for example, the agonist may include buprenorphine or a pharmaceutically acceptable salt thereof, while the antagonist may include naloxone or a pharmaceutically acceptable salt thereof. The local pH of the film composition is desirably maintained at about 2 to about 4.

EXAMPLES

Example 1

Composition of Buprenorphine/Naloxone Films at Various Strengths

Film strips including a combination of buprenorphine and naloxone were prepared. Four different strength film compositions were prepared, which include a ratio of buprenorphine to naloxone of 16/4, 12/3, 8/2, and 2/0.5. The compositions are summarized in Table 1 below.

TABLE 1

Various Compositions of Film Dosages

	Buprenorphine/ Naloxone Films Unit Formula (mg per film strip) Buprenorphine/ Naloxone Ratios			
Components	16/4	12/3	8/2	2/0.5
Active Components				
Buprenorphine HCl	17.28	12.96	8.64	2.16
Naloxone HCl Dihydrate	4.88	3.66	2.44	0.61
Inactive Components				
Polyethylene Oxide, NF (MW 200,000)	27.09	20.32	13.55	—
Polyethylene Oxide, NF (MW 100,000)	12.04	9.03	6.02	19.06
Polyethylene Oxide, NF (MW 900,000)	4.82	3.62	2.41	2.05
Maltitol, NF	12.04	9.03	6.02	5.87
Flavor	6.0	4.5	3.0	2.4
Citric Acid, USP	5.92	4.44	2.96	2.96
HPMC	4.22	3.16	2.11	2.34
Ace-K	3.0	2.25	1.5	1.2
Sodium Citrate, anhydrous	2.68	2.01	1.34	1.34
Colorant	0.03	0.02	0.01	0.01
Total (mg)	100	75	50	40

Example 2

Absorption Studies for Suboxone® Products

Various film and tablet products were prepared and tested for absorption data, including Cmax and AUC absorption levels. The products tested included Suboxone® tablets made with either 2 mg or 16 mg buprenorphine as well as either 0.5 mg or 4.0 mg naloxone. For 16 mg buprenorphine tablets, two 8 mg buprenorphine tablets were combined together to provide the level of components of a 16 mg buprenorphine tablet. In instances where a 12 mg buprenorphine tablet was evaluated, this dosage was obtained by combining one 8 mg buprenorphine tablet and two 2 mg buprenorphine tablets. These products were tested for absorption levels, with the amounts listed in Table 2 below.

TABLE 2

Absorption Data for Suboxone ® products

Sample	C max	AUC
Buprenorphine (2 mg) Suboxone ® Tablet	0.780 ng/ml	6.789 hr * ng/ml
Naloxone (0.5 mg) Suboxone ® Tablet	51.30 pg/ml	128.60 hr * pg/ml
Buprenorphine (16 mg) Suboxone ® Tablet	4.51 ng/ml	44.99 hr * ng/ml
Naloxone (4 mg) Suboxone ® Tablet	259.00 pg/ml	649.60 hr * pg/ml

Using the data from Table 2, absorption data for the Suboxone® tablets for other levels of buprenorphine and naloxone are set forth in Table 2A below.

TABLE 2A

Extrapolated Absorption Data for Suboxone ® products

Sample	C max	AUC
Buprenorphine (4 mg) Suboxone ® Tablet	1.35 ng/ml	12.25 hr * ng/ml
Naloxone (1 mg) Suboxone ® Tablet	80.97 pg/ml	203 hr * pg/ml
Buprenorphine (8 mg) Suboxone ® Tablet	2.29 ng/ml	23.17 hr * ng/ml
Naloxone (2 mg) Suboxone ® Tablet	140.31 pg/ml	351.8 hr * pg/ml
Buprenorphine (12 mg) Suboxone ® Tablet	3.23 ng/ml	34.08 hr * ng/ml
Naloxone (3 mg) Suboxone ® Tablet	199.7 pg/ml	500.6 hr * pg/ml

Example 3

Evaluation of Bioequivalence of Suboxone® Tablets

Using the data generated for Suboxone® tablets in Table 2 above, acceptable bioequivalence ranges are generated to provide an equivalent treatment level as the Suboxone® tablet. As currently understood, a product provides a bioequivalent effect if it provides absorption levels between about 80% to about 125% of the Suboxone® tablet. Absorption in this range is considered to be bioequivalent.

TABLE 3

Acceptable Bioequivalence Ranges for Suboxone ® Tablets (80 to 125%)

Description of Sample	C max	AUC
Buprenorphine 2 mg	0.624 to 0.975 ng/ml	5.431 to 8.486 hr * ng/ml
Naloxone 0.5 mg	41.04 to 64.13 pg/ml	102.88 to 160.75 hr * pg/ml
Buprenorphine 16 mg	3.608 to 5.638 ng/ml	35.992 to 56.238 hr * ng/ml
Naloxone 4 mg	207.20 to 323.75 pg/ml	519.68 to 812.00 hr * pg/ml

Thus, to be considered bioequivalent to the Suboxone® tablet, the Cmax of buprenorphine is between about 0.624 and 5.638, and the AUC of buprenorphine is between about 5.431 to about 56.238. Similarly, to be considered bioequivalent to the Suboxone® tablet, the Cmax of naloxone is between about 41.04 to about 323.75, and the AUC of naloxone is between about 102.88 to about 812.00.

Example 4

Absorption Studies for Film Products at pH 3.5

Various film products were prepared and tested for absorption data, including Cmax and AUC absorption levels. The products tested included inventive film strips, the film strips having either 2 mg or 16 mg buprenorphine as well as either 0.5 mg or 4.0 mg naloxone. These products were tested for absorption levels, with the amounts listed in Table 4 below.

TABLE 4

Absorption Data for inventive film products at pH 3.5

Sample	C max	AUC
Buprenorphine (2 mg) Sublingual Film	0.947 ng/ml	7.82 hr * ng/ml
Naloxone (0.5 mg) Sublingual Film	51.10 pg/ml	128.60 hr * pg/ml
Buprenorphine (16 mg) Sublingual Film	5.47 ng/ml	55.30 hr * ng/ml
Naloxone (4 mg) Sublingual Film	324.00 pg/ml	873.60 hr * pg/ml

As can be seen, in this experiment, the values for buprenorphine absorbance were squarely in the bioequivalence range evaluated above. The inventive films were therefore determined to have provided a bioequivalent absorption of buprenorphine at a local pH of 3.5 as the commercially available Suboxone® tablet. The values for absorption of naloxone were very close to the bioequivalent range of Suboxone®. The slightly higher absorption of Naloxone was not due to the local pH but rather to the amount of buffer (buffer capacity as discussed in the application). This is confirmed by the fact that the lower 2/0.5 mg dose is in range for the Naloxone and this is due to the higher buffer capacity for the 2/0.5 dose as pointed out in the buffer capacity chart.

Example 5

Preparation of Films for In Vivo Study

Film dosages were prepared for use in an in vivo study to determine the bioavailability of buprenorphine/naloxone tablets and film formulations. Specifically, the films were tested to determine whether the film provides a bioequivalent effect to that of a tablet formulation.

Three film formulations including 8 mg buprenorphine and 2 mg naloxone were prepared, each being buffered to a different pH. The first film did not include any buffer, providing a local pH of about 6.5. The second was buffered to a local pH level of about 3-3.5. The third was buffered to a local pH value of about 5-5.5. The formulations are set forth in Table 5 below.

TABLE 5

Formulations of Test Films at Various pH Levels

	Test formulation 1 8 mg/2 mg pH = 6.5		Test formulation 2 8 mg/2 mg pH = 3-3.5		Test formulation 3 8 mg/2 mg pH = 5-5.5	
Component	% w/w	Mg/film	% w/w	Mg/film	% w/w	Mg/film
Buprenorphine HCl	21.61	8.64	17.28	8.64	17.28	8.64
Naloxone HCl Dihydrate	6.10	2.44	4.88	2.44	4.88	2.44
Polymer	5.05	2.02	4.82	2.41	4.82	2.41
Polymer	28.48	11.39	27.09	13.55	27.09	13.55
Polymer	12.65	5.06	12.04	6.02	12.04	6.02
Polymer	4.43	1.77	4.22	2.11	4.22	2.11
Sweetener	12.65	5.06	12.04	6.02	12.04	6.02
Sweetener	3	1.2	3	1.5	3	1.5
Flavor	6	2.4	6	3	6	3
Citric acid	0	0	5.92	2.96	2.51	1.26
Sodium citrate	0	0	2.68	1.34	6.08	3.04
FD&C yellow #6	0.025	0.01	0.03	0.02	0.03	0.02
Total	100	40	100	50	100	50

Example 6

Analysis of In Vivo Absorption of Film Having a pH of 6.5

The film dosage composition of film having a local pH of 6.5 was analyzed. Specifically, Test Formulation 1, as prepared in Example 5 was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative film was compared to the absorption of buprenorphine and of naloxone provided by a one dose tablet (Suboxone®). The test film was compared to determine whether it provided a bioequivalent effect as the tablet product.

The results for Test Formulation 1, which had a local pH of about 6.5, as compared to the one dose tablet, are set forth in Tables 6 and 7 below.

TABLE 6

Buprenorphine In Vivo Absorption Data for Test Formulation 1

	Suboxone ® sublingual				Test Formulation 1 (pH = 6.5)			
Parameter	n	Mean	SD	CV %	n	Mean	SD	CV %
T_{max} (hr)	15	1.60	0.47	29.41	15	1.50	0.62	41.23
C_{max} (ng/mL)	15	2.27	0.562	24.77	15	2.60	0.872	33.53
AUC_{last} (hr * ng/mL)	15	27.08	10.40	38.41	15	31.00	12.93	41.72
AUC_{inf} (hr * ng/mL)	15	29.58	11.15	37.68	15	33.37	13.88	41.61
$T_{1/2}$ (hr)	15	44.76	20.86	46.60	15	40.73	14.93	36.66

TABLE 7

Naloxone In Vivo Absorption Data for Test Formulation 1

	Suboxone ® sublingual				Test Formulation 1 (pH = 6.5)			
Parameter	n	Mean	SD	CV %	n	Mean	SD	CV %
T_{max} (hr)	15	0.90	0.23	25.32	15	0.68	0.18	25.75
C_{max} (pg/mL)	15	94.6	39.1	41.33	15	410	122	29.75
AUC_{last} (hr * pg/mL)	15	297.1	120.7	40.62	15	914.8	158.1	17.29
AUC_{inf} (hr * pg/mL)	15	306.1	122.6	40.06	15	924.2	158.8	17.18
$T_{1/2}$ (hr)	15	6.62	2.60	39.26	15	6.86	2.08	30.27

As can be seen, the in vivo data indicates that buprenorphine is absorbed very well from the film formulation at a local pH of 6.5, and matched closely the absorption seen in the Suboxone® one dose tablet. However, the absorption was also maximized for the naloxone, which was undesirable. It was determined that a film having a combination of buprenorphine and naloxone and a local pH of 6.5 did not provide a bioequivalent effect as the Suboxone® tablet for both buprenorphine and naloxone.

Example 7

Analysis of In Vivo Absorption of Film Having a pH of 5-5.5

Having determined the absorption of buprenorphine and naloxone in film having a local pH of 6.5, a film dosage composition of film having a local pH of 5-5.5 was analyzed. Specifically, Test Formulation 3, as prepared in Example 5 was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative films were compared to the absorption of buprenorphine and of naloxone provided by the Suboxone® one dose tablet. The test film was compared to determine whether it provided a bioequivalent effect as the Suboxone® tablet.

The results for Test Formulation 3, which had a local pH of about 5-5.5, as compared to the Suboxone® tablet, are set forth in Tables 8 and 9 below.

TABLE 8

Buprenorphine In Vivo Absorption Data for Test Formulation 3

	Suboxone ® sublingual				Test Formulation 3 (pH = 5-5.5)			
Parameter	n	Mean	SD	CV %	n	Mean	SD	CV %
T_{max} (hr)	15	1.60	0.47	29.41	14	1.50	0.43	28.50
C_{max} (ng/mL)	15	2.27	0.562	24.77	14	3.47	1.57	45.40
AUC_{last} (hr * ng/mL)	15	27.08	10.40	38.41	14	33.25	16.01	48.16

TABLE 8-continued

Buprenorphine In Vivo Absorption Data for Test Formulation 3

	Suboxone ® sublingual				Test Formulation 3 (pH = 5-5.5)			
Parameter	n	Mean	SD	CV %	n	Mean	SD	CV %
AUC_{inf} (hr * ng/mL)	15	29.58	11.15	37.68	13	38.34	15.38	40.13
$T_{1/2}$ (hr)	15	44.76	20.86	46.60	13	41.71	17.70	42.42

TABLE 9

Naloxone In Vivo Absorption Data for Test Formulation 3

	Suboxone ® sublingual				Test Formulation 3 (pH = 5-5.5)			
Parameter	n	Mean	SD	CV %	n	Mean	SD	CV %
T_{max} (hr)	15	0.90	0.23	25.32	14	0.98	0.62	63.51
C_{max} (pg/mL)	15	94.6	39.1	41.33	14	173	84.5	48.79
AUC_{last} (hr * pg/mL)	15	297.1	120.7	40.62	14	455.2	195.5	42.94
AUC_{inf} (hr * pg/mL)	15	306.1	122.6	40.06	13	474.4	203.1	42.81
$T_{1/2}$ (hr)	15	6.62	2.60	39.26	13	9.45	6.90	73.00

As can be seen, the in vivo data indicated that the absorption of buprenorphine increased as the local pH level decreased. It appeared that by decreasing the local pH from 6.5 to 5.5, the absorption of buprenorphine was being moved to a level further away from that of the one dose tablet. In addition, the naloxone values did not provide a bioequivalent result as the one dose tablet. Thus, it was determined that the film having a local pH of 5.5 did not provide a bioequivalent result as that of the Suboxone® tablet for both buprenorphine and naloxone.

It was noted that by reducing the local pH of the film to a level of 5.5, there would be provided an increased level of absorption of buprenorphine. Thus, it may be desirable to buffer a film composition incorporating buprenorphine itself to a level of about 5.5 to provide an increased absorption.

Example 8

Analysis of In Vivo Absorption of Film Having a pH of 3-3.5

Having determined the absorption of buprenorphine and naloxone in films having a local pH of 6.5 and 5.5, a film dosage composition of film having a local pH of about 3-3.5 was analyzed. It was assumed that the absorption of buprenorphine would continue to be increased as it had demonstrated at a local pH of 5.5. Thus, it was assumed that at a local pH of 3.5, the film would not be bioequivalent to that of the tablet.

Specifically, Test Formulation 2, as prepared in Example 5, was analyzed in vivo to determine the absorption of buprenorphine and of naloxone. The comparative films were compared to the absorption of buprenorphine and of naloxone provided by the Suboxone® one dose tablet. The test film was compared to determine whether it provided a bioequivalent effect as the tablet product.

The results for Test Formulation 2, which had a local pH of about 3-3.5, as compared to the Suboxone® tablet, are set forth in Tables 10 and 11 below.

TABLE 10

Buprenorphine In Vivo Absorption Data for Test Formulation 2

	Suboxone ® sublingual				Test Formulation 2 (pH = 3-3.5)			
Parameter	n	Mean	SD	CV %	n	Mean	SD	CV %
T_{max} (hr)	15	1.60	0.47	29.41	14	1.68	0.58	34.68
C_{max} (ng/mL)	15	2.27	0.562	24.77	14	2.68	0.910	33.99
AUC_{last} (hr * ng/mL)	15	27.08	10.40	38.41	14	29.73	12.05	40.54
AUC_{inf} (hr * ng/mL)	15	29.58	11.15	37.68	14	31.45	12.98	41.26
$T_{1/2}$ (hr)	15	44.76	20.86	46.60	14	30.03	13.95	46.46

TABLE 11

Naloxone In Vivo Absorption Data for Test Formulation 2

	Suboxone ® sublingual				Test Formulation 2 (pH = 3-3.5)			
Parameter	n	Mean	SD	CV %	n	Mean	SD	CV %
T_{max} (hr)	15	0.90	0.23	25.32	14	0.84	0.19	22.19
C_{max} (pg/mL)	15	94.6	39.1	41.33	14	130	72.9	56.04
AUC_{last} (hr * pg/mL)	15	297.1	120.7	40.62	14	362.2	155.9	43.03
AUC_{inf} (hr * pg/mL)	15	306.1	122.6	40.06	12	350.4	142.3	40.61
$T_{1/2}$ (hr)	15	6.62	2.60	39.26	12	8.07	4.75	58.84

As can be seen, the in vivo data indicated that the absorption of buprenorphine was substantially bioequivalent to that of the one dose tablet when the film composition local pH was lowered to about 3-3.5. This result was surprising as it did not appear to follow the pH partition theory. Further, at a local pH of about 3-3.5, it was seen that the absorption of naloxone was substantially bioequivalent to that of the one dose tablet.

Thus, it was determined that the film product including buprenorphine and naloxone at a local pH of 3-3.5 was substantially bioequivalent to that of the Suboxone® one dose tablet.

Example 9

Normalized Values for Naloxone in Films and Tablets

Various film compositions including buprenorphine and naloxone in 8/2 mg and 2/0.5 mg dosages, and having different local pH values from 6.5 to 3.5, were prepared and analyzed. The data was normalized and compared to the one dose tablet. The results are set forth in Table 12 below.

TABLE 12

Normalized Values for Naloxone Film Compared to Tablet

pH	Dose (mg) Buprenorphine/Naloxone	AUC (Normalized)	Cmax	Mg Citric Acid	Ratio Citric Acid(mg)/ Naloxone (mg)
6.5	8/2	3.02	4.33	1.34	0.67
5.5	8/2	1.55	1.83	1.34	0.67
3.5	8/2	1.14	1.37	1.34	0.67
3.5	2/0.5	0.98	0.90	1.34	2.68
5.5	2/0.5	1.41	1.41	1.34	2.68

The data indicates that not only is the local pH of significant importance, but the amount of buffer present in the formula is also important. The improvement from the 8/2 dose to the 2/0.5 dose (at a local pH of 3.5) demonstrates this importance. The 8/2 dose has a ratio of buffer/naloxone of 0.67, and this dose provided borderline acceptable bioequivalent results. In contrast, the 2/0.5 dose has a ratio of buffer/naloxone of 2.68, and provides a more bioequivalent absorption value than the 8/2 dose.

In fact, the data shows that the 2/0.5 dose at a local pH of 3.5 had an even lower buccal absorption than the one dose tablet, as seen from the normalized values for the AUC and Cmax. This demonstrates that even less absorption of the naloxone occurs for the film formulation at a local pH of 3.5 than the tablet formulation. Given the goal of reducing the absorption of naloxone, it appears that the film product buffered at a local pH of 3.5 with a buffer ratio of buffer/Naloxone of 2.68 provides even better results than the Suboxone® tablet formulation.

What is claimed is:

1. A film dosage composition comprising:
a. A polymeric carrier matrix;
b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
d. A buffer in an amount to provide a local pH for said composition of a value sufficient to optimize absorption of said buprenorphine, wherein said local pH is from about 3 to about 3.5 in the presence of saliva.

2. The composition of claim **1**, wherein said film dosage composition provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.

3. The composition of claim **1**, wherein said polymeric carrier matrix comprises at least one polymer in an amount of at least 25% by weight of said composition.

4. The composition of claim **1**, wherein said buffer is present in an amount of from about 2:1 to about 1:5 by weight of buffer to buprenorphine.

5. The composition of claim **1**, wherein said polymeric carrier matrix comprises at least one self-supporting film forming polymer.

6. The film dosage composition of claim **1**, wherein said buprenorphine is present in an amount of from about 2 mg to about 16 mg per dosage.

7. The film dosage composition of claim **1**, wherein said buffer comprises sodium citrate, citric acid, and combinations thereof.

8. The film dosage composition of claim **1**, wherein said buffer comprises acetic acid, sodium acetate, and combinations thereof.

9. A method of treating narcotic dependence of a user, comprising the steps of:
a. providing a composition comprising:
i. A polymeric carrier matrix;
ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
iv. A buffer in an amount to provide a local pH of about 3 to about 3.5 for said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and
b. administering said composition to the oral cavity of a user.

10. The composition of claim **9**, wherein said method provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.

11. The method of claim **9**, wherein said film dosage composition is administered to the user through buccal administration, sublingual administration, and combinations thereof.

12. The method of claim **9**, wherein said film dosage composition remains in the oral cavity of the user for a period of at least 1 minute.

13. The method of claim **9**, wherein said film dosage composition remains in the oral cavity of the user for a period of between about 1 and 1.5 minutes.

14. The method of claim **9**, wherein said film dosage composition remains in the oral cavity of the user for a period of up to 3 minutes.

15. An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.

16. The formulation of claim **15**, wherein said formulation provides a mean AUC of between about 5.431 hr·ng/ml to about 56.238 hr·ng/ml for buprenorphine.

17. The formulation of claim **15**, wherein said formulation provides a mean AUC of between about 102.88 hr·pg/ml to about 812.00 hr·pg/ml for naloxone.

18. The formulation of claim **15**, wherein said formulation comprises about 2 to about 16 mg of buprenorphine or a salt thereof.

19. The formulation of claim **15**, wherein said formulation comprises about 0.5 to about 4 mg of naloxone or a salt thereof.

* * * * *

EXHIBIT D

US008603514B2

(12) **United States Patent**
Yang et al.

(10) **Patent No.: US 8,603,514 B2**
(45) **Date of Patent: Dec. 10, 2013**

(54) **UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS**

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(73) Assignee: **MonoSol RX, LLC**, Warren, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 779 days.

(21) Appl. No.: **11/775,484**

(22) Filed: **Jul. 10, 2007**

(65) **Prior Publication Data**

US 2008/0044454 A1 Feb. 21, 2008

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/768,809, filed on Jan. 30, 2004, now Pat. No. 7,357,891, and a continuation-in-part of application No. PCT/US02/32575, filed on Oct. 11, 2002, and a continuation-in-part of application No. 10/074,272, filed on Feb. 14, 2002, now Pat. No. 7,425,292, said application No. 10/768,809 is a continuation-in-part of application No. PCT/US02/32594, filed on Oct. 11, 2002, and a continuation-in-part of application No. 10/074,272, said application No. 10/768,809 is a continuation-in-part of application No. PCT/US02/32542, filed on Oct. 11, 2002, and a continuation-in-part of application No. 10/074,272, application No. 11/775,484, which is a continuation-in-part of application No. 10/856,176, filed on May 28, 2004, now Pat. No. 7,666,337, and a continuation-in-part of application No. 10/768,809.

(60) Provisional application No. 60/443,741, filed on Jan. 30, 2003, provisional application No. 60/386,937, filed on Jun. 7, 2002, provisional application No. 60/328,868, filed on Oct. 12, 2001, provisional application No. 60/414,276, filed on Sep. 27, 2002, provisional application No. 60/473,902, filed on May 28, 2003.

(51) **Int. Cl.**
A61F 13/00 (2006.01)
A61K 9/00 (2006.01)
A61K 9/70 (2006.01)

(52) **U.S. Cl.**
USPC **424/435**; 424/484

(58) **Field of Classification Search**
None
See application file for complete search history.

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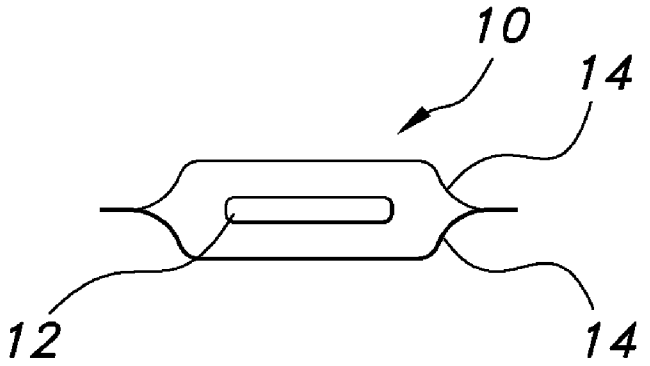
Primary Examiner — Anand Desai
Assistant Examiner — Melissa Mercier
(74) *Attorney, Agent, or Firm* — Hoffmann & Baron, LLP

(57) **ABSTRACT**

The present invention relates to rapid dissolve thin film drug delivery compositions for the oral administration of active components. The active components are provided as taste-masked or controlled-release coated particles uniformly distributed throughout the film composition. The compositions may be formed by wet casting methods, where the film is cast and controllably dried, or alternatively by an extrusion method.

76 Claims, 34 Drawing Sheets



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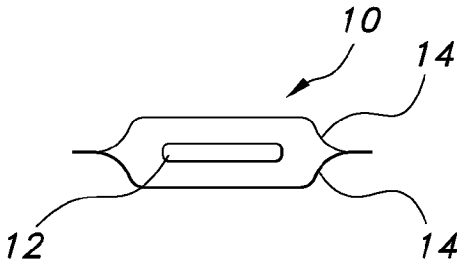
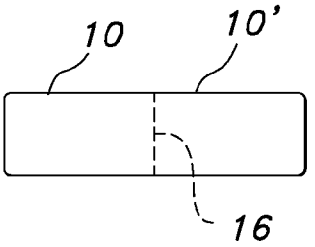


FIG. 1



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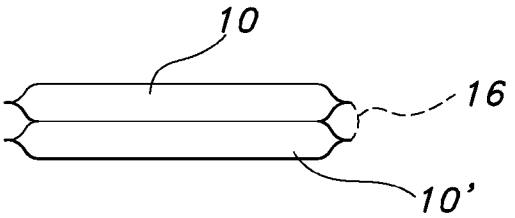

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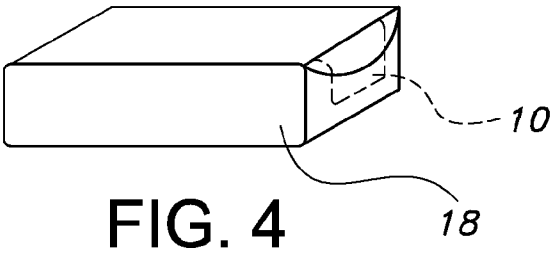

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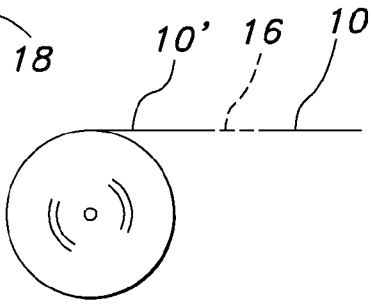

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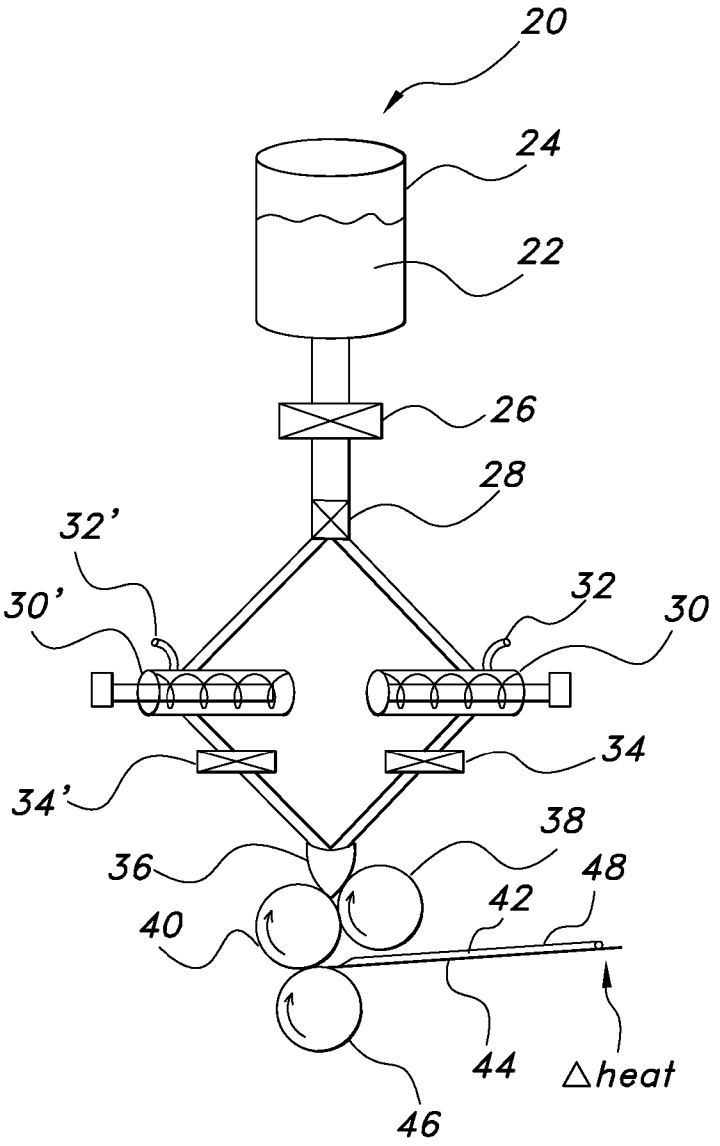

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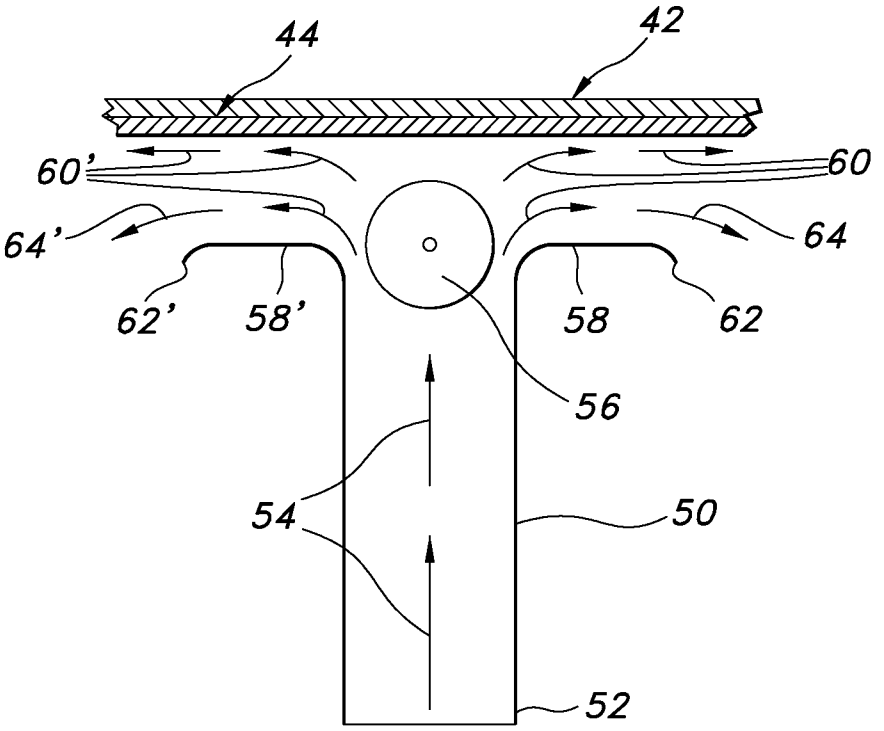

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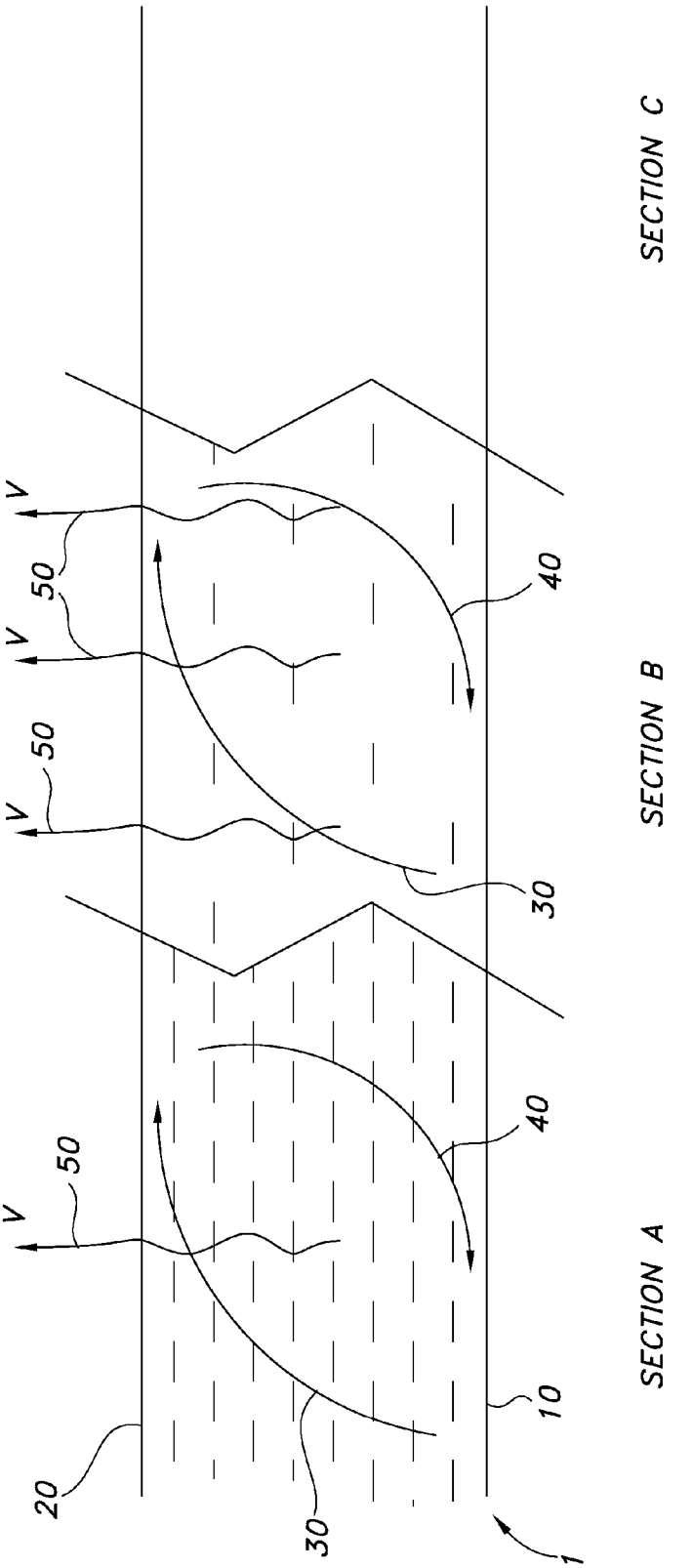

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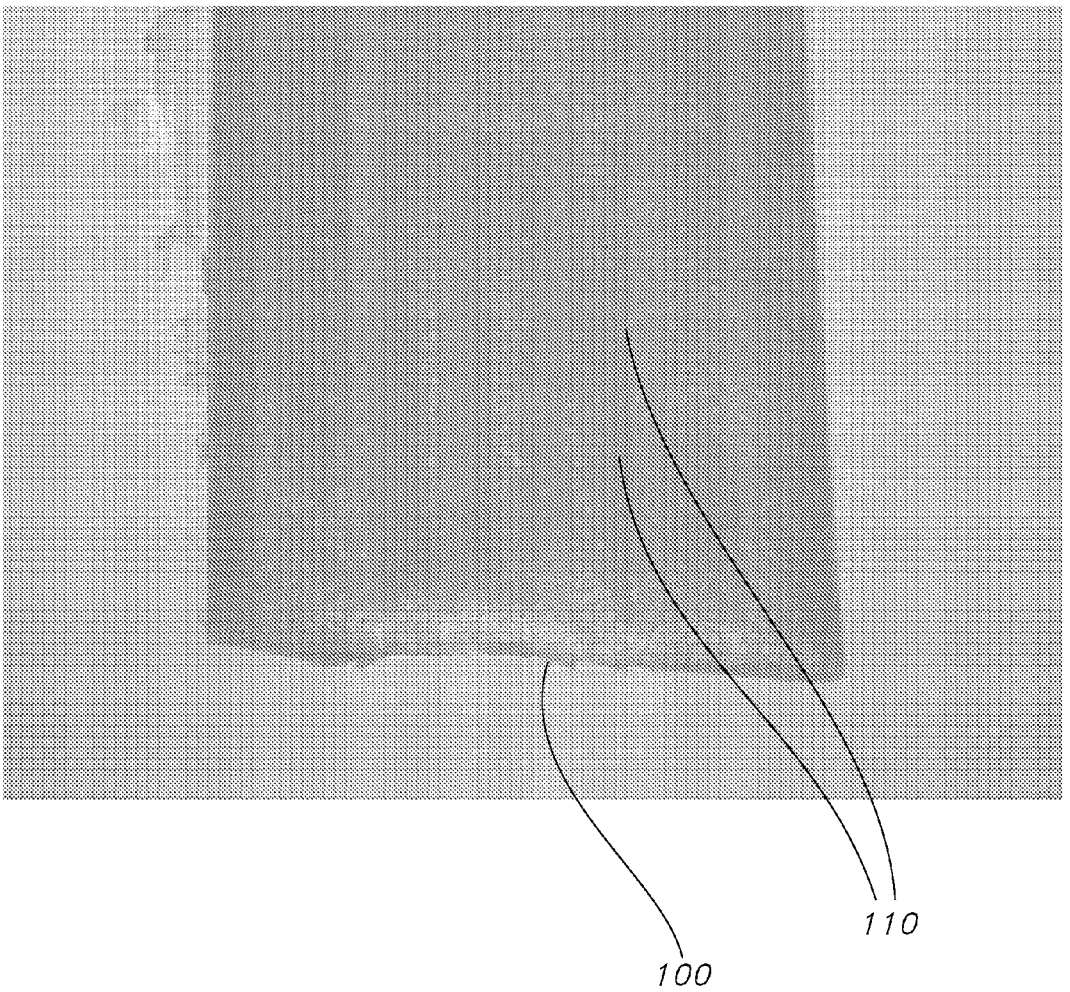

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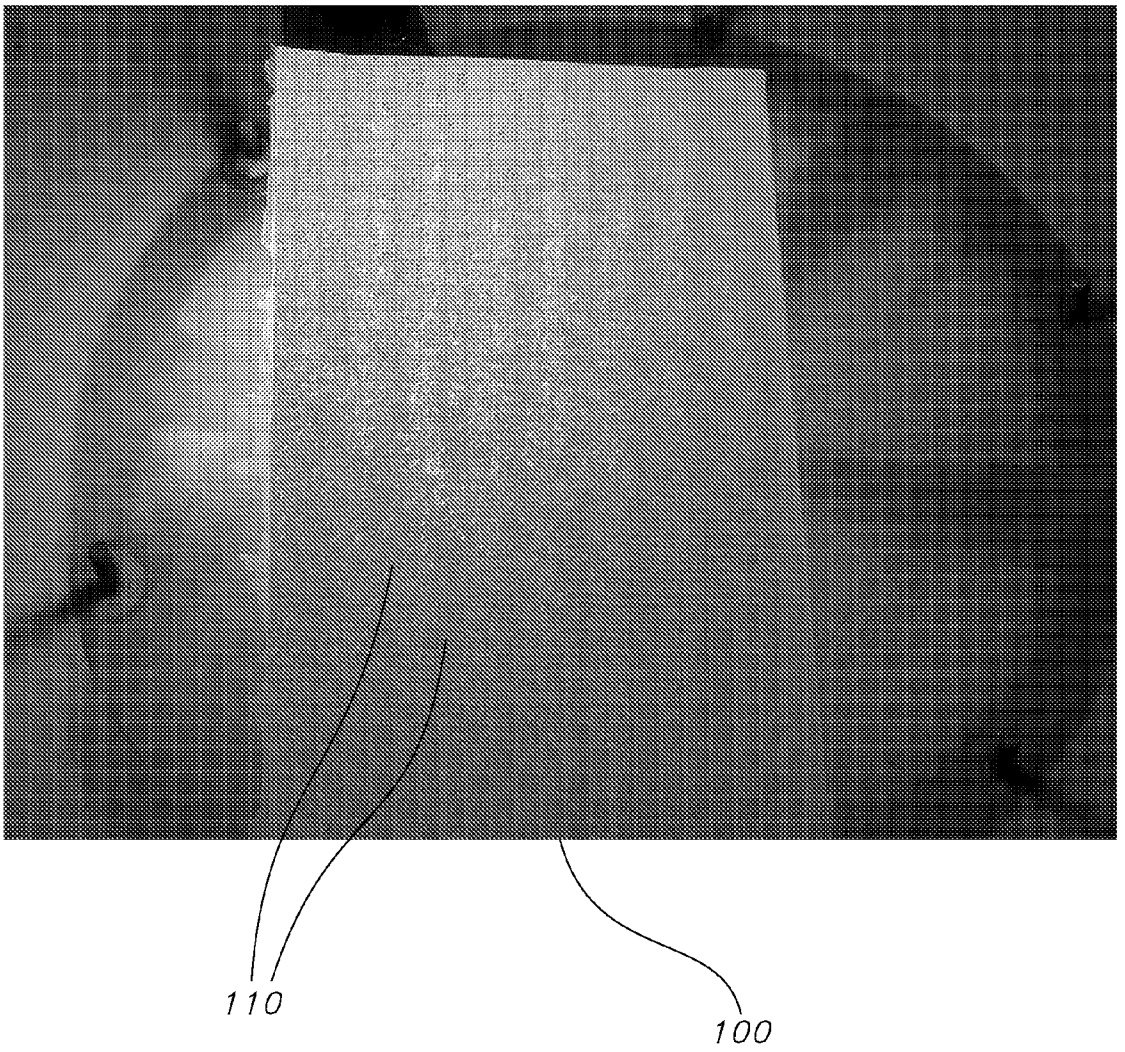


FIG. 10

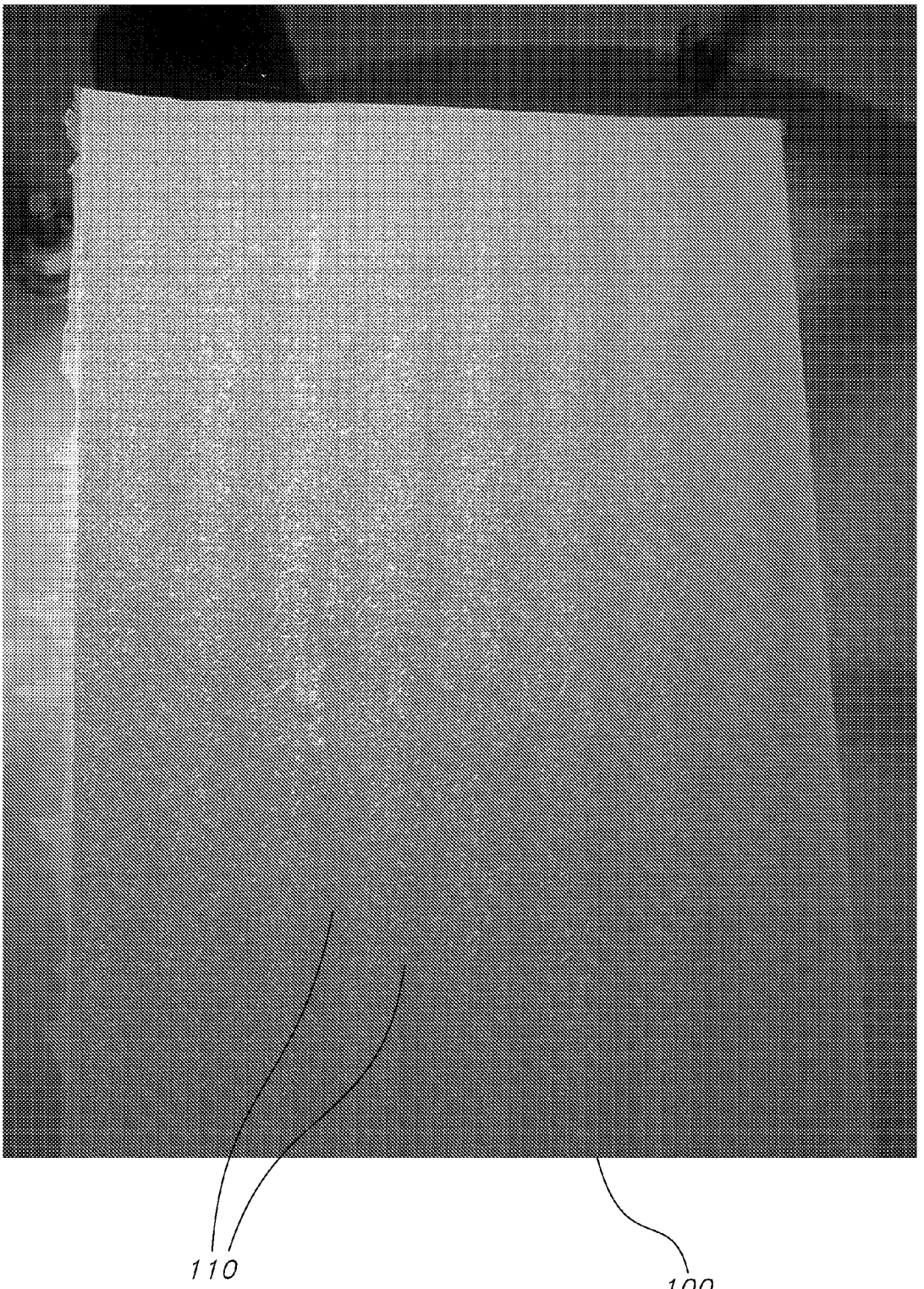


FIG. 11

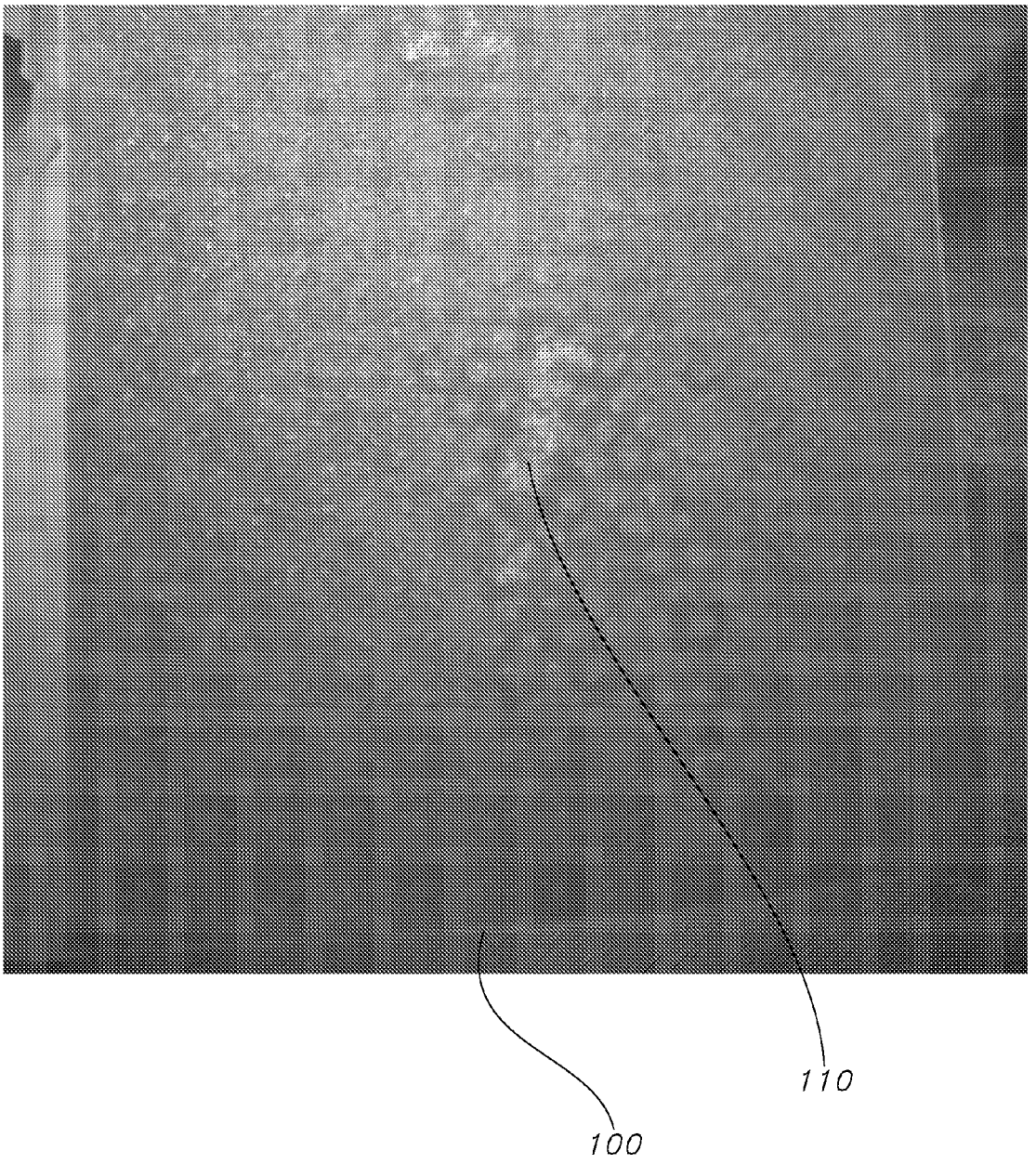


FIG. 12

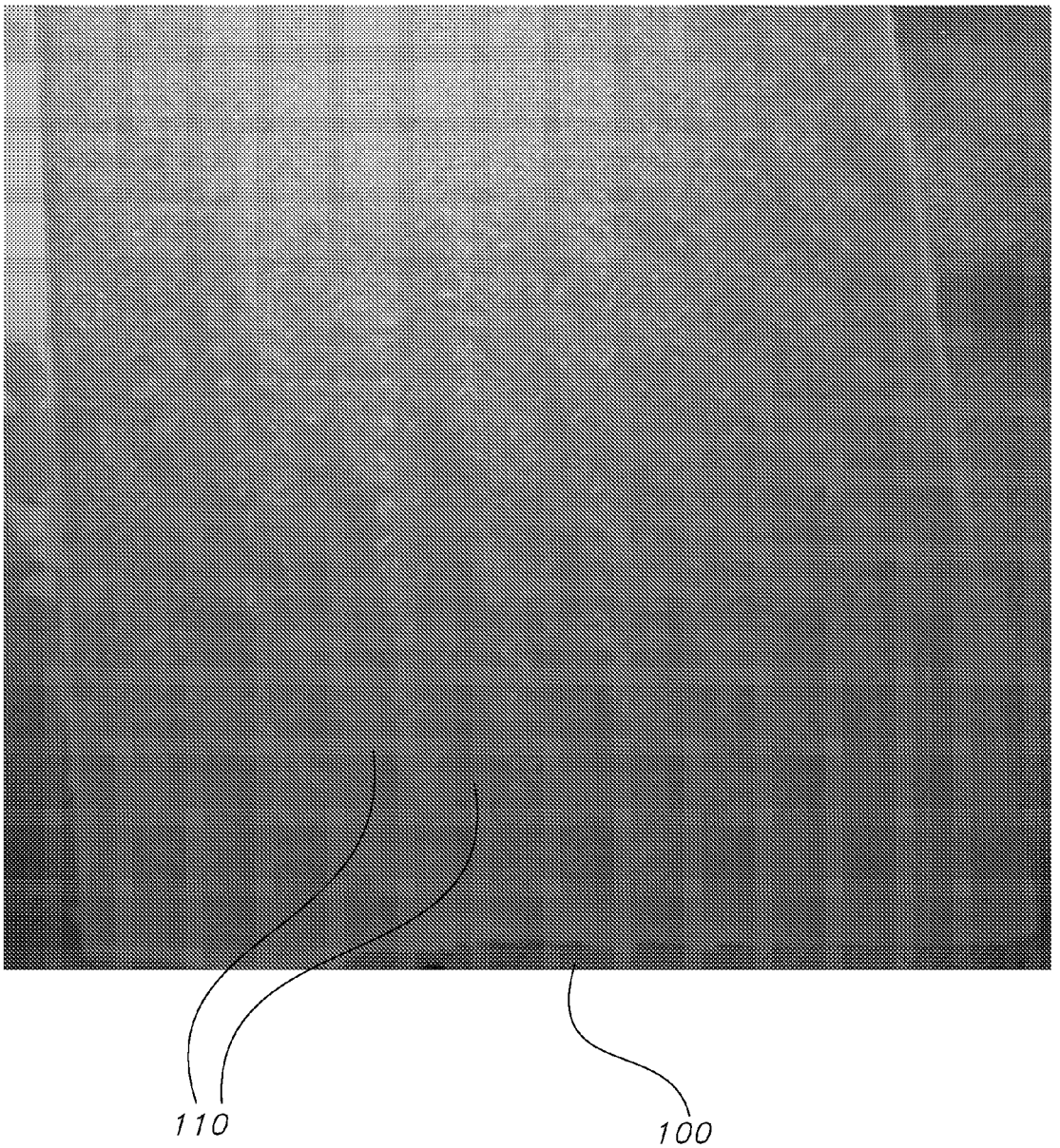


FIG. 13

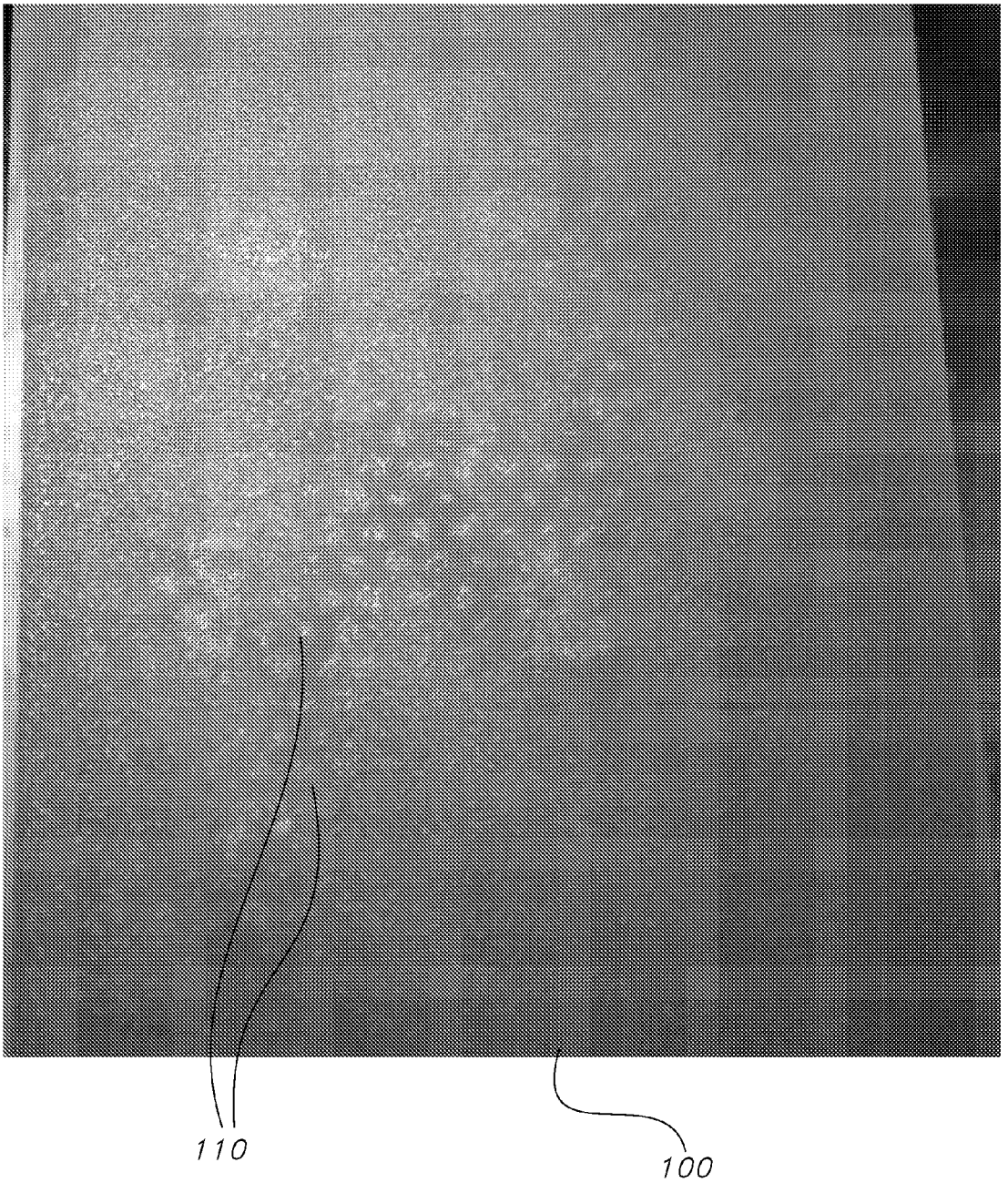


FIG. 14

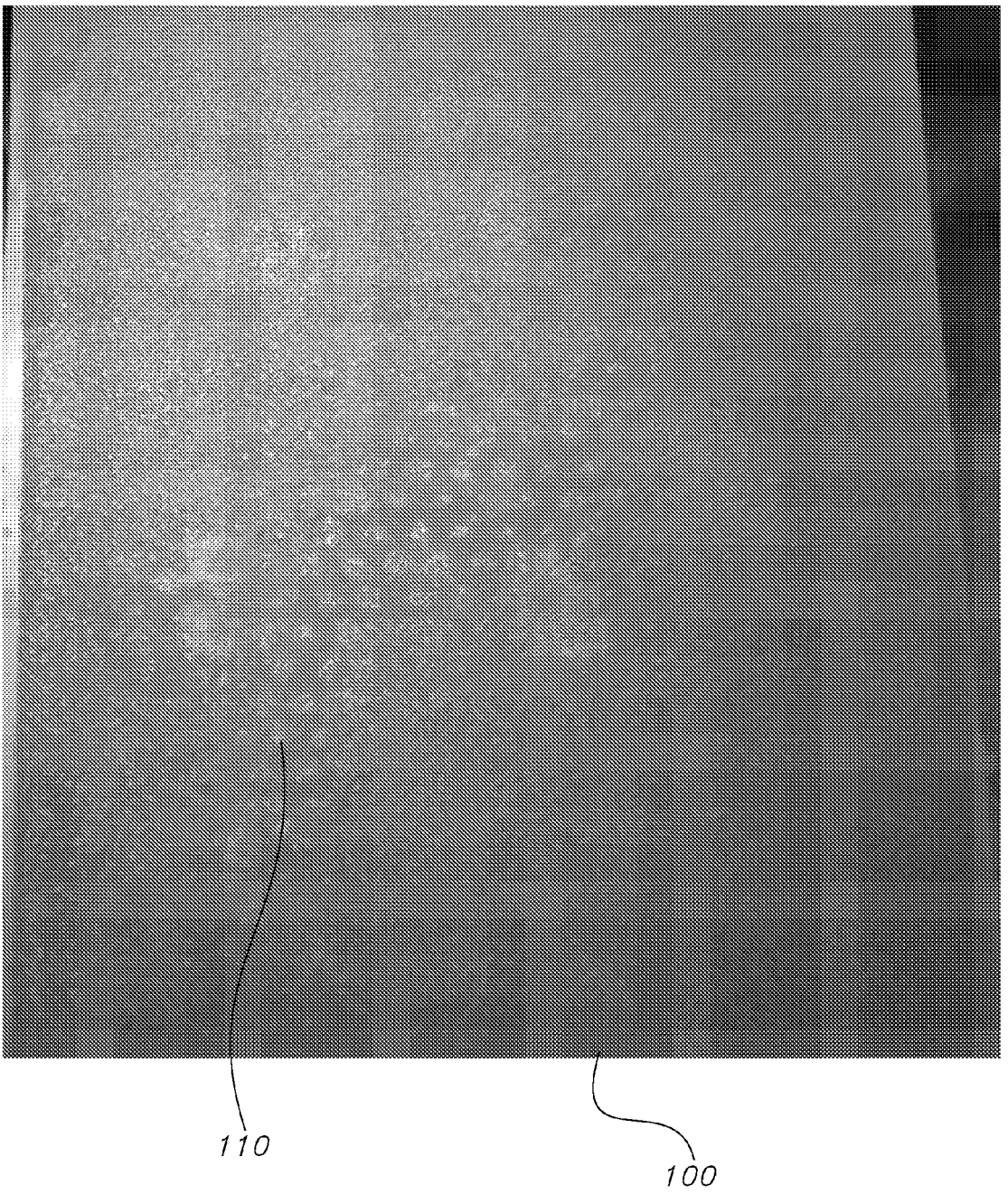


FIG. 15

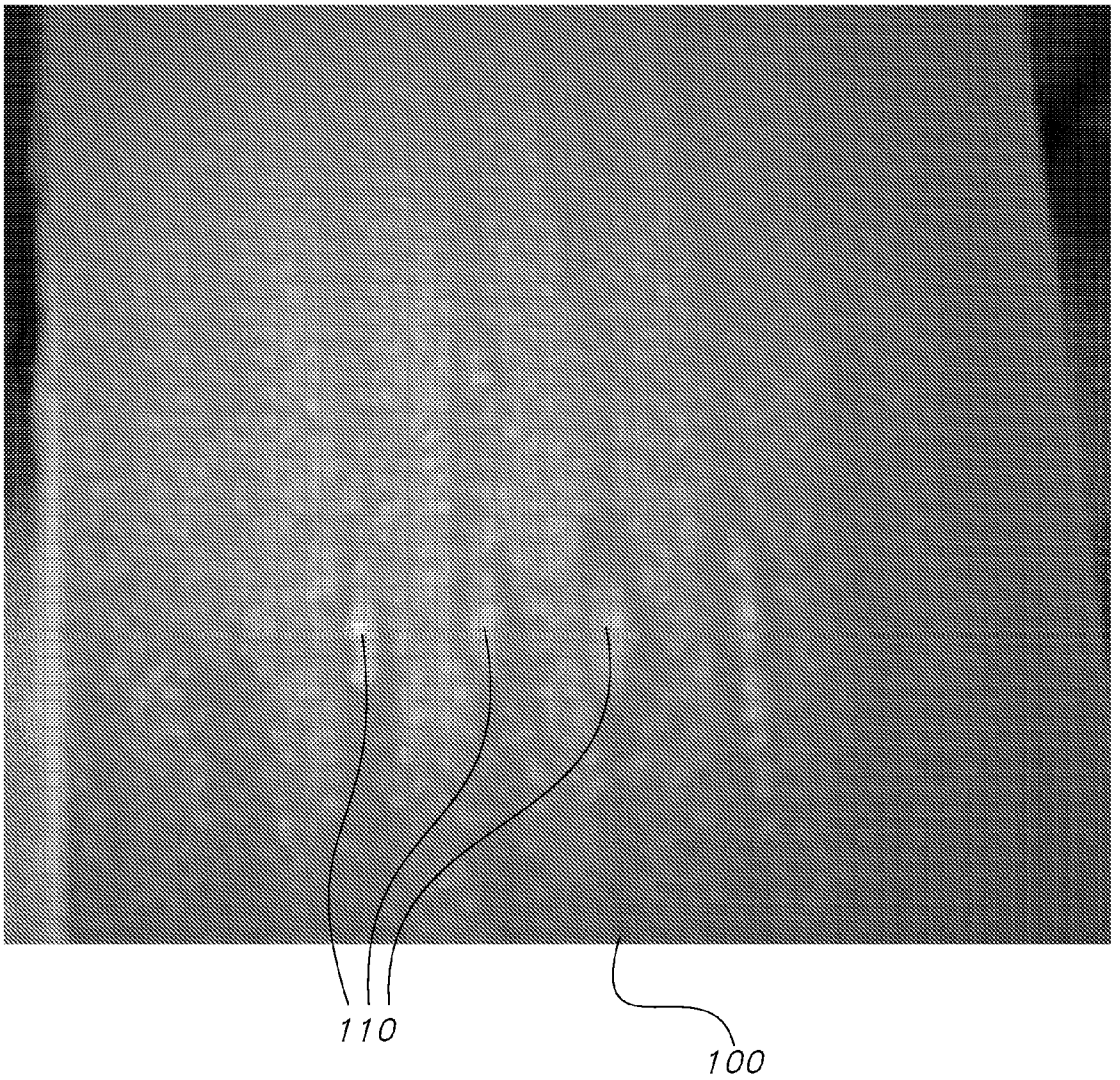


FIG. 16

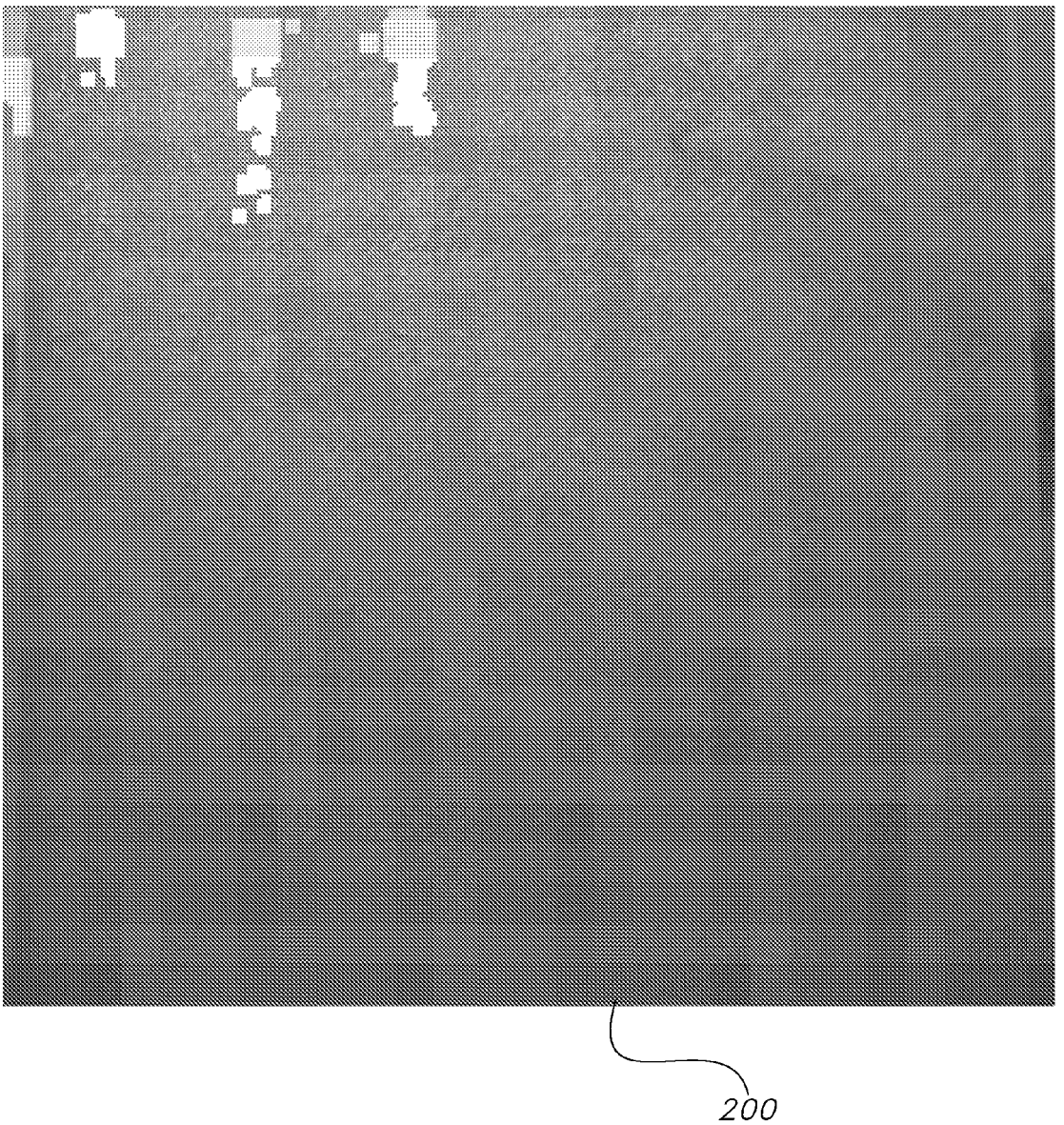


FIG. 17

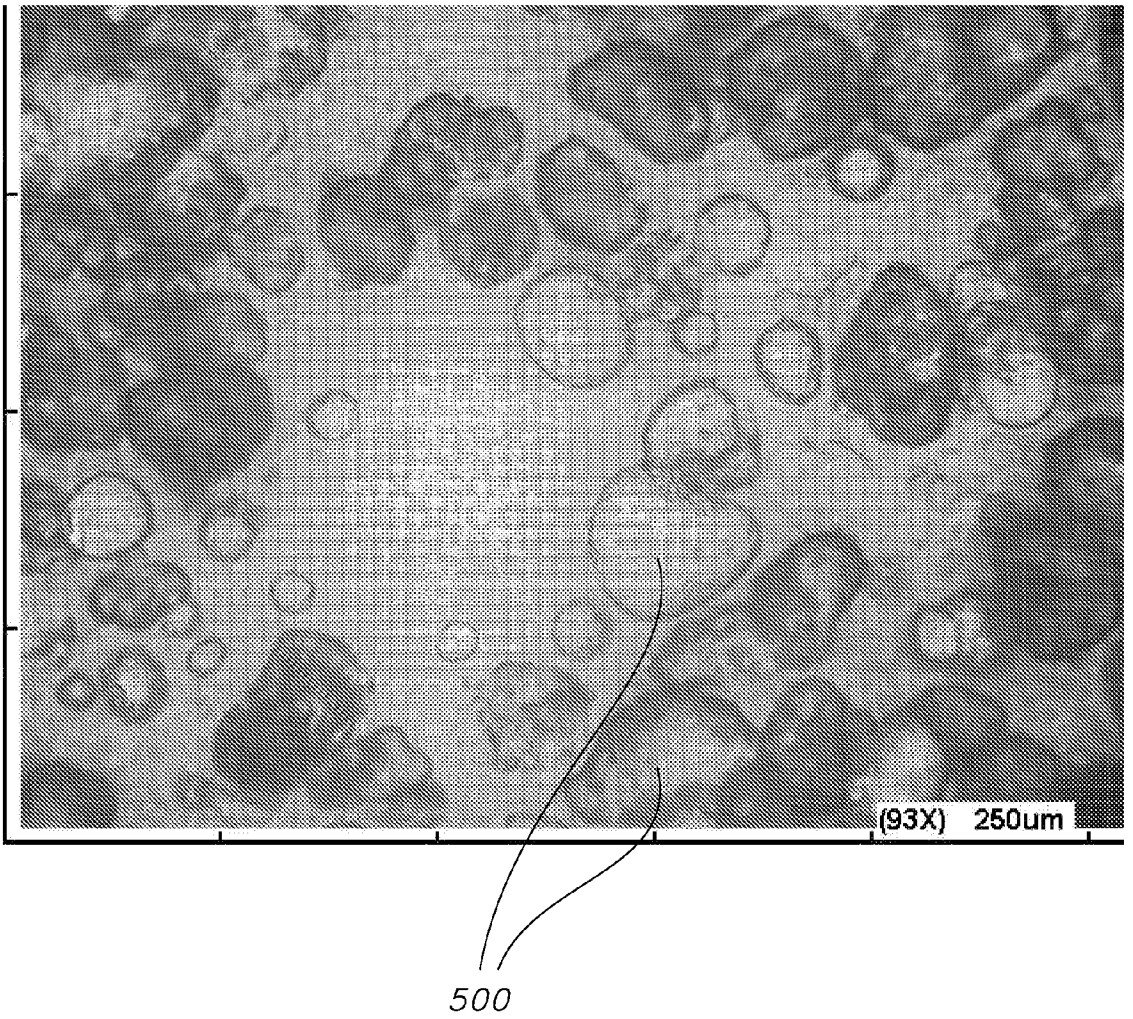


FIG. 18

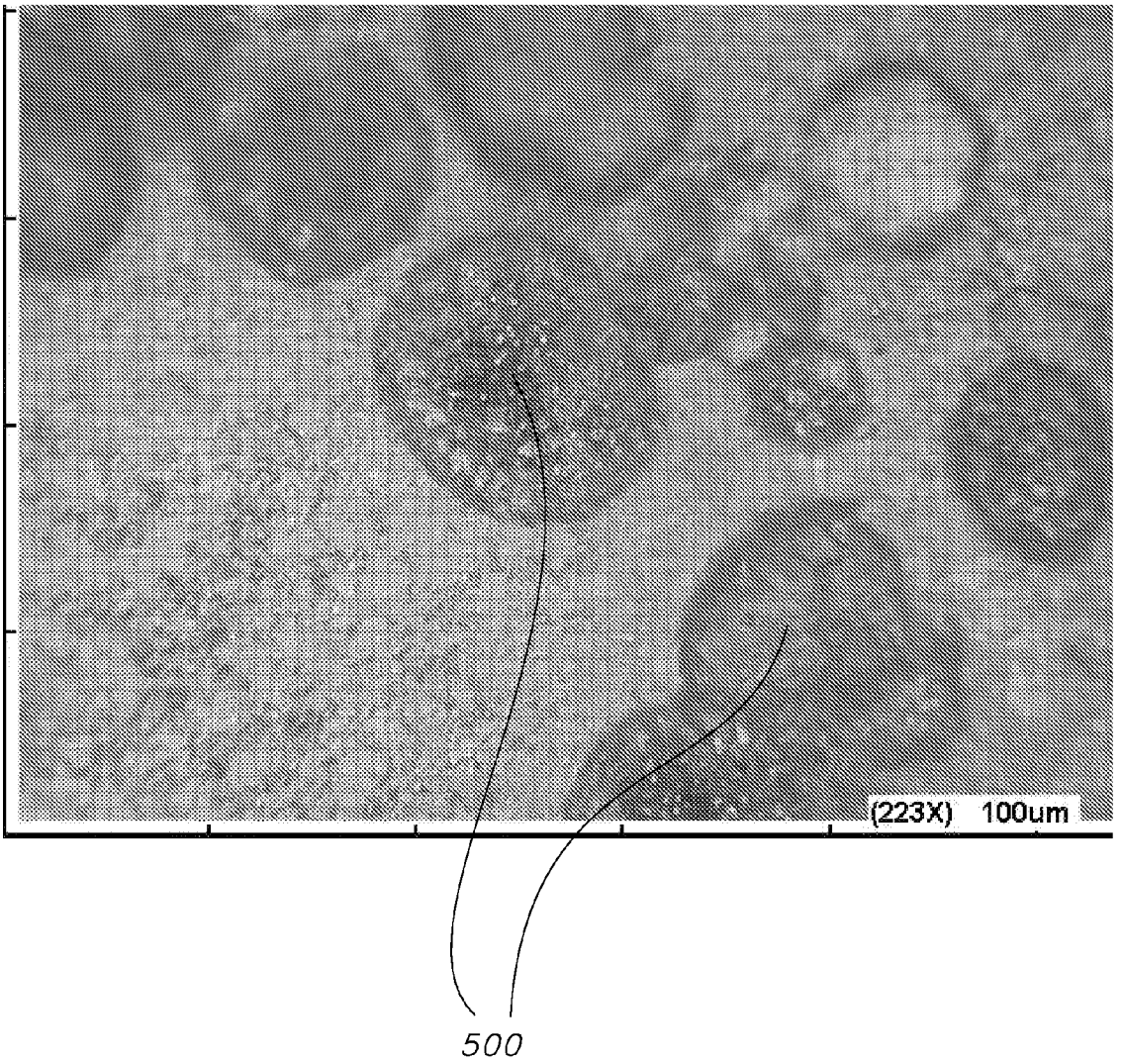


FIG. 19

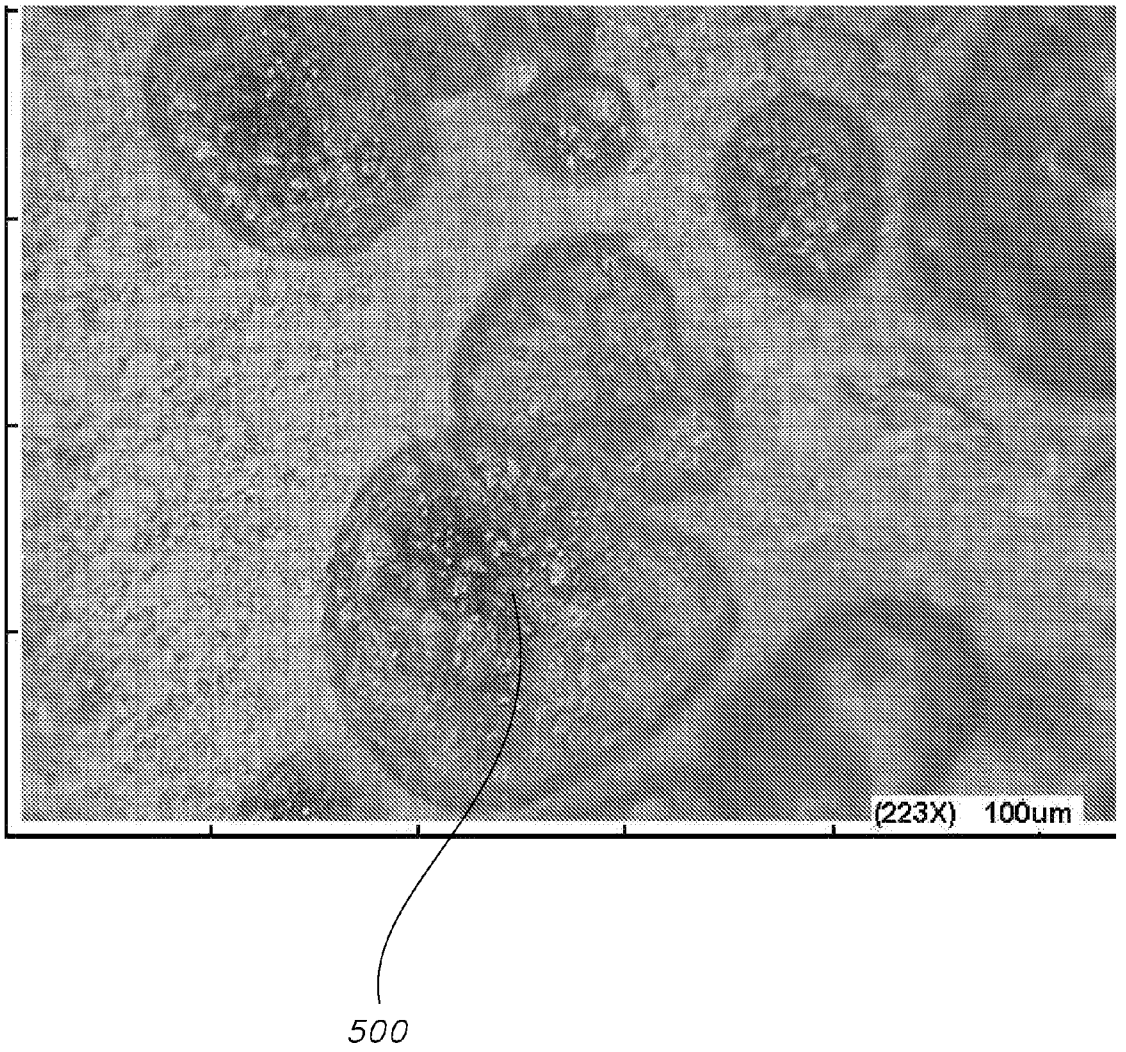


FIG. 20

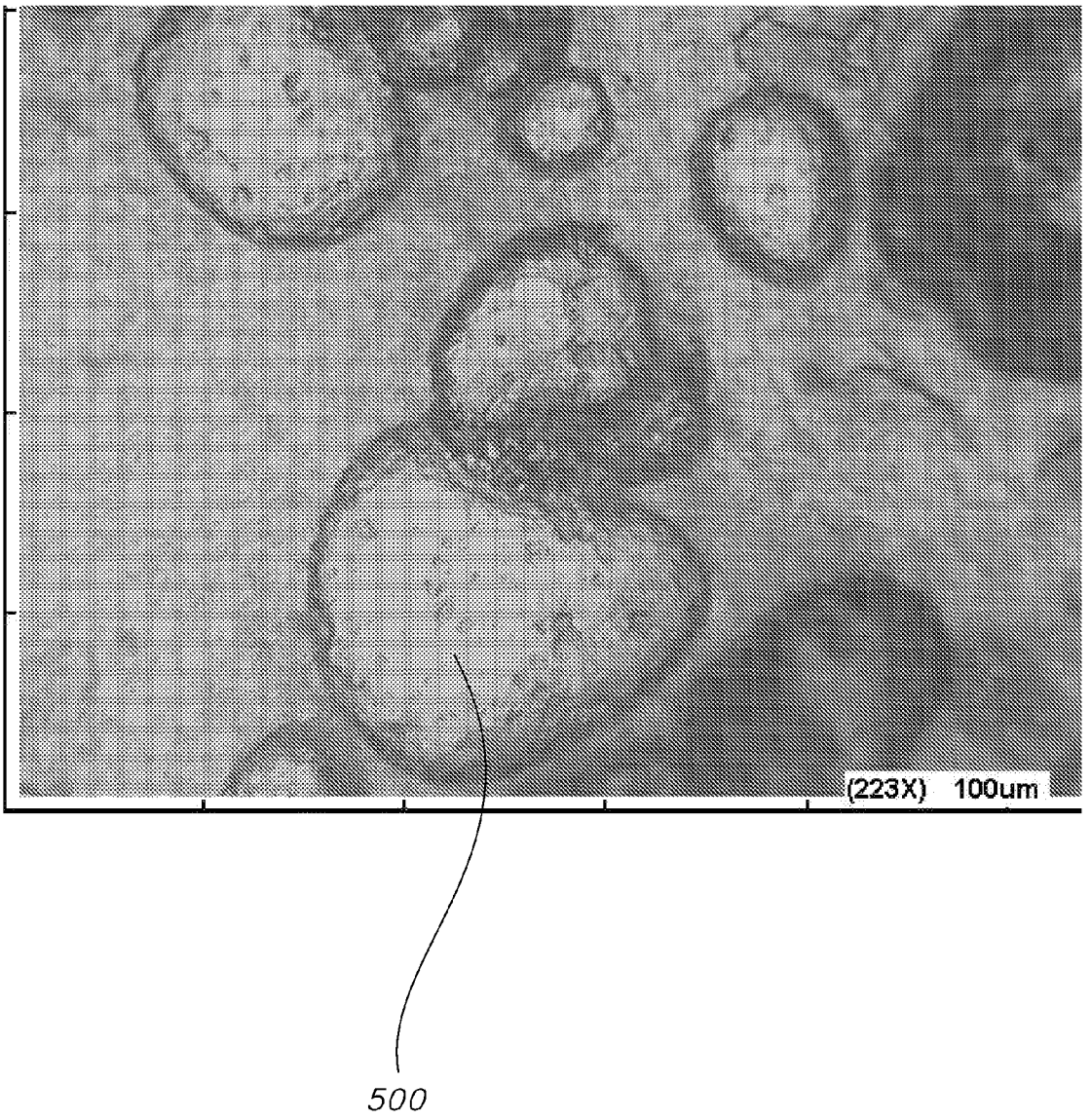


FIG. 21

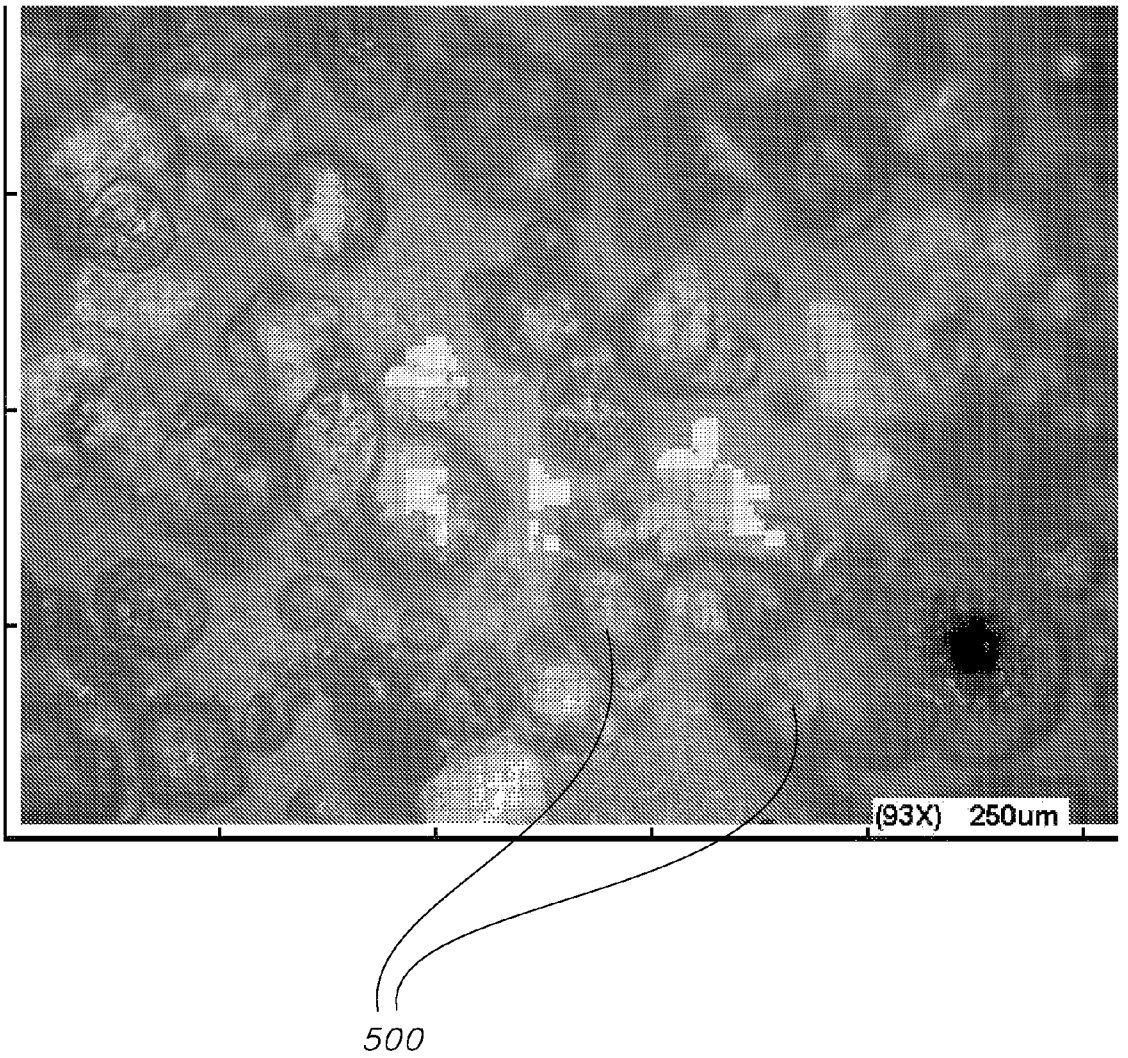


FIG. 22

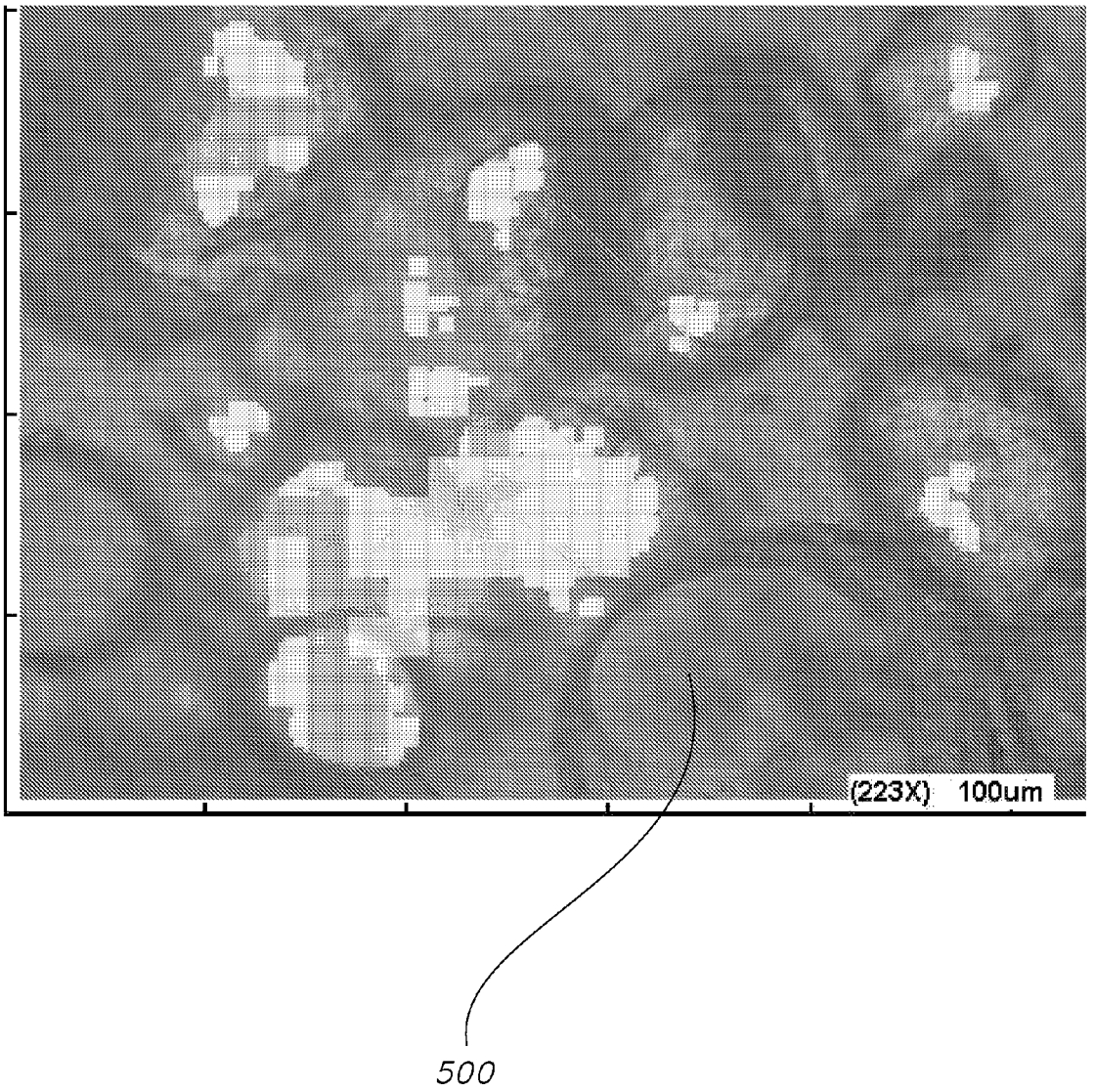


FIG. 23

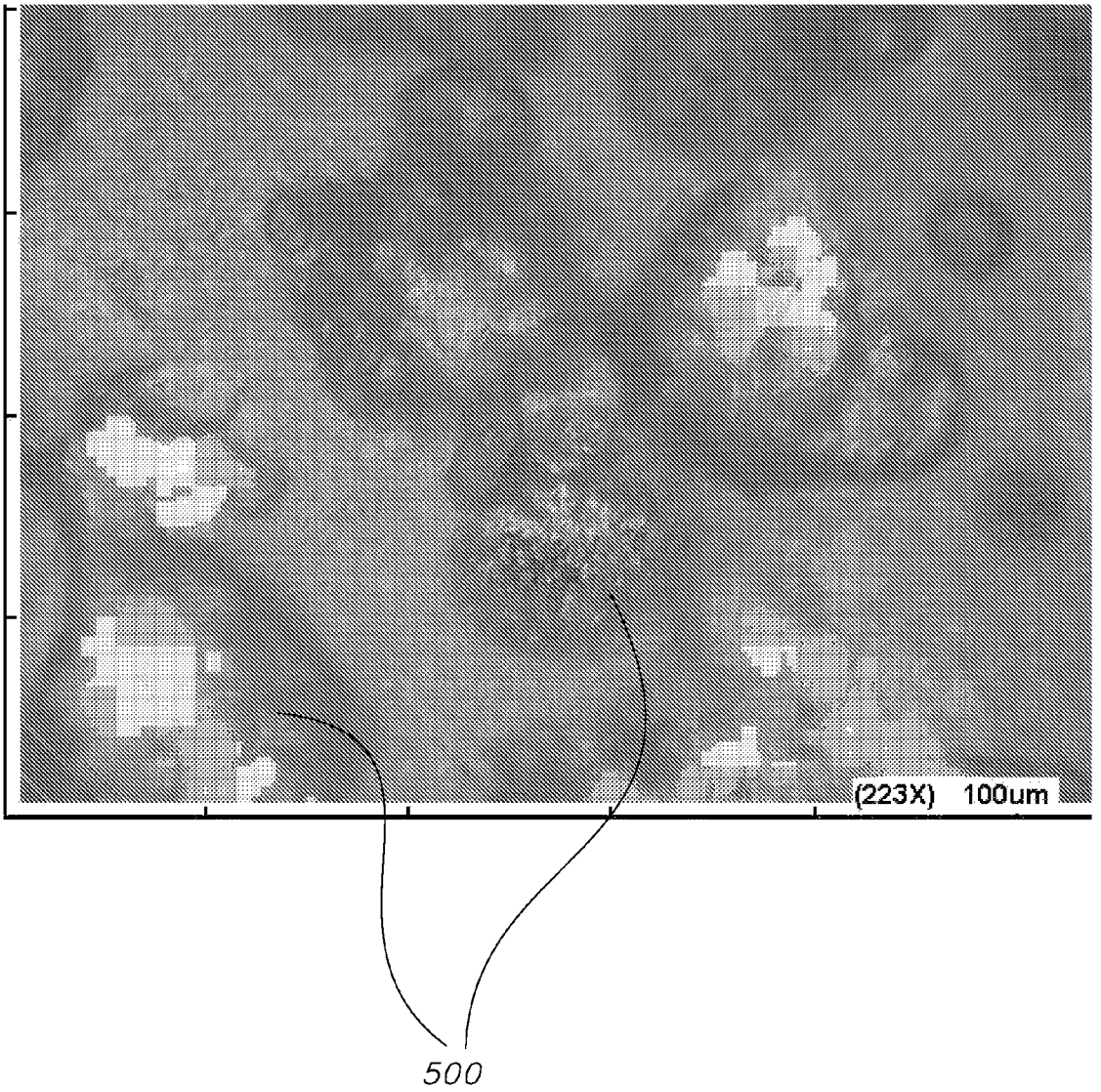


FIG. 24

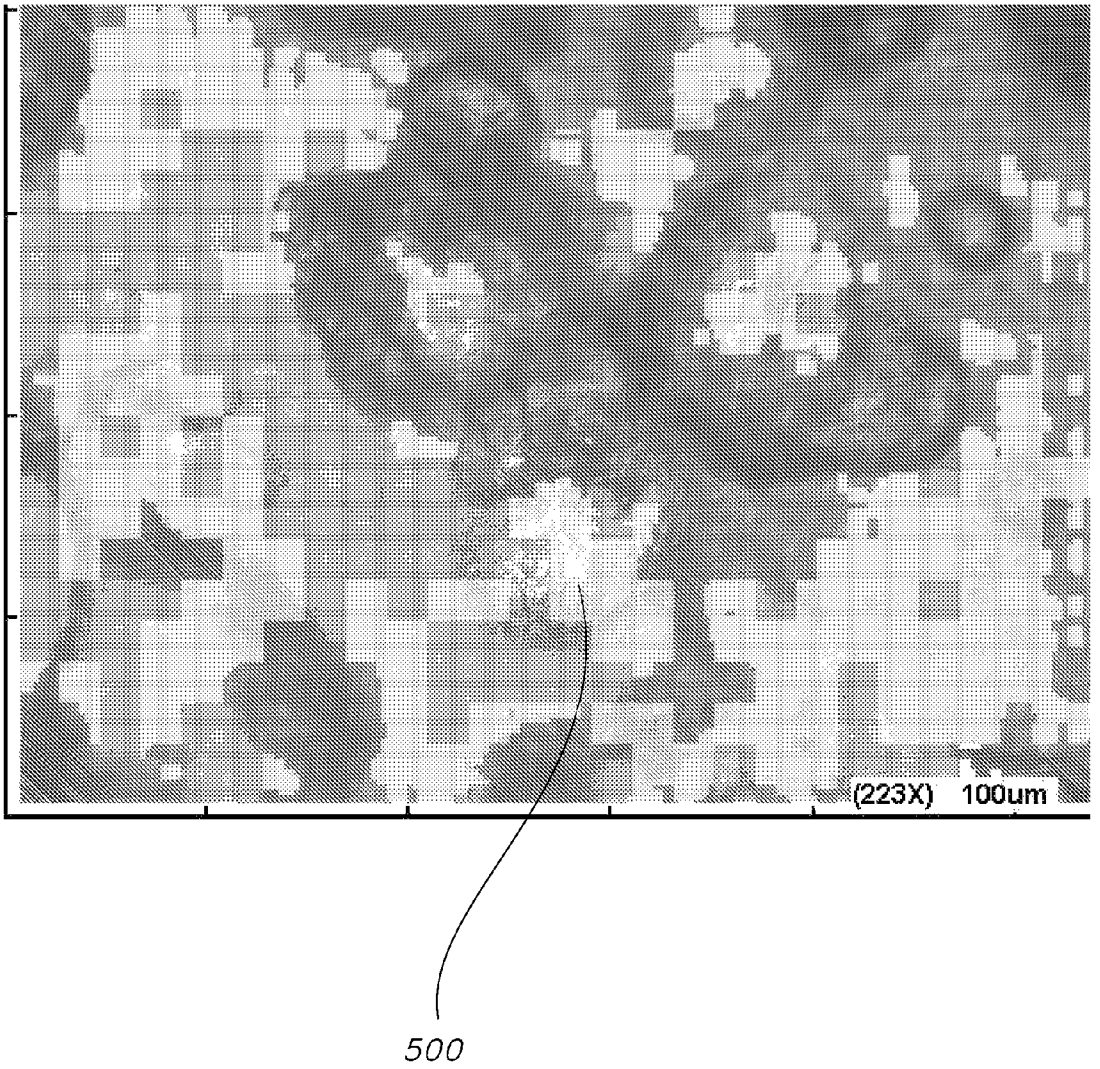


FIG. 25

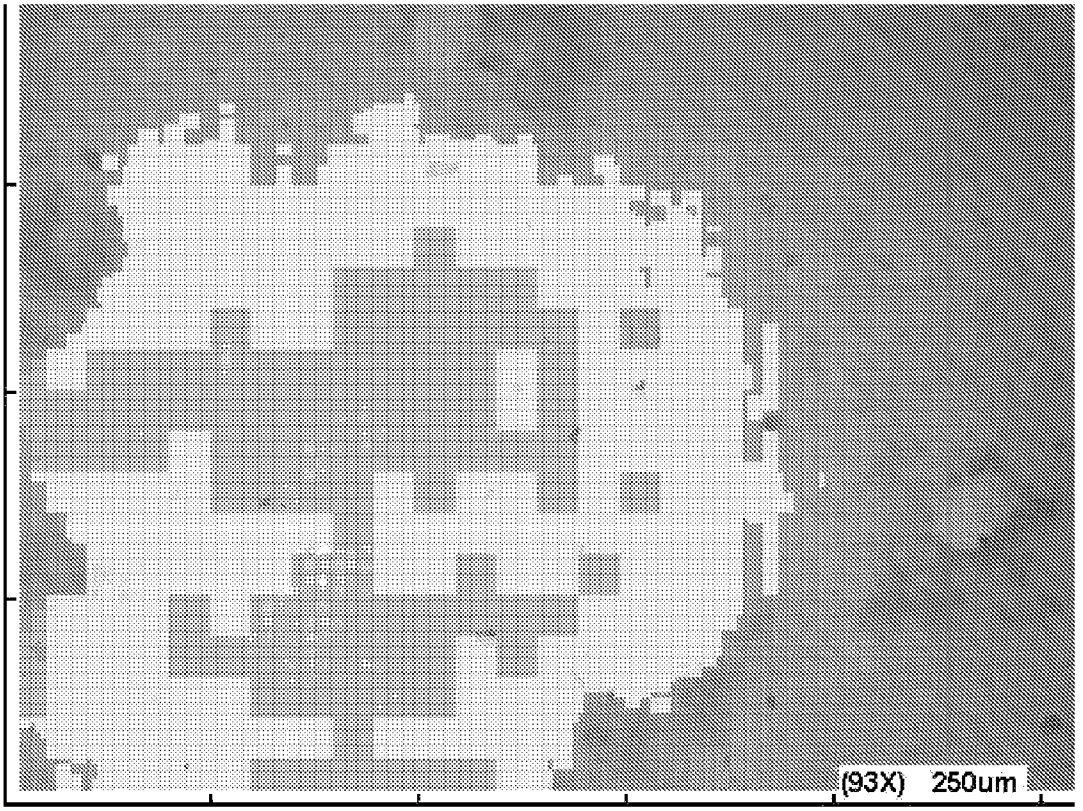


FIG. 26

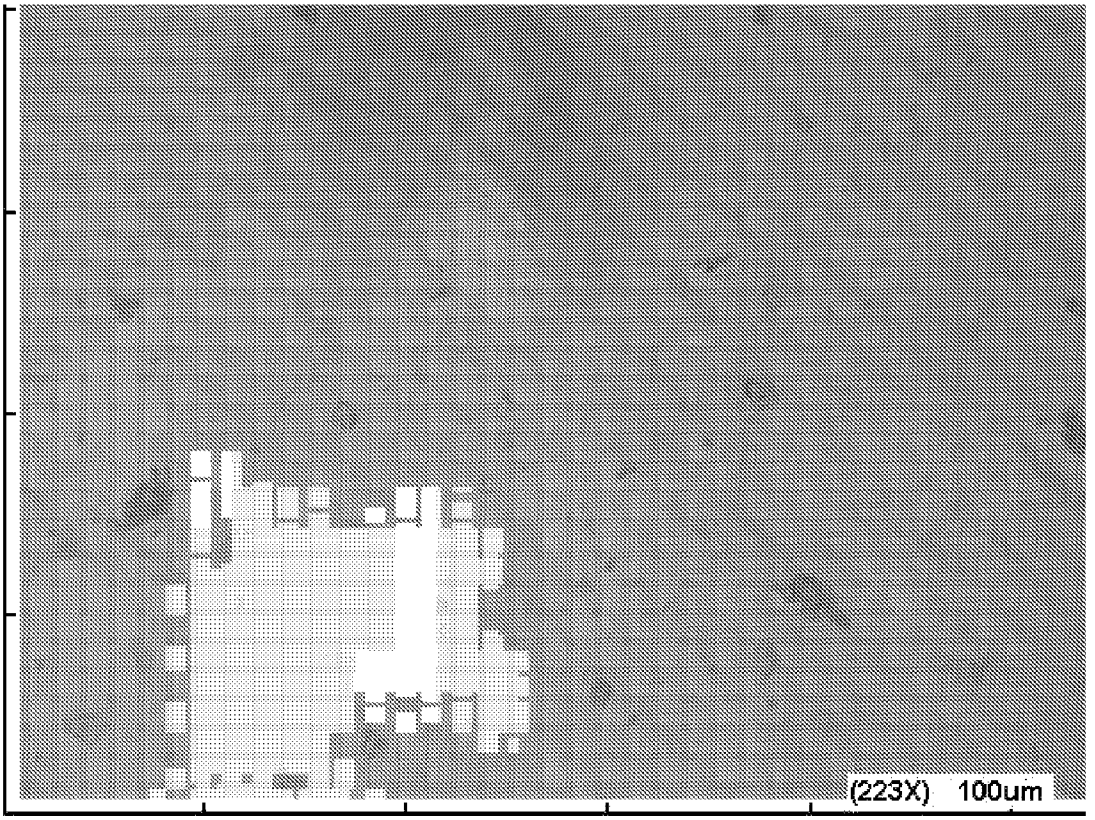


FIG. 27

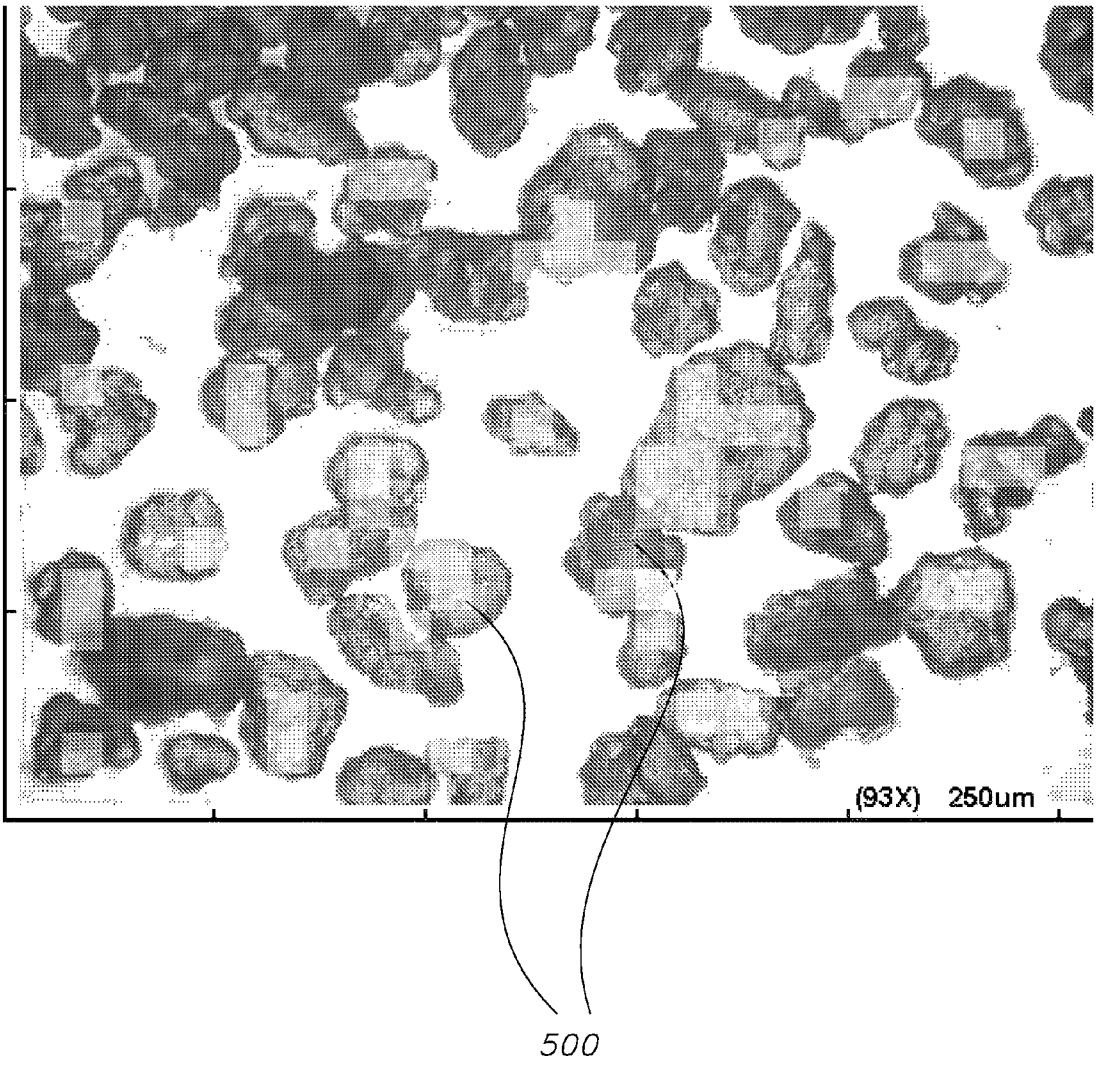


FIG. 28

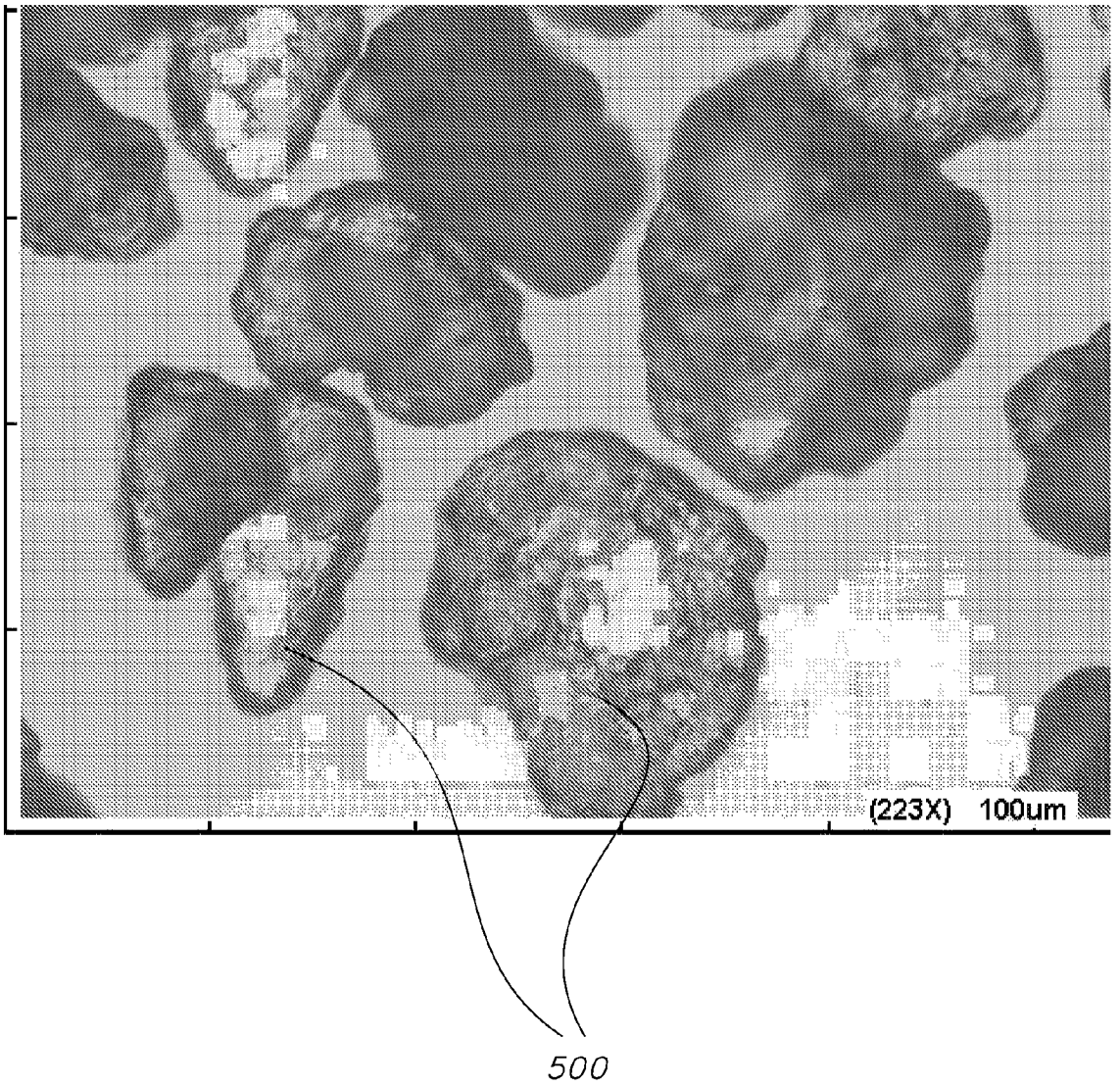


FIG. 29

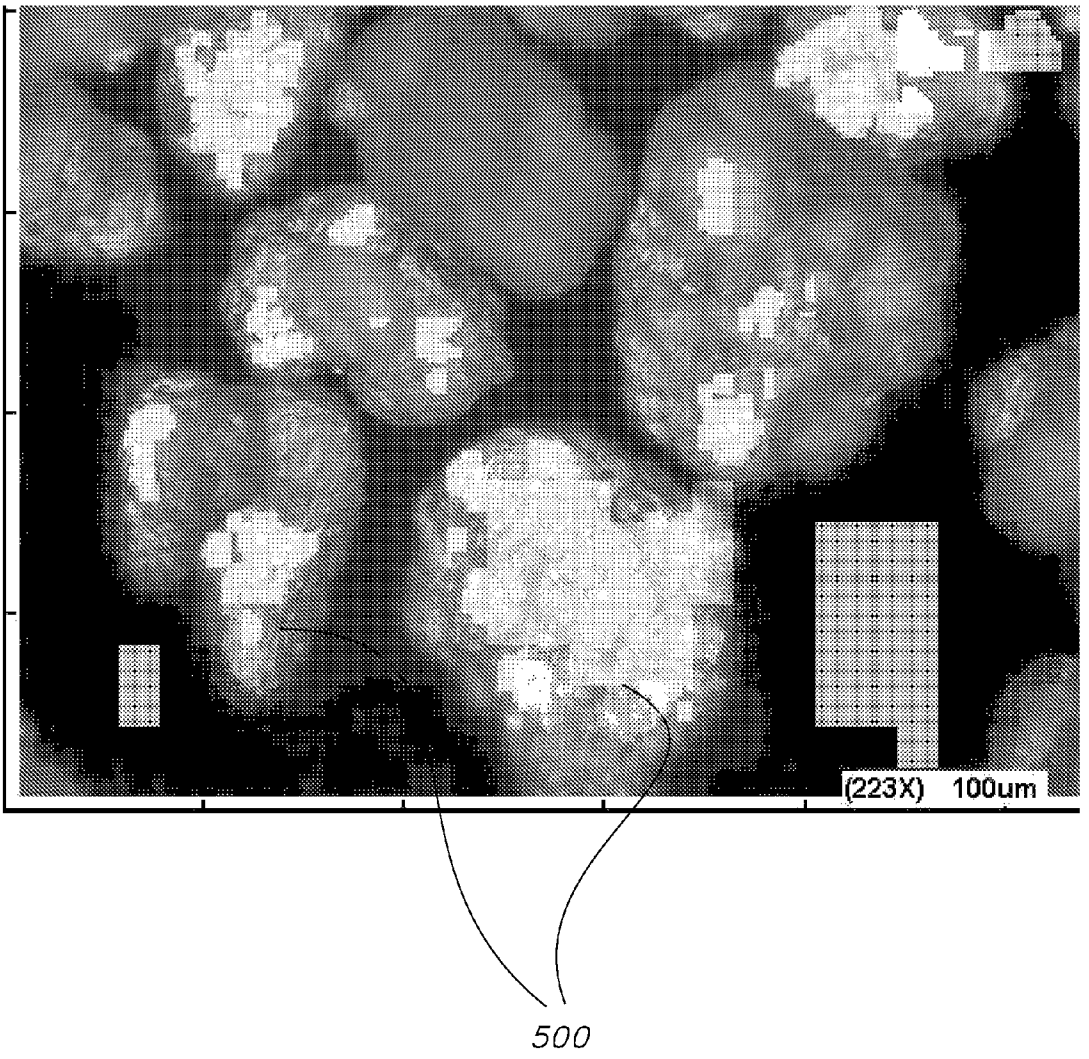


FIG. 30

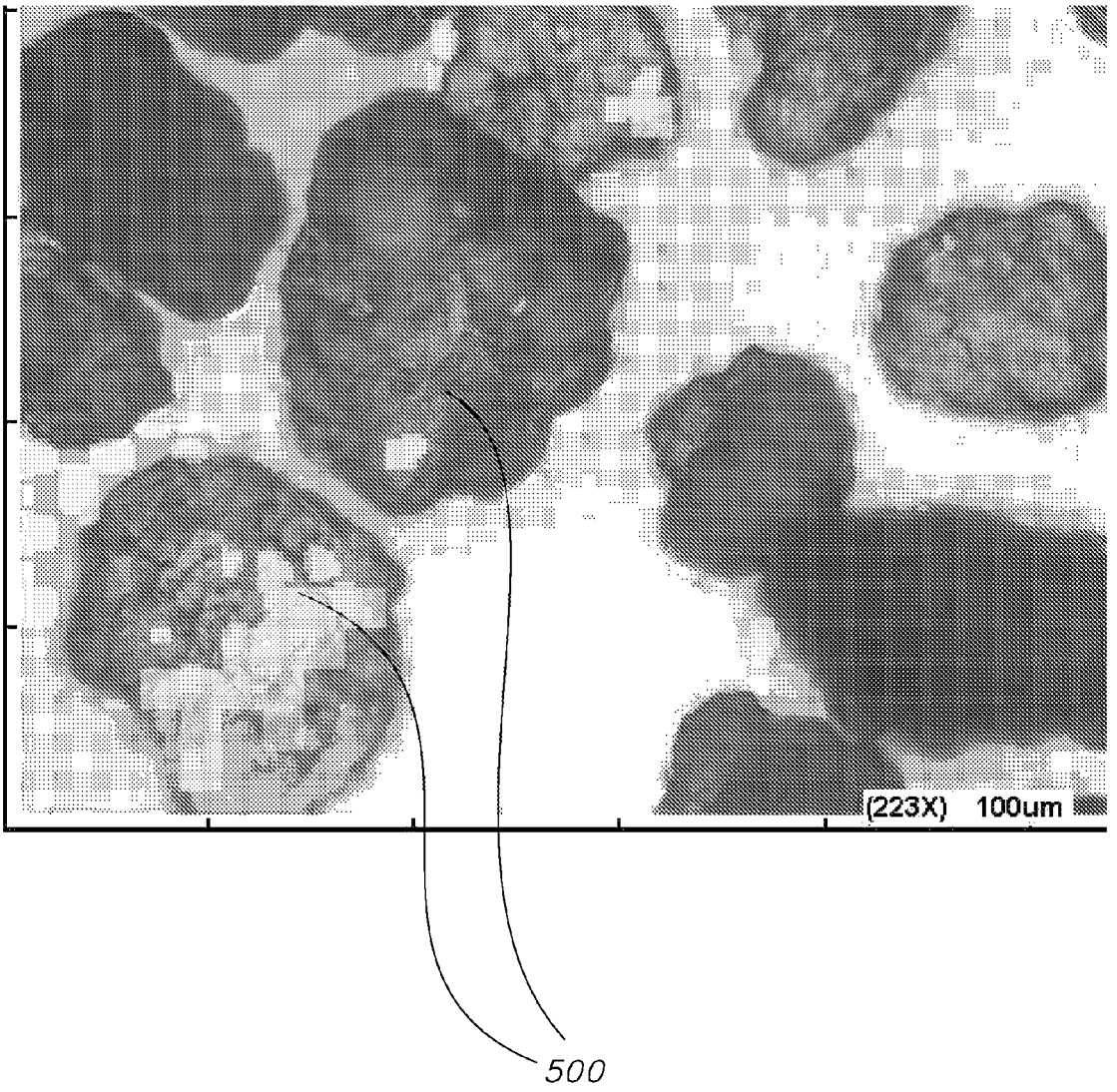
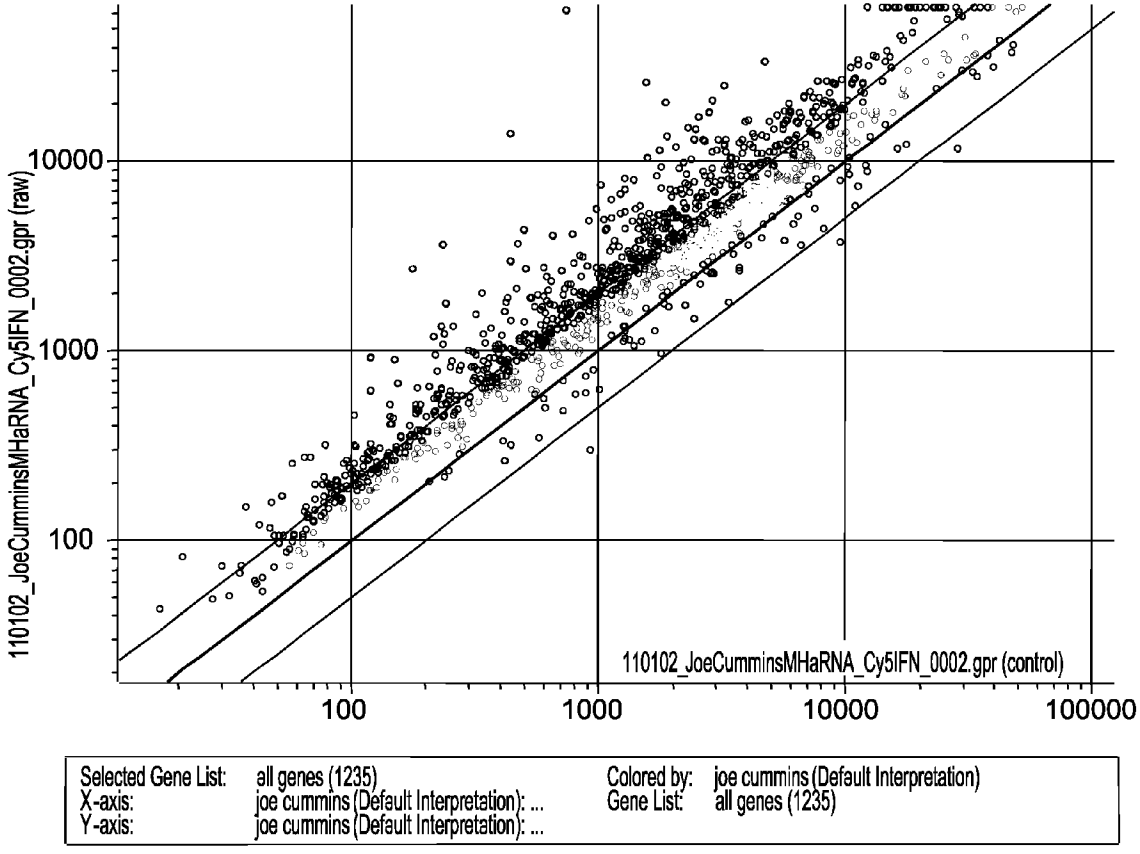
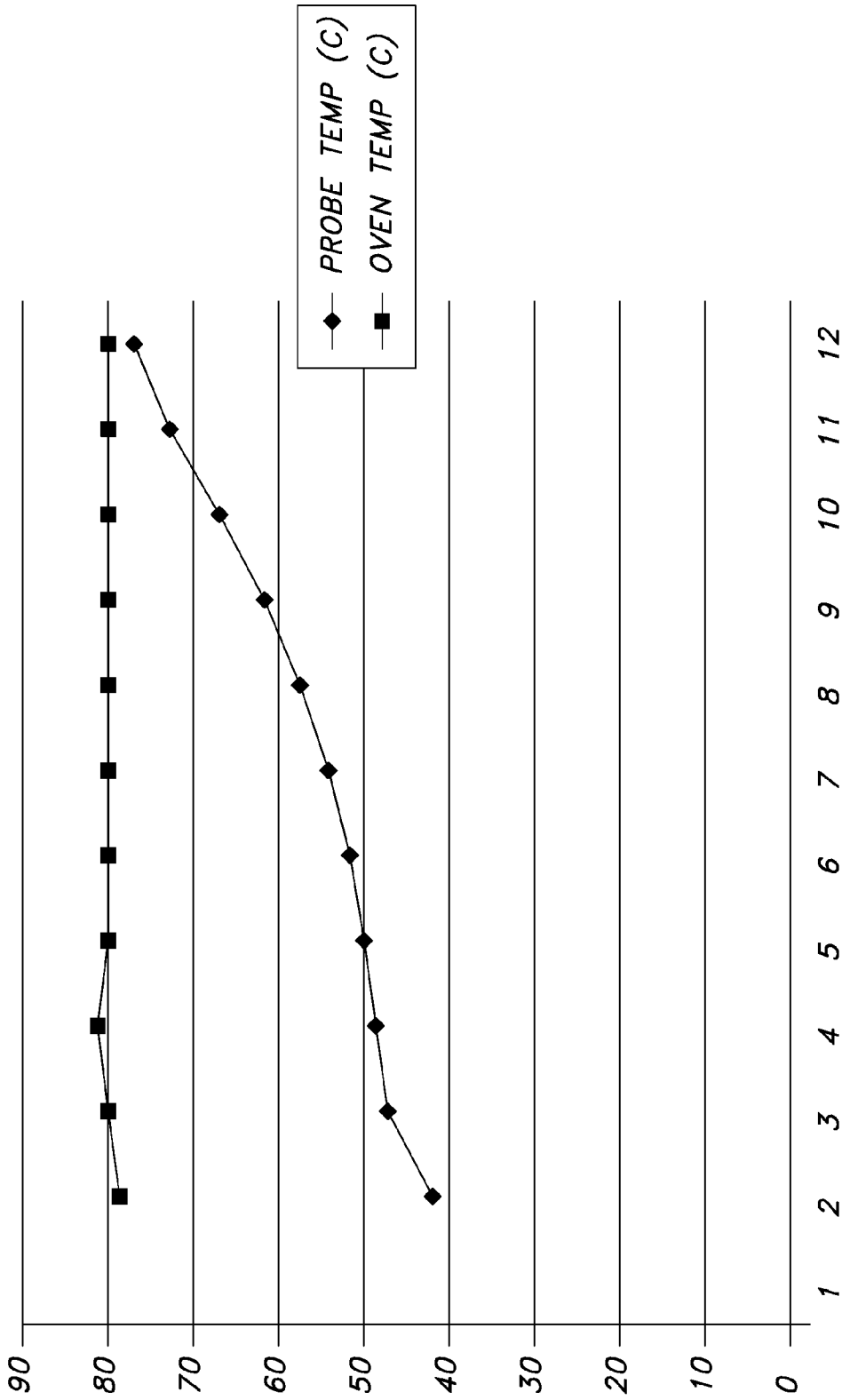


FIG. 31



Normalized to GAPDH, most of the ISGs are induced.

FIG. 32


PROBE TEMP (C)
OVEN TEMP (C)
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80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 33

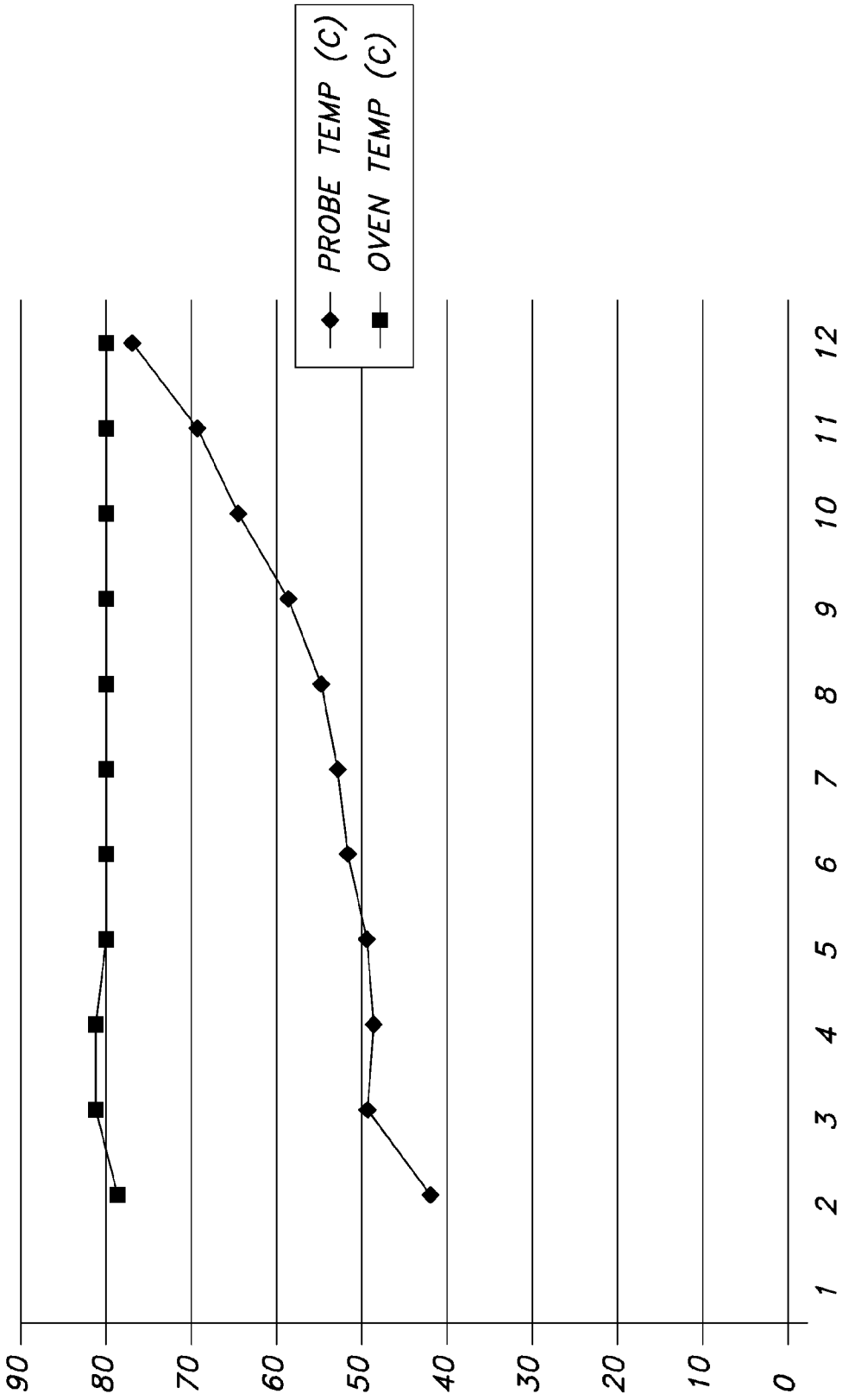
PROBE TEMP (C)
OVEN TEMP (C)
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 34

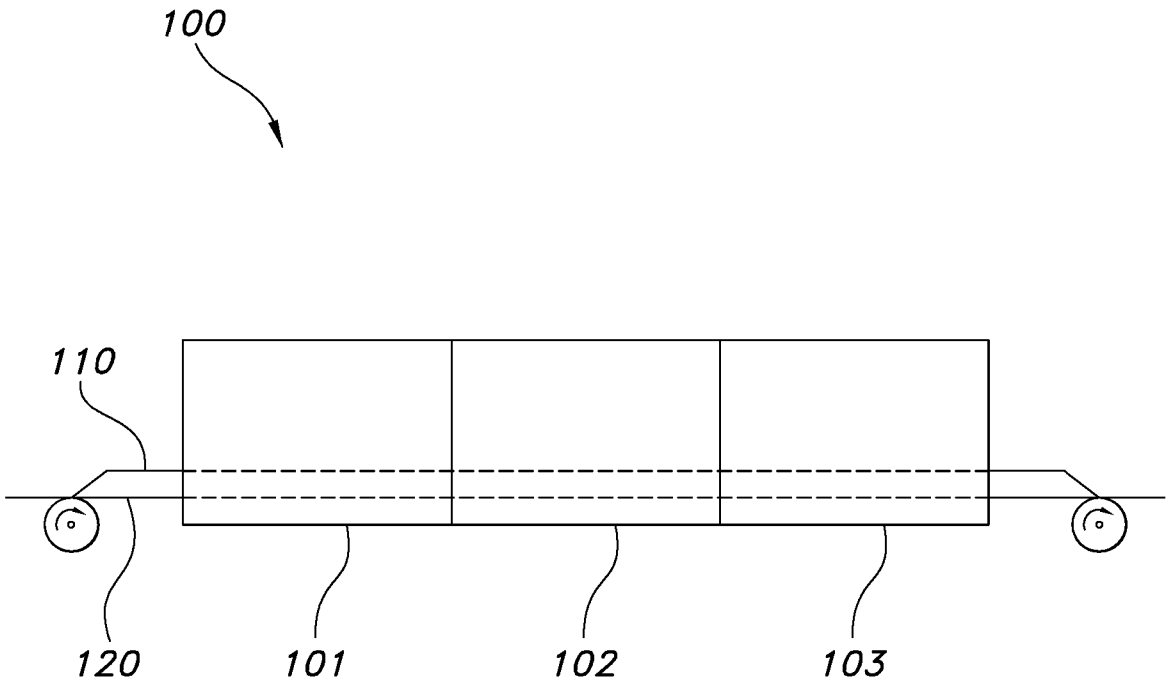

FIG. 35

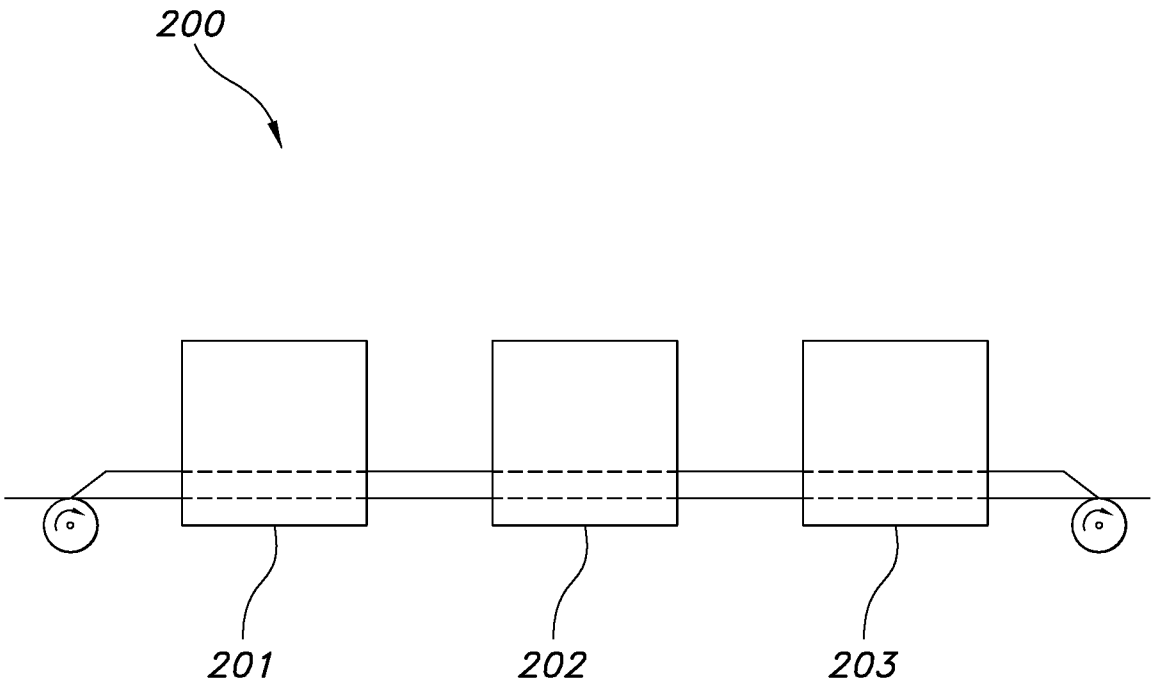

FIG. 36

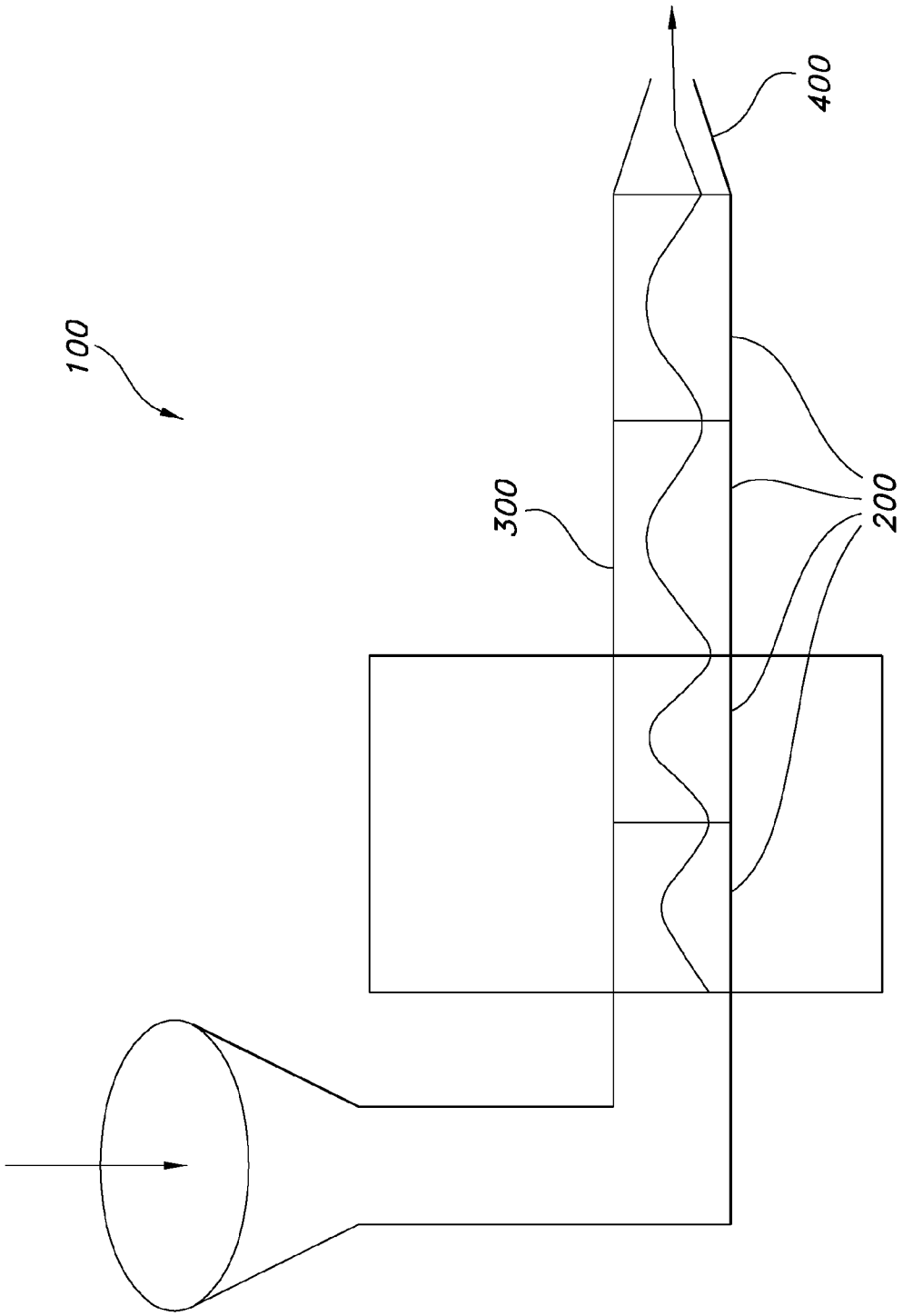

FIG. 37

FIG. 38

Ex.	Polymer Component Reference	% Solids of solution	Viscosity (cp) at 5 rpm	% moisture	Film thickness (mils)	Film strength	Tear Resistance	Tendency to go to roof of mouth	180° bend test	Film molding	Dis-solution (sec)	Rating of dissolution in mouth	Time in oven (min)
EI	PEO/PVP (60/40)	45.0	14800	2.21	3.8	Adequate	Excellent	Low	Passed	No	3	Fast to Moderate	9
EJ	PEO/PVP (40/60)	50.0	6600	2.86	4	Weak	Low to moderate	High	Passed	No	3	Fast	8
EK	PEO/Starch (80/20)	40.0	3440	2.27	4.5	Adequate to good	Excellent	High	Passed	No	3	Fast to Moderate	8
EL	PEO/CMC (80/20)	37.5	121,200	1.96	4.1	Good	Excellent	High	Passed	No	5	Slow	9
EM	PEO/CMC (60/40)	30.0	82,000	4.21	3.45	Weak	Good	High	Passed	No	3	Slow to Moderate	9
EN	PEO/CMC (40/60)	30.0	185,000	3.07	3.5	Adequate	Very low	High	Failed	No	4	Slow	9
EO	PEO/HPC (80/20)	37.5	21,200	1.65	4	Good	Excellent	High	Passed	No	4	Fast	8
EP	PEO/HPC (60/40)	37.5	17,000	2.84	3.8	Adequate	Excellent	High	Passed	No	4	Fast	9
EQ	PEO/HPC (40/60)	42.5	43,400	2.83	4.5	Poor to adequate	Poor to good	High	Passed	No	7	Fast to Moderate	7
ER	PEO/HPC (20/80)	42.5	46,400	2.33	4.4	Adequate to good	Poor	Low	Passed	No	14-15	Slow	9
ES	PEO/HPMC (80/20)	37.5	29,000	2.14	4.4	Adequate	Good	High	Passed	Yes	4	Fast to Moderate	8
ET	PEO/HPMC (60/40)	37.5	47,000	2.37	3.9	Poor to adequate	Slight	High	Passed	Yes	3	Fast to Moderate	9
EU	PEO/HPMC (40/60)	35.0	54,800	3.55	4.5	Adequate to good	Low	Low	Passed	Yes	8	Slow	8
EV	PEO/HPMC (20/80)	35.0	96,600	4.43	4.5	Good	Low	Low	Passed	No	22	Slow	10
EW	PEO/PVA (80/20)	37.5	41,600	2.92	9	Weak	Moderate	High	Passed	No	3	Moderate	10

UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 10/768,809, filed Jan. 30, 2004, which claims benefit to U.S. Provisional Application No. 60/443,741 filed Jan. 30, 2003; U.S. application Ser. No. 10/768,809 is also a continuation-in-part of PCT/US02/32575, filed Oct. 11, 2002, which claims priority to U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002, and is a continuation-in-part of U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001; U.S. application Ser. No. 10/768,809 is also a continuation-in-part of PCT/US02/32594, filed Oct. 11, 2002, which claims priority to U.S. Provisional Application No. 60/414,276, filed Sep. 27, 2002, and U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002, and is a continuation-in-part of U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001; and U.S. application Ser. No. 10/768,809 is also a continuation-in-part of PCT/US02/32542, filed Oct. 11, 2002, which claims priority to U.S. Provisional Application No. 60/386,937, filed Jun. 7, 2002, and U.S. Provisional Application No. 60/371,940, filed Apr. 11, 2002, and is a continuation-in-part of U.S. application Ser. No. 10/074,272, filed Feb. 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed Oct. 12, 2001; this application is also a continuation-in-part of U.S. application Ser. No. 10/856,176, filed May 28, 2004, which claims priority to U.S. Provisional Application No. 60/473,902, filed May 28, 2003; U.S. application Ser. No. 10/856,176 is also a continuation-in-part of U.S. application Ser. No. 10/768,809; the contents all of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to rapidly dissolving films and methods of their preparation. The films contain a polymer component and active ingredients as taste-masked or controlled-release coated particles uniformly distributed throughout the film.

BACKGROUND OF THE RELATED TECHNOLOGY

Active ingredients, such as drugs or pharmaceuticals, may be prepared in a tablet form to allow for accurate and consistent dosing. However, this form of preparing and dispensing medications has many disadvantages including that a large proportion of adjuvants that must be added to obtain a size able to be handled, that a larger medication form requires additional storage space, and that dispensing includes counting the tablets which has a tendency for inaccuracy. In addition, many persons, estimated to be as much as 28% of the population, have difficulty swallowing tablets. While tablets may be broken into smaller pieces or even crushed as a means of overcoming swallowing difficulties, this is not a suitable solution for many tablet or pill forms. For example, crushing or destroying the tablet or pill form to facilitate ingestion, alone or in admixture with food, may also destroy the controlled release properties.

As an alternative to tablets and pills, films may be used to carry active ingredients such as drugs, pharmaceuticals, and the like. However, historically films and the process of making drug delivery systems therefrom have suffered from a number of unfavorable characteristics that have not allowed them to be used in practice.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Pat. No. 4,136,145 to Fuchs, et al. ("Fuchs"). These films may be formed into a sheet, dried and then cut into individual doses. The Fuchs disclosure alleges the fabrication of a uniform film, which includes the combination of water-soluble polymers, surfactants, flavors, sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas.

Examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. This result can be attributed to Fuchs' process parameters, which although not disclosed likely include the use of relatively long drying times, thereby facilitating intermolecular attractive forces, convection forces, air flow and the like to form such agglomeration.

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.

The problems of self-aggregation leading to non-uniformity of a film were addressed in U.S. Pat. No. 4,849,246 to Schmidt ("Schmidt"). Schmidt specifically pointed out that the methods disclosed by Fuchs did not provide a uniform film and recognized that that the creation of a non-uniform film necessarily prevents accurate dosing, which as discussed above is especially important in the pharmaceutical area. Schmidt abandoned the idea that a mono-layer film, such as described by Fuchs, may provide an accurate dosage form and instead attempted to solve this problem by forming a multi-layered film. Moreover, his process is a multi-step process that adds expense and complexity and is not practical for commercial use.

Other U.S. patents directly addressed the problems of particle self-aggregation and non-uniformity inherent in conventional film forming techniques. In one attempt to overcome non-uniformity, U.S. Pat. No. 5,629,003 to Horstmann et al. and U.S. Pat. No. 5,948,430 to Zerbe et al. 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. Such processes also run the risk of exposing the active, i.e., a drug, or vitamin C, or other components to prolonged exposure to moisture and elevated temperatures, which may render it ineffective or even harmful.

In addition to the concerns associated with degradation of an active during extended exposure to moisture, the conventional drying methods themselves are unable to provide uniform films. The length of heat exposure during conventional processing, often referred to as the "heat history", and the manner in which such heat is applied, have a direct effect on the formation and morphology of the resultant film product. Uniformity is particularly difficult to achieve via conventional drying methods where a relatively thicker film, which is well-suited for the incorporation of a drug active, is desired. Thicker uniform films are more difficult to achieve because the surfaces of the film and the inner portions of the film do not experience the same external conditions simultaneously during drying. Thus, observation of relatively thick films made from such conventional processing shows a non-uniform structure caused by convection and intermolecular forces and requires greater than 10% moisture to remain flexible. The amount of free moisture can often interfere over time with the drug leading to potency issues and therefore inconsistency in the final product.

Conventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like. The difficulty in achieving a uniform film is directly related to the rheological properties and the process of water evaporation in the film-forming composition. When the surface of an aqueous polymer solution is contacted with a high temperature air current, such as a film-forming composition passing through a hot air oven, the surface water is immediately evaporated forming a polymer film or skin on the surface. This seals the remainder of the aqueous film-forming composition beneath the surface, forming a barrier through which the remaining water must force itself as it is evaporated in order to achieve a dried film. As the temperature outside the film continues to increase, water vapor pressure builds up under the surface of the film, stretching the surface of the film, and ultimately ripping the film surface open allowing the water vapor to escape. As soon as the water vapor has escaped, the polymer film surface reforms, and this process is repeated, until the film is completely dried. The result of the repeated destruction and reformation of the film surface is observed as a "ripple effect" which produces an uneven, and therefore non-uniform film. Frequently, depending on the polymer, a surface will seal so tightly that the remaining water is difficult to remove, leading to very long drying times, higher temperatures, and higher energy costs.

Other factors, such as mixing techniques, also play a role in the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval. Air can be trapped in the composition during the mixing process or later during the film making process, which can leave voids in the film product as the moisture evaporates during the drying stage. The film frequently collapse around the voids resulting in an uneven film surface and therefore, non-uniformity of the final film product. Uniformity is still affected even if the voids in the film caused by air bubbles do not collapse. This situation also provides a non-uniform film in that the spaces, which are not uniformly distributed, are occupying area that would otherwise be occupied by the film composition. None of the above-mentioned patents either addresses or proposes a solution to the problems caused by air that has been introduced to the film.

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, such films are produced through a selection of a polymer or combination of polymers that will provide a desired viscosity, a film-forming process such as reverse roll coating, and a controlled, and desirably rapid, drying process which serves to maintain the uniform distribution of non-self-aggregated components without the necessary addition of gel formers or polyhydric alcohols and the like which appear to be required in the products and for the processes of prior patents, such as the aforementioned Horstmann and Zerbe patents. 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.

SUMMARY OF THE INVENTION

In one aspect, this invention provides rapid-dissolve film products for drug delivery whereby the active agents are taste-masked or controlled-release coated particles uniformly distributed throughout the film. The uniform films of this invention can be divided into equally sized dosage units having substantially equal amounts of each compositional component present. This advantage is particularly useful because it permits large area films to be initially formed, and subsequently cut into individual dosage units without concern for whether each unit is compositionally equal. Pharmaceutical film dosage forms to date have not been marketed largely due to the inability to achieve this result. Thus, for example, the films of the present invention have particular applicability as pharmaceutical dosage delivery systems because each dosage unit, e.g., each individual dosage film unit, will contain the proper predetermined amount of drug.

In a further aspect of the present invention, methods of forming the films of this invention are provided, by wet casting methods and hot melt extrusion methods. In a wet casting method, the film product is formed by combining a polymer and a polar solvent, forming the combination into a film, and drying the film in a controlled manner. Preferably, the film is dried initially only applying heat to the bottom side of the film, in order to maintain a non-self-aggregating uniform heterogeneity. Desirably, during the initial bottom drying stage, substantially no convection currents, i.e., hot air currents, are permitted to travel across the top of the film until the visco-elastic properties of the film are such that the film components are "locked" in place and cannot move to cause non-uniformity. At that stage, other methods of heating to effect drying may be employed.

The films may be formed with a polar solvent which may be water, a polar organic solvent, or a combination thereof. An active ingredient may be added to the polymer and water combination prior to the drying step. Alternatively, or in addition to controlling the drying the film, the polymer may be selected in order to provide a viscosity that maintains the non-self-aggregating uniform heterogeneity. Moreover, the composition desirably is mixed in a manner to minimize the incorporation of air into the mixture and is desirably deaerated, such as by conditioning at room temperature, vacuum

treatment or the like, to allow trapped air to escape prior to the drying process. This serves to eliminate bubble and void formation in the final film product, thereby further improving uniformity. Reverse roll coating is one particularly useful coating technique may also be used to form the film.

Another embodiment of the present invention may include a rapid-dissolve film product containing at least one water-soluble polymer including polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer, wherein the film product may be free of added plasticizers. Preferably, the rapid-dissolve film product includes at least one water-soluble polymer containing about 20% to 100% by weight polyethylene oxide, about 0% to 80% by weight hydroxypropylmethyl cellulose, and about 0% to 80% by weight hydroxypropyl cellulose; an active component; sweetener; at least one flavoring; and at least one colorant, wherein the film product optionally is free of added plasticizers, surfactants, and polyalcohols.

In another aspect of the present invention, the films employing polyethylene oxide as the film-forming polymer may be formed by a hot melt extrusion process, whereby an edible film-forming polymer is provided, and active components are added during manufacture, and the mixture is blended at elevated temperature in the absence of additional solvent to form a uniform matrix, and extruded to form a film. Desirably, the film will be further shaped by rollers to a specified thickness, and allowed to cool and harden to form a self supporting film. A particularly desirable film forming polymer for extrusion manufacture is polyethylene oxide, which is heated to about 65° C. to about 80° C. during blending to provide a pliable uniform matrix. The extrusion may be accomplished with a single screw extrusion apparatus or other suitable extrusion apparatus.

A particular advantage of the aforementioned extrusion processes when employed with particulate coated active ingredients is that the absence of additional solvent during the manufacturing process lessens the likelihood of dissolution or release of the taste-masked or controlled-release coated active agent during manufacture due to dissolution or solvent effects.

Another aspect of the present invention provides films containing coated particles that include an active agent and a taste-masking and/or controlled-release coating. Accordingly, there is provided a drug delivery composition that includes (i) a flowable water-soluble film forming matrix; (ii) a particulate bioeffecting agent uniformly stationed therein; and (iii) a taste-masking agent or controlled-release agent coated or intimately associated with the particulate to provide taste-masking of the bioeffecting agent. In some embodiments, the combined particulate and taste-masking agent have a particle size of 200 microns or less and the flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of the particulate bioeffecting agent therein.

In some other embodiments, the taste-masking or controlled-release coated particles may have a particle size of 50 to 250 microns, and the flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of the particulate bioeffecting agent therein. The importance of particle size is heightened in orally ingestible thin films, where uniformity is also of particular importance, and the prior art has failed to recognize such critically important features.

Desirably, the size of the combined particulate and taste-masking agent have a particle size of 150 microns or less, or 100 microns or less. The flowable water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness. Desirably, the coated particles are embedded entirely within the finished films. In other words the dry films of the present invention desirably have smooth surfaces free of exposed agents or coated particles that could impart grittiness or maldistribution of the active. Thus, in one aspect of the invention there is provided a film vehicle which contains a uniform distribution of actives, as defined herein, being suitably free of particles which accumulate on the film surface when dried.

Desirably, the taste-masking or controlled-release agent is a thin film coating over portions of the bioeffecting agent. Useful taste-masking agents include polymeric materials. Water-soluble polymers are also useful. Desirably, the water-soluble polymer has an average molecular weight of equal to or greater than about 40,000. Furthermore, water-soluble polymers may be acrylic polymers, cellulosic polymers, and combinations thereof. Additionally, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof may also be used as taste-masking agents.

In some embodiments described herein, a thin film drug delivery composition includes: (a) an edible water-soluble film forming matrix; and (b) a coated particulate active component uniformly stationed therein, wherein the coating on the particulate active component is a taste-masking or controlled-release agent and wherein the coated particulate active component has a particle size of 50 to 250 microns and is uniformly distributed in the film composition.

In some other embodiments, there is provided a thin film drug delivery composition, which includes: (a) an edible water-soluble film forming matrix including at least one water-soluble polymer including polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and (b) a coated particulate active component uniformly stationed therein, wherein the coating on the particulate active component is a taste-masking and/or controlled-release agent, and wherein the active component is uniformly distributed in the film composition.

Some other embodiments provide a drug delivery vehicle including:

a dry mucoadhering film having a thickness defined by opposed surfaces; the film including:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle including a pharmaceutically active agent; and a taste-masking agent;

wherein the particle having a particle size of less than about 200 microns and the taste-masking agent being present in amounts of about 15-80% by weight of the particle.

Still other embodiments provide a method of preparing a thin film drug delivery vehicle including:

(a) providing a pharmaceutically active agent/taste-masking agent complex;

(b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of the complex therein;

(c) casting the mixture onto a planar carrier surface to form a thin film on the carrier surface; and

(d) controllably drying the thin film to form a distribution variance of the complex having less than about 10% variance throughout any given area of the thin film.

In still other embodiments, there is provided a method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components including:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component including a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

In yet other embodiments, there is provided a process for making a self-supporting, edible film having a substantially uniform distribution of components including:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component including a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a side view of a package containing a unit dosage film of the present invention.

FIG. **2** shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

FIG. **3** shows a side view of the adjacently coupled packages of FIG. **2** arranged in a stacked configuration.

FIG. **4** shows a perspective view of a dispenser for dispensing the packaged unit dosage forms, dispenser containing the packaged unit dosage forms in a stacked configuration.

FIG. **5** is a schematic view of a roll of coupled unit dose packages of the present invention.

FIG. **6** is a schematic view of an apparatus suitable for preparation of a pre-mix, addition of an active, and subsequent formation of the film.

FIG. **7** is a schematic view of an apparatus suitable for drying the films of the present invention.

FIG. **8** is a sequential representation of the drying process of the present invention.

FIG. **9** is a photographic representation of a film dried by conventional drying processes.

FIG. **10** is a photographic representation of a film dried by conventional drying processes.

FIG. **11** is a photographic representation of a film dried by conventional drying processes.

FIG. **12** is a photographic representation of a film dried by conventional drying processes.

FIG. **13** is a photographic representation of a film dried by conventional drying processes.

FIG. **14** is a photographic representation of a film dried by conventional drying processes.

FIG. **15** is a photographic representation of a film dried by conventional drying processes.

FIG. **16** is a photographic representation of a film dried by conventional drying processes.

FIG. **17** is a photographic representation of a film dried by the inventive drying process.

FIG. **18** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **19** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **20** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **21** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **22** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **23** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **24** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **25** is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

FIG. **26** is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80° C.

FIG. **27** is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80° C.

FIG. **28** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **29** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **30** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **31** is a photomicrographic representation of fat coated particles at room temperature prior to processing.

FIG. **32** is a graphical representation of a microarray on the blood of a human after ingestion by the human of a film of the present invention containing a bovine derived protein.

FIG. **33** is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

FIG. **34** is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

FIG. **35** is a schematic representation of a continuously-linked zone drying apparatus in accordance with the present invention.

FIG. **36** is a schematic representation of a separate zone drying apparatus in accordance with the present invention.

FIG. **37** is a schematic representation of a single screw extrusion apparatus for use in producing films of the present invention.

FIG. **38** is a table providing examples of thin film compositions of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity

includes the substantial absence of aggregates or conglomerates as is common in conventional mixing and heat drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity of component distribution throughout the area of a given film.

The film products of the present invention may be produced by a wet casting method, using a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. In an alternative embodiment, a hot melt extrusion process may be used.

The film products of the present invention contain active agents in taste-masked or controlled-release coated particles uniformly distributed throughout the film. The active agents may be flavors, cooling agents, pharmaceuticals, vitamins, nutraceuticals, or other bioeffecting agents.

The coatings on the taste-masked or controlled-release particles desirably have a protective function, in addition to the taste-masked or controlled-release activity. The coatings desirably are sufficiently physically capable of withstanding the mechanical and thermal forces associated manufacturing processes, such as mixing, casting, rolling, drying, and hot melt extrusion.

Additionally, the coatings desirably do not prematurely release the active agent or substantially expose the active agent to the environment, e.g., solvent or air, such that the active has the potential to hydrolyze, oxidize, or otherwise be deleteriously affected by undesired release from the particle coating. Moreover, maintenance of the physical and chemical integrity of the coating not only preserves the activity of the active agent, but also allows for the coating to perform its taste-masked or controlled-release function when consumed.

In embodiments of this invention employing particulate active agents, whether coated or not, it is important that the particles not release the active agent during manufacture of the film, yet provide suitable release in the stomach or mouth during dosing, or during dissolution testing. Thus, the particles must reside intact during mixing, coating, film forming, and drying steps, so that the particles remain ready to dissolve in the finished film only in an appropriate environment. Accordingly, manufacturing conditions must be balanced with the composition of the particles to provide stability during manufacture, yet appropriate release of drug. Note that by employing daughter mixers **30** and **30'** (see FIG. **6**) in wet casting embodiments of this invention, and not adding active drug to the master batch **22**, there is less concern over stability of the particles during possibly extended periods after the master batch is mixed but prior to film forming operations. With the daughter mixers **30** and **30'**, the active agent or other ingredients that are incompatible with extended hold times in the master batch can be mixed just prior to the film forming operations with only minimal contact with the liquid ingredients prior to film forming. Even so, the particles should be stable in the liquid film forming ingredients for a sufficient period of time to compensate for the time required to form and dry the film after the film forming ingredients leave the daughter mixers. This time period may be as long as 30 minutes.

Similarly, a particular advantage to the extrusion processes of this invention is that solvents are not normally used in the extrusion methods as described herein. Accordingly, there is a greater likelihood that a coated active agent, if present, will be stable during the manufacture. Without a solvent in the film forming process, there is less likelihood that a coated particle will dissolve and release the active agent prematurely.

Film-Forming Polymers

The polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, polyethylene oxide (PEO), pullulan, hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HPC), hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof.

Polymers for Wet-Cast Films

Polymers for wet-cast films may employ a polar solvent, such as water or alcohol, during the manufacturing process to soften or dissolve the polymeric film forming materials. Preferably, the polymers will be water soluble. As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films of the present invention include biodegradable polymers, copolymers, block polymers and combinations thereof. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly (lactic acid) (PLA), polydioxanoes, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of polyurethane and poly(lactic acid), copolymers of α-amino acids, copolymers of α-amino acids and caproic acid, copolymers of α-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Del. and are generically identified as a "lactide/glycolide

co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100 L, believed to be 100% lactide having a melting point within the range of 338°-347° F. (170°-175° C.); lactide/glycolide 100 L, believed to be 100% glycolide having a melting point within the range of 437°-455° F. (225°-235° C.); lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347° F. (170°-175° C.).

The Biodel materials represent a family of various polyanhydrides which differ chemically.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

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.

The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

It has also been observed that certain polymers which when used alone would ordinarily require a plasticizer to achieve a flexible film, can be combined without a plasticizer and yet achieve flexible films. For example, HPMC and HPC when used in combination provide a flexible, strong film with the appropriate plasticity and elasticity for manufacturing and storage. No additional plasticizer or polyalcohol is needed for flexibility.

Polymers for Extruded Films

In an alternative embodiment of this invention, hot melt extrusion may be used to form films. For extrusion processes, the polymers must be thermoplastic, meaning the polymers can be melted in a suitable apparatus, blended with other ingredients as desired, and extruded under pressure through an orifice to provide a film.

Among the polymers recited above, polyethylene oxide (PEO), when used alone or in combination with a hydrophilic cellulosic polymer, is particularly suited to hot melt extrusion processes, and achieves flexible, strong films. Additional plasticizers or polyalcohols may optionally be included. Non-limiting examples of suitable cellulosic polymers for combination with PEO include HPC and HPMC. PEO and HPC have essentially no gelation temperature, while HPMC has a gelation temperature of 58-64° C. (Methocel EF available from Dow Chemical Co.). Moreover, these films are sufficiently flexible even when substantially free of organic solvents, which may be removed without compromising film properties. As such, if there is no solvent present, then there is no plasticizer in the films. PEO based films also exhibit good resistance to tearing, little or no curling, and fast dissolution rates when the polymer component contains appropriate levels of PEO.

To achieve the desired film properties, the level and/or molecular weight of PEO in the polymer component may be varied. Modifying the PEO content affects properties such as tear resistance, dissolution rate, and adhesion tendencies. Thus, one method for controlling film properties is to modify the PEO content. For instance, in some embodiments rapid dissolving films are desirable. By modifying the content of the polymer component, the desired dissolution characteristics can be achieved.

In accordance with the present invention, PEO desirably ranges from about 20% to 100% by weight in the polymer component. In some embodiments, the amount of PEO desirably ranges from about 1 mg to about 200 mg.

In some embodiments of the instant invention, a hydrophilic cellulosic polymer such as HPMC may also be used as a water soluble polymer, in from about 0% to about 80% by weight, or in a ratio of up to about 4:1 with the PEO, and desirably in a ratio of about 1:1.

In some embodiments, it may be desirable to vary the PEO levels to promote certain film properties. To obtain films with high tear resistance and fast dissolution rates, levels of about 50% or greater of PEO in the polymer component are desirable. To achieve adhesion prevention, i.e., preventing the film from adhering to the roof of the mouth, PEO levels of about 20% to 75% are desirable. In some embodiments, however, adhesion to the roof of the mouth may be desired, such as for administration to animals or children. In such cases, higher levels of PEO may be employed. More specifically, structural integrity and dissolution of the film can be controlled such that the film can adhere to mucosa and be readily removed, or adhere more firmly and be difficult to remove, depending on the intended use.

The molecular weight of the PEO may also be varied. High molecular weight PEO, such as about 4 million, may be desired to increase mucoadhesivity of the film. More desirably, the molecular weight may range from about 100,000 to 900,000, more desirably from about 100,000 to 600,000, and most desirably from about 100,000 to 300,000. In some embodiments, it may be desirable to combine high molecular weight (600,000 to 900,000) with low molecular weight (100,000 to 300,000) PEOs in the polymer component.

For instance, certain film properties, such as fast dissolution rates and high tear resistance, may be attained by combining small amounts of high molecular weight PEOs with larger amounts of lower molecular weight PEOs. Desirably, such compositions contain about 60% or greater levels of the lower molecular weight PEO in the PEO-blend polymer component.

To balance the properties of adhesion prevention, fast dissolution rate, and good tear resistance, desirable film compositions may include about 50% to 75% low molecular weight PEO, optionally combined with a small amount of a higher

molecular weight PEO, with the remainder of the polymer component containing a hydrophilic cellulosic polymer (HPC or HPMC).

Controlled Release Films

The term "controlled release" is intended to mean the release of active at a pre-selected or desired rate. This rate will vary depending upon the application. Desirable rates include fast or immediate release profiles as well as delayed, sustained or sequential release. Combinations of release patterns, such as initial spiked release followed by lower levels of sustained release of active are contemplated. Pulsed drug releases are also contemplated.

The polymers that are chosen for the films of the present invention may also be chosen to allow for controlled disintegration of the active. This may be achieved by providing a substantially water insoluble film that incorporates an active that will be released from the film over time. This may be accomplished by incorporating a variety of different soluble or insoluble polymers and may also include biodegradable polymers in combination. Alternatively, coated controlled-release active particles may be incorporated into a readily soluble film matrix to achieve the controlled-release property of the active inside the digestive system upon consumption.

Films that provide a controlled-release of the active are particularly useful for buccal, gingival, sublingual and vaginal applications. The films of the present invention are particularly useful where mucosal membranes or mucosal fluid is present due to their ability to readily wet and adhere to these areas.

The convenience of administering a single dose of a medication which releases active ingredients in a controlled fashion over an extended period of time as opposed to the administration of a number of single doses at regular intervals has long been recognized in the pharmaceutical arts. The advantage to the patient and clinician in having consistent and uniform blood levels of medication over an extended period of time are likewise recognized. The advantages of a variety of sustained release dosage forms are well known. However, the preparation of a film that provides the controlled-release of an active has advantages in addition to those well-known for controlled-release tablets. For example, thin films are difficult to inadvertently aspirate and provide an increased patient compliance because they need not be swallowed like a tablet. Moreover, certain embodiments of the inventive films are designed to adhere to the buccal cavity and tongue, where they controllably dissolve. Furthermore, thin films may not be crushed in the manner of controlled release tablets which is a problem leading to abuse of drugs such as Oxycontin.

The actives employed in the present invention may be incorporated into the film compositions of the present invention in a controlled release form. For example, particles of drug may be coated with polymers such as ethyl cellulose or polymethacrylate, commercially available under brand names such as Aquacoat ECD and Eudragit E-100, respectively. Solutions of drug may also be absorbed on such polymer materials and incorporated into the inventive film compositions. Other components such as fats and waxes, as well as sweeteners and/or flavors may also be employed in such controlled release compositions.

The actives may be taste-masked prior to incorporation into the film composition, as set forth in PCT Application No. PCT/US02/32594, titled, Uniform Films For Rapid Dissolve Dosage Form Incorporating Taste-Masking Compositions, (based on U.S. Provisional Application No. 60/414,276, Express Mail Label No.: EU552991605 US of the same title, filed Sep. 27, 2003) the entire subject matter of which is incorporated by reference herein. Taste-masking of actives, as disclosed therein, is described herein below.

Particle Formation

The active agents employed in the present invention are incorporated into the film compositions of the present invention in a taste-masked or controlled-release form. Taste-masking is useful to avoid unpleasant taste effects, such as bitterness, often associated with the active agents such as pharmaceuticals. In this embodiment, particles of drug may be coated with taste-masking agents, for example polymers, oils, or waxes. Additionally, organoleptic agents, such as, but not limited to sweeteners and/or flavors, may also be employed in such taste-masked compositions, including in the coating layer of the taste masking agent. In alternative embodiments, the particle coatings impart controlled-release, delayed-release, or sustained-release characteristics, delaying the release of active agent from the particle in the mouth or gut of the consumer.

The taste-masked or controlled-release particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof.

Useful organoleptic agents include flavors and sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Compositions employing particulate active agents incorporated into films with taste-masked coatings are disclosed in PCT application WO 2003/030883, titled "Uniform Films For Rapid Dissolve Dosage Form Incorporating Taste-Masking Compositions," the entire subject matter of which is incorporated by reference herein. As used in this application, any reference to taste-masking by coating particulate active agents should also be understood to encompass controlled-release coatings of particulate active agents.

An important consideration for the film based drug delivery compositions involving a controlled-release or taste-mask particle technology is that the drug containing particles remain chemically stable and do not release the active drug during the mixing and film forming operations of the manufacturing process. Accordingly, with respect to films formed by a wet casting method, the controlled-release or taste-mask particle compositions should be sufficiently stable in the mixer prior to the film forming steps, and the casting and drying steps, so that the particles remain intact in the finished product. In the hot melt extrusion film manufacturing process, the particles must be stable in the extrusion apparatus and any subsequent steps, so that the particles remain intact in the finished product.

In one embodiment, the taste-masking or controlled-release agent is a thin film coating over a particulate bioeffecting agent. Useful coatings in this embodiment include polymeric and non-polymeric materials.

Non-limiting examples of polymers include acrylic polymers, cellulosic polymers or vinyl polymers. Non-limiting examples of non-polymeric materials include crown ethers, fully hydrogenated oils and waxes. Moreover, the taste masking agents may be water soluble, water insoluble or partially water soluble.

For example, the coating material may be carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch, including tapioca starch, rice starch, corn starch, potato starch, and wheat starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin;

dextran; proteins, such as, gelatin, zein, gluten, soy protein, soy protein isolate, and whey protein; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

Useful acrylic polymers include those available under the trade name Eudragit® from Röhm America, LLC, such as methacrylic acid co-polymers sold under the trade names Eudragit E®, Eudragit L®, Eudragit RD® and Eudragit S®, and polyethylacrylate-methylmethacrylate sold under the trade name, Eudragit NE®. These acrylic polymers are generally water soluble materials.

Useful cellulosic polymers include alkylcelluloses such as methyl or ethyl cellulose, and hydroxyalkylcelluloses, such as hydroxylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxymethylpropyl cellulose, and combinations thereof. Useful alkylcelluloses include those sold under the trade names Methocel E™ by Dow Chemicals. Additionally, useful ethylcelluloses are commercially available commercially available from FMC Corporation under brand name Aquacoat ECD. These polymers are generally water soluble materials.

Moreover, the pharmaceutically active agents may be sprayed and congealed with fully hydrogenated oils or waxes considered safe for human consumption and are relatively stable. Useful, but non-limiting, pharmaceutically acceptable oils include mineral oil, peanut oil, soybean oil, sunflower oil, corn oil, olive oil, hard palm oil and rapeseed oil.

Furthermore, crown ether compounds, such as cyclodextrins, are also useful for coating the pharmaceutically active agents. The pharmaceutically active agents are taste masked with crown ethers through entrapment or coaccervation methods. Useful cyclodextrins are commercially available under the trade name of Trappsol® from CTD, Inc.

In some embodiments, the aforementioned polymeric coatings that affect taste masking may be desirable over complexation with ion exchange resins, as has been disclosed in, for example, European Patent No. EP1267829 B1, because of the high drug loadings that are possible with the polymeric coatings as compared to complexation with ion exchange resins. Despite allegations to the contrary, we have found the highest useful drug loading on an ion exchange resin is about 30% by weight. By contrast, the particle coating of this invention can be used with 50-95% drug loading, meaning that a taste-masked particle can contain up to about 95% by weight active and as little as 5% by weight taste-masking polymer. This is a substantially greater drug loading than known ion exchange resins, and very important given the limited size and weight of a film dosage unit, in which maximizing drug loading into a uniform film is an important consideration.

In some embodiments, the taste-masking or control-release agent may be present in the amount of about 5-80% by weight of the particle. In another embodiment, the taste-masking agent is present in the amount of about 5-60% by weight of the particle. In yet another embodiment, the taste-masking agent is present in the amount of about 25-35% by weight of the particle. The precise loading of drug in the taste-mask coated particle is a function of many parameters, including the drug, the coating, and any flavors present in the particle or the film forming matrix.

Pharmaceutically active agents may be taste-masked with the above-described taste-masking agents by a variety of techniques. The techniques coat the pharmaceutically active agents or portions of the pharmaceutically active agents with taste-masking agents to avoid unpleasant taste effects, such as bitterness, often associated with the pharmaceutically active agents or drugs. Useful coating techniques include, but are not limited to, fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating and the like.

The fluidized bed coating method is commonly used in pharmaceutical industries for taste masking pharmaceutically active agents. Fluidized bed coaters achieve fluidization of the pharmaceutically active agents by introducing a continuous stream of process gas into a chamber. The coating material is deposited onto the suspended agent as it passes through the spray path of the coating material. The coated agent is dried. A relative low water solubility polymer is typically used to coat the active particles' surface. Minimum limits on particle sizes are about 100 to 120 microns. Smaller particle sizes are difficult to achieve due to process limitation and product loss. Water insoluble pharmaceutically active agents may be suitable coated with water soluble taste masking agents with this method.

In the spray congealing method both the pharmaceutically active agents and the coating materials are sprayed simultaneously into a chamber supplied with process gas to create a uniformly coated active. This method typically involves the coating of the actives with material that could be melted at reasonable temperatures, for example fatty materials or polymers such as certain Eudragit® polymers. The mix of materials are sprayed through a fine nozzle and cooled through a temperature-control air stream or a cold surface. Consideration of mixture temperature is important. The melting temperature of the coating agent selected should not exceed a degradation temperature of the pharmaceutically active agent.

In the agglomeration or granulation method, the pharmaceutically active agents are mixed with the taste-masking agents and a solvent by mechanical means or by spray drying. The solvent is gradually removed by vacuum or heating, or both. Particles are then agglomerated. The agglomerated particles are not typically coated entirely with the taste masking agent and some bitterness may result accordingly. The bitterness, however, may be further reduced by incorporating such coated particles in the films of the present invention.

In typical entrapment coating methods, certain compounds having specific properties that can trap pharmaceutically active agents into its molecule cages must first be selected. Compounds, like certain specifically made starches and crown ether type molecules, such as cyclodextrins and zeolites, are useful with this method. The compounds and the agents are entrapped by ionic attraction. The entrapped agents are then precipitated from solution.

The coaccervation coating method uses two polymers with opposite charges in solution. When the solution is neutralized an insoluble matrix will precipitate from solution and trap the pharmaceutically active agents therein. Examples include interactions of gum arabic and gelatin solutions and interactions of cyclodextrins and protein solutions.

In the infusion method pharmaceutically active agents and flavors or sweeteners are dissolved and infused into a polymer matrix to form a dry powder. In spin coating methods, pharmaceutically active agents are combined with sugars or fats and spun into coated particles. Details of the method are disclosed in U.S. Pat. No. 5,028,632, the contents of which is incorporated herein by reference. In ion exchange coating, ionic bonding of pharmaceutically active agents to ion exchange resins masks the tastes of the agents.

Extrusion and spheronization methods may also be used for taste-masking pharmaceutically active particulates. Ratios of active(s) and polymer(s) (such as, starch, cellulose, gum and/or combinations thereof) are first mixed and thicken by adding a small amount of water. The thickened mixture is

then extruded through a single or double nozzle screw. Small spherical particles are formed by a Marumerization® process. Desirable particle sizes are obtained through process control and particulate sieving.

Lyophilization (Freeze-Drying) methods may also be used with the practice of the present invention A combination of polymer(s) (such as, starch, gum, cellulose and/or combinations thereof) with active(s) are mixed and dissolved (or dispersed) in aqueous medium. This mixture is then freeze-dried on a pre-form substrate. Desirable particles sizes can be obtained by process control and product sieving.

In some instances, taste-masking may amount to the addition of two components together, neither of which are particularly pleasing to the taste, but which, due to their chemical makeup, counteract each other or allow for a third substance or more of one of the substances to be added without a concomitant reduction in pleasantness of the taste.

The edible water-soluble delivery system of the present invention further includes one or more members selected from antifoaming agents, plasticizing agents, surfactants, emulsifying agents, thickening agents, binding agents, cooling agents, saliva-stimulating agents, sweetening agents, antimicrobial agents, antigens and combinations thereof.

The particles used in the present invention desirably have a particle size of less than about 200 microns and the taste-masking agent is present in amounts of about 15-80% by weight of the particle. A particle size of about 150 microns or less is also useful. Desirably, the particle size of the particle is about 100 microns or less. Desirably, the thickness of the film is less than about 380 microns, for example, less than about 250 microns. Furthermore, the taste-masking agent may be present in the amount of about 20-60% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle.

In some embodiments, the particulate bioeffecting agent coated with a taste-masking or controlled-release polymer may have a particle size of between 50 to 250 microns. Desirably, the size of the combined particulate and taste-masking agent have a particle size of 150 microns or less, for example 100 microns or less. Particle sizes less than 50 microns may be unsuitable in some embodiments because it is inefficient to coat such small particles due to the large surface area.

Particle sizes of greater than 250 microns may be unsuitable in some embodiments because the larger particles can "bridge" during the film forming process, meaning that the particle can extend from the bottom surface to the top surface of the film, or even protrude beyond the surface of the film. Such bridging may cause streaking and non-uniformity of the finished film. Any protruding particles also may be subject to environmental stresses and premature decomposition, leading to non-uniformity of dosing.

The aforementioned particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are especially desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

When an active agent is present in the film, the amount of active per unit area is determined by the uniform distribution of the film. For example, when the films are cut into individual dosage forms, the amount of the active in the dosage form can be known with a great deal of accuracy. This is achieved because the amount of the active in a given area is substantially identical to the amount of active in an area of the same dimensions in another part of the film. The accuracy in dosage is particularly advantageous when the active is a medicament, i.e., a drug.

The uniformity is determined by the presence of no more than a 10% by weight of drug variance throughout the matrix. Desirably, the drug variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. Moreover, the particulates have a particle size of 200 microns or less. Furthermore, the film matrix desirably has a thickness of less than about 380 microns.

Active Agents

The active components that may be incorporated into the films of the present invention include, without limitation, pharmaceutical and cosmetic actives, drugs, medicaments, proteins, antigens or allergens such as ragweed pollen, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

Drugs

A wide variety of medicaments, bioactive active substances and pharmaceutical compositions may be included in the dosage forms of the present invention. Examples of useful drugs include ace-inhibitors, antianginal 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, biological response modifiers, 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, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Examples of medicating active ingredients contemplated for use in the present invention include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in

combination with magnesium hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin®), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

Other preferred drugs for other preferred active ingredients for use in the present invention include anti-diarrheals such as immodium AD, anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, chlorpheniramine maleate, dextromethorphan, pseudoephedrine HCl and diphenhydramine may be included in the film compositions of the present invention.

Also contemplated for use herein are anxiolytics such as alprazolam (available as Xanax®); anti-psychotics such as clozopin (available as Clozaril®) and haloperidol (available as Haldol®); non-steroidal anti-inflammatories (NSAID's) such as dicyclofenacs (available as Voltaren®) and etodolac (available as Lodine®), anti-histamines such as loratadine (available as Claritin®), astemizole (available as Hismanal™), nabumetone (available as Relafen®), and Clemastine (available as Tavist®); anti-emetics such as granisetron hydrochloride (available as Kytril®) and nabilone (available as Cesamet™); bronchodilators such as Bentolin®, albuterol sulfate (available as Proventil®); anti-depressants such as fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), and paroxtine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enalaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®); anti-Alzheimer's agents, such as nicergoline; and Ca^H-antagonists such as nifedipine (available as Procardia® and Adalat®), and verapamil hydrochloride (available as Calan®).

Erectile dysfunction therapies include, but are not limited to, drugs for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful non-limiting drugs include sildenafils, such as Viagra®, tadalafils, such as Clalis®, vardenafils, apomorphines, such as Uprima®, yohimbine hydrochlorides such as Aphrodyne®, and alprostadils such as Caverject®.

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidien, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-ordibasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

Anti-inflammatory agents include steroidal anti-inflammatory drugs, such as cortisone, triamcinalone, prednisone, prednisolone, and the like.

Other Actives

The pharmaceutically active agents employed in the present invention may include allergens or antigens, such as, but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

An anti-oxidant may also be added to the film to prevent the degradation of an active, especially where the active is photosensitive.

Cosmetic active agents may include breath freshening compounds like menthol, other flavors or fragrances, especially those used for oral hygiene, as well as actives used in dental and oral cleansing such as quaternary ammonium bases. The effect of flavors may be enhanced using flavor enhancers like tartaric acid, citric acid, vanillin, or the like.

Dosages

The film products of the present invention are capable of accommodating a wide range of amounts of the active ingredient. The films are capable of providing an accurate dosage amount (determined by the size of the film and concentration of the active in the original polymer/water combination) regardless of whether the required dosage is high or extremely low. Therefore, depending on the type of active or pharmaceutical composition that is incorporated into the film, the active amount may be as high as about 300 mg, desirably up to about 150 mg or as low as the microgram range, or any amount therebetween.

The film products and methods of the present invention are well suited for high potency, low dosage drugs. This is accomplished through the high degree of uniformity of the films. Therefore, low dosage drugs, particularly more potent racemic mixtures of actives are desirable.

Flavors

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

Useful flavors or flavoring agents include 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. Non-limiting 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 the like. These flavorings can be used individually or in combination. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in combination. Flavorings such as aldehydes and esters including cinnamylacetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and the like may also be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamicaldehyde (cinna-

mon); 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); 12,6-dimethyl-5-heptenal, i.e. melonal (melon); 2 dimethyloctanal (greenfruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations 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. 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. ln general, amounts of about 0.1 to about 30 wt % are useful with the practice of the present invention.

Sweeteners

Suitable sweeteners include both natural and artificial sweeteners. Non-limiting examples of suitable sweeteners include, e.g.:

water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), high fructose corn syrup, maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, and dihydrochalcones;

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;

dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame), 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,dihydrophenylglycine, L-aspartyl-2,5-dihydro-L-phenylalanine, L-aspartyl-L-(1-cyclohexyen)-alanine, and the like;

water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as a chlorinated derivatives of ordinary sugar (sucrose), known, for example, as sucralose; and

protein based sweeteners such as thaurnatoccous danielli (Thaurnatin 1 and 11).

naturally occurring high intensity sweeteners, such as Lo Han Kuo, stevia, steviosides, monellin, and glycyrrhizin.

ln 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. 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.

Colors

Color additives useful in this invention include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide.

Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. lnorganic pigments are preferred, such as the oxides or iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

Film Forming Processes

The films of the present invention may be formed by several different techniques known in the art of forming films, for example, wet casting, or hot melt extrusion methods.

Desirably, the thickness of the film is less than about 380 microns, for example, less than about 250 microns.

Wet-Cast Films

ln the wet casting processes, the films may have a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting, deposition, or extrusion film forming method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Pat. No. 4,631,837 to Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

The objective of the drying process is to provide a method of drying the films that avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. ln conventional oven drying methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. ln such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the

area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface.

This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the bottom up, such films result.

The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_l) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

$$V_o=(2gr^r)(\rho_p-\rho_l)/9\mu$$

At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

Stokian analyses have shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v, can be expressed as:

$$v/V_o=1/(1+\kappa\phi)$$

where κ=a constant, and ϕ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o=1+2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At higher volume fractions, the viscosity of the dispersion can be expressed as

$$\mu/\mu_o=1+2.5\phi+C_1\phi^2+C_2\phi^3+\ldots$$

where C is a constant.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The 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. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., <500 μm. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated from the yield stress values. In the case of isolated spherical particles, the maximum shear stress developed in settling through a medium of given viscosity can be given as

$$\tau_{max}=3V_t\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability 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. For viscoelastic fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt %, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate range. During mixing, pumping, and film casting, shear rates in the range of 10-10^5 sec.$^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelas-

ticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)}=\alpha_o^{(n-1/n)}-((n-1)/(2n-1))(\tau/K)^{1/n}(2\pi/\lambda)^{(3+n)/n}h^{(2n+1)/n}t$$

where α is the surface wave amplitude, α_o is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote thin film formation and uniformity.

Wet-Cast Film Forming Methods

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most desirably less than about 2%. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a pre-mix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

FIG. **6** shows an apparatus **20** suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch **22**, which includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank **24**. The components for pre-mix or master batch **22** are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank **24**. Then a pre-determined amount of the master batch is controllably fed via a first metering pump **26** and control valve **28** to either or both of the first and second mixers, **30**, **30'**. The present invention, however, is not limited to the use of two mixers, **30**, **30'**, and any number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers **30**, **30'**, such as parallel sequencing as depicted in FIG. **6**, and other sequencing or arrangements of mixers, such as series or combination of parallel and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, **32**, **32'**, in each of the mixers, **30**, **30'**. Desirably, the residence time of the pre-mix or master batch **22** is minimized in the mixers **30**, **30'**. While complete dispersion of the drug into the pre-mix or master batch **22** is desirable, excessive residence times may result in leaching or dissolving of the drug, especially in the case for a soluble drug. Thus, the mixers **30**, **30'** are often smaller, i.e. lower residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch **22**. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan **36** through the second metering pumps, **34**, **34'**. The metering roller **38** determines the thickness of the film **42** and applies it to the application roller. The film **42** is finally formed on the substrate **44** and carried away via the support roller **46**.

The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

Roll coating, or more specifically reverse roll coating, is useful for forming films in accordance with the present invention. This procedure provides excellent control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller **40** (see FIG. **6**) by the precision setting of the gap between the upper metering roller **38** and the applicator roller. The coating is transferred from the applicator roller to the substrate **44** as it passes around the support roller **46** adjacent to the application roller. Both three roll and four roll processes are common.

The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is nor-

mally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

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. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch premix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

The particles of the present invention may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film prior to the drying of the film. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, but non-limiting, techniques include the use of an additional roller to place the particles on the film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securably disposed onto the film, such as being embedded into the film. Moreover, such particles are desirably not fully encased or fully embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a "gap" between a "knife" and a support roller. As the coating and substrate pass through, the excess is scraped off.

Air knife coating is where the coating is applied to the substrate and the excess is "blown off" by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Anti-Foaming and De-Foaming Compositions

Anti-foaming and/or de-foaming components may also be used with the films of the present invention. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. As described above, such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other anti-foam and/or de-foaming agents may suitable be used.

Simethicone is generally used in the medical field as a treatment for gas or colic in babies. Simethicone is a mixture of fully methylated linear siloxane polymers containing repeating units of polydimethylsiloxane which is stabilized with trimethylsiloxy end-blocking unites, and silicon dioxide. It usually contains 90.5-99% polymethylsiloxane and 4-7% silicon dioxide. The mixture is a gray, translucent, viscous fluid which is insoluble in water.

When dispersed in water, simethicone will spread across the surface, forming a thin film of low surface tension. In this way, simethicone reduces the surface tension of bubbles air located in the solution, such as foam bubbles, causing their collapse. The function of simethicone mimics the dual action of oil and alcohol in water. For example, in an oily solution any trapped air bubbles will ascend to the surface and dissipate more quickly and easily, because an oily liquid has a lighter density compared to a water solution. On the other hand, an alcohol/water mixture is known to lower water density as well as lower the water's surface tension. So, any air bubbles trapped inside this mixture solution will also be easily dissipated. Simethicone solution provides both of these advantages. It lowers the surface energy of any air bubbles that trapped inside the aqueous solution, as well as lowering the surface tension of the aqueous solution. As the result of this unique functionality, simethicone has an excellent anti-foaming property that can be used for physiological processes (anti-gas in stomach) as well as any for external processes that require the removal of air bubbles from a product.

In order to prevent the formation of air bubbles in the films of the present invention, the mixing step can be performed under vacuum. However, as soon as the mixing step is completed, and the film solution is returned to the normal atmosphere condition, air will be re-introduced into or contacted with the mixture. In many cases, tiny air bubbles will be again trapped inside this polymeric viscous solution. The incorporation of simethicone into the film-forming composition either substantially reduces or eliminates the formation of air bubbles.

Simethicone may be added to the film-forming mixture as an anti-foaming agent in an amount from about 0.01 weight percent to about 5.0 weight percent, more desirably from about 0.05 weight percent to about 2.5 weight percent, and most desirably from about 0.1 weight percent to about 1.0 weight percent.

Drying Wet Cast Films

The wet film may be dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film **48** (see FIG. **6**). Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film,

both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, 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. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

The films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, proteins, or antigens, which may have a low degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

In alternative embodiments, it may be desirable to dry films at high temperatures. High heat drying produces uniform films, and leads to greater efficiencies in film production. Films containing sensitive active components, however, may face degradation problems at high temperatures. Degradation is the "decomposition of a compound . . . exhibiting well-defined intermediate products." The American Heritage Dictionary of the English Language (4^{th} ed. 2000). Degradation of an active component is typically undesirable as it may cause instability, inactivity, and/or decreased potency of the active component. For instance, if the active component is a drug or bioactive material, this may adversely affect the safety or efficacy of the final pharmaceutical product. Additionally, highly volatile materials will tend to be quickly released from this film upon exposure to conventional drying methods.

Degradation of an active component may occur through a variety of processes, such as, hydrolysis, oxidation, and light degradation, depending upon the particular active component. Moreover, temperature has a significant effect on the rate of such reactions. The rate of degradation typically doubles for every 10° C. increase in temperature. Therefore, it is commonly understood that exposing an active component to high temperatures will initiate and/or accelerate undesirable degradation reactions.

Proteins are one category of useful active ingredients that will degrade, denature, or otherwise become inactive when they are exposed to high temperatures for extended periods of time. Proteins serve a variety of functions in the body such as enzymes, structural elements, hormones and immunoglobulins. Examples of proteins include enzymes such as pancreatin, trypsin, pancrelipase, chymotrypsin, hyaluronidase, sutilains, streptokinaw, urokinase, altiplase, papain, bromelainsdiastase, structural elements such as collagen and albumin, hormones such as thyroliberin, gonadoliberin, adrenocorticottropin, corticotrophin, cosyntropin, sometrem, somatropion, prolactin, thyrotropin, somatostatin, vasopressin, felypressin, lypressin, insulin, glucagons, gastrin, pentagastrin, secretin, cholecystokinin-pancreozymin, and immunomodulators which may include polysaccharides in addition to glycoproteins including cytokines which are useful for the inhibition and prevention of malignant cell growth such as tumor growth. A suitable method for the production of some useful glycoproteins is disclosed in U.S. Pat. No. 6,281,337 to Cannon-Carlson, et al., which in incorporated herein in its entirety.

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.

As discussed herein, the flowable mixture is prepared to be uniform in content in accordance with the teachings of the present invention. Uniformity must be maintained as the flowable mass was formed into a film and dried. During the drying process of the present invention, several factors produce uniformity within the film while maintaining the active component at a safe temperature, i.e., below its degradation temperature. First, the films of the present invention have an extremely short heat history, usually only on the order of minutes, so that total temperature exposure is minimized to the extent possible. The films are controllably dried to prevent aggregation and migration of components, as well as preventing heat build up within. Desirably, the films are dried from the bottom. Controlled bottom drying, as described herein, prevents the formation of a polymer film, or skin, on the top surface of the film. As heat is conducted from the film bottom upward, liquid carrier, e.g., water, rises to the film surface. The absence of a surface skin permits rapid evaporation of the liquid carrier as the temperature increases, and thus, concurrent evaporative cooling of the film. Due to the short heat exposure and evaporative cooling, the film components such as drag or volatile actives remain unaffected by high temperatures. In contrast, skinning on the top surface traps liquid carrier molecules of increased energy within the film, thereby causing the temperature within the film to rise and exposing active components to high, potentially deleterious temperatures.

Second, thermal mixing occurs within the film due to bottom heating and absence of surface skinning. Thermal mixing occurs via convection currents in the film. As heat is applied to the bottom of the film, the liquid near the bottom increases in temperature, expands, and becomes less dense. As such, this hotter liquid rises and cooler liquid takes its place. While rising, the hotter liquid mixes with the cooler liquid and

shares thermal energy with it, i.e., transfers heat. As the cycle repeats, thermal energy is spread throughout the film.

Robust thermal mixing achieved by the controlled drying process of the present invention produces uniform heat diffusion throughout the film. In the absence of such thermal mixing, "hot spots" may develop. Pockets of heat in the film result in the formation of particle aggregates or danger areas within the film and subsequent non-uniformity. The formation of such aggregates or agglomerations is undesirable because it leads to non-uniform films in which the active may be randomly distributed. Such uneven distribution may lead to large differences in the amount of active per film, which is problematic from a safety and efficacy perspective.

Furthermore, thermal mixing helps to maintain a lower overall temperature inside the film. Although the film surfaces may be exposed to a temperature above that at which the active component degrades, the film interior may not reach this temperature. Due to this temperature differential, the active does not degrade.

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.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus **50** is depicted in FIG. **7**. Drying apparatus **50** is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film **42** which is disposed on substrate **44**. Hot air enters the entrance end **52** of the drying apparatus and travels vertically upward, as depicted by vectors **54**, towards air deflector **56**. The air deflector **56** redirects the air movement to minimize upward force on the film **42**. As depicted in FIG. **7**, the air is tangentially directed, as indicated by vectors **60** and **60'**, as the air passes by air deflector **56** and enters and travels through chamber portions **58** and **58'** of the drying apparatus **50**. With the hot air flow being substantially tangential to the film **42**, lifting of the film as it is being dried is thereby minimized. While the air deflector **56** is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends **62** and **62'** of the drying apparatus **50** are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors **64** and **64'**, which tend to provide a pulling or drag effect of the film **42** to prevent lifting of the film **42**. Lifting of the film **42** may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film **42** as the film **42** and/or substrate **44** lift away from the processing equipment.

FIG. **8** is a sequential representation of the drying process of the present invention. After mechanical mixing, the film may be placed on a conveyor for continued thermal mixing during the drying process. At the outset of the drying process, depicted in Section A, the film **1** preferably is heated from the bottom **10** as it is travels via conveyor (not shown). Heat may be supplied to the film by a heating mechanism, such as, but not limited to, the dryer depicted in FIG. **7**. As the film is heated, the liquid carrier, or volatile ("V"), begins to evaporate, as shown by upward arrow **50**. Thermal mixing also initiates as hotter liquid, depicted by arrow **30**, rises and cooler liquid, depicted by arrow **40**, takes its place. Because no skin forms on the top surface **20** of the film **1**, as shown in Section B the volatile liquid continues to evaporate **50** and thermal mixing **30**/**40** continues to distribute thermal energy throughout the film. Once a sufficient amount of the volatile liquid has evaporated, thermal mixing has produced uniform heat diffusion throughout the film **1**. 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. Although minor amounts of liquid carrier, i.e., water, may remain subsequent to formation of the visco-elastic, the film may be dried further without movement of the particles, if desired.

In one embodiment, a specific example of an appropriate drying method is that disclosed by Magoon in U.S. Pat. No. 4,631,837. Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an important property of water. Although water transmits energy by conduction and convection both within and to its surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this creates a "refractance window." This means that infrared energy is permitted to radiate through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the film.

Another method of controlling the drying process involves a zone drying procedure, employing an apparatus containing a drying tunnel having one or more drying zones and a continuous belt conveying the film through the drying zones. The conditions of each drying zone may vary, for example, temperature and humidity may be selectively chosen. It may be desirable to sequentially order the zones to provide a stepped up drying effect.

The speed of the zone drying conveyor may be constant, or altered at a particular stage of the drying procedure to increase or decrease exposure of the film to the conditions of the desired zone. Whether continuous or modified, the zone drying dries the film without surface skinning.

According to an embodiment of the zone drying apparatus **100**, shown in FIG. **35**, the film **110** may be fed onto the continuous belt **120**, which carries the film through the different drying zones. The first drying zone that the film travels through **101** may be a warm and humid zone. The second zone **102** may be hotter and drier, and the third zone **103** may also be hot and dry. These different zones may be continuous, or alternatively, they may be separated, as depicted by the zone drying apparatus **200** in FIG. **36**. The zone drying apparatus, in accordance with the present invention, is not limited to three drying zones. The film may travel through lesser or additional drying zones of varying heat and humidity levels, if desired, to produce the controlled drying effect of the present invention.

To further control temperature and humidity, the drying zones may include additional atmospheric conditions, such as inert gases. The zone drying apparatus further may be adapted

to include additional processes during the zone drying procedure, such as, for example, spraying and laminating processes, so long as controlled drying is maintained in accordance with the invention.

The films may initially have a thickness of about 500 μm to about 1,500 μm, or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm, or about 0.1 mils to about 10 mils. Desirably, the dried films will have a thickness of about 2 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

Extrusion Film Forming Methods

In alternative embodiments, the film products of the present invention may be formed by extrusion rather than casting methods. Extrusion is particularly useful for film compositions containing polyethylene oxide-based polymer components. For instance, a single screw extrusion process may be employed in accordance with the present invention. According to such an extrusion process, pressure builds in the polymer melt so that it may be extruded through a die or injected into a mold.

As further explanation, a single screw extruder for use in the process of the present invention may include a barrel **300** containing a number of zones **200**, as shown in the extruder **100** depicted in FIG. **37**. These zones **200** may have varying temperatures and pressures. For instance, it may be desirable for the zones to increase in temperature as the composition proceeds through the barrel **300** to the extrusion die **400**. Any number of zones may be included in accordance with the present invention. In addition, the speed of extrusion may be controlled to produce desired film properties. For example, the extrusion composition may be held for an extended time period in the screw mixing chamber. Although this discussion is directed to single screw extrusion, other forms of extrusion are known to those skilled in the art and are considered well within the scope of the present invention.

A further advantage to extrusion film forming methods is that no added solvent is normally employed, which simplifies the film forming process particularly where controlled release or taste-masked active agents are employed. Where the active agent is in a particle coated with a water soluble polymer, the absence of added solvent during manufacture reduces the likelihood of dissolution or release of the taste-masked or controlled-release coated active agent during manufacture due to dissolution or solvent effects.

It may be particularly desirable to employ extrusion methods for forming film compositions containing polyethylene oxide (PEO) polymer components. In this embodiment, the compositions may contain PEO or PEO blends in the polymer component, and may be substantially free of solvents. A particularly useful polymer that may be blended with PEO is a hydrophilic cellulosic polymer, such as hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), or hydroxymethyl cellulose (HMC). The aforementioned polymers are known in the art of hot melt extrusion as suitable thermoplastic, water soluble polymers for drugs. See, for example, McGinity et al., in Encycl. Pharm. Tech., 3d Ed., vol. 2, pp. 2004-2020 (2006). The PEO containing film forming compositions may optionally be essentially free of added plasticizers, surfactants, and polyalcohols. The compositions may be extruded as a sheet at processing temperatures of less than about 90° C. in an extrusion apparatus.

In a typical extrusion method, a pre-mix of water soluble polymers such as PEO or PEO blends is fed into the extrusion apparatus, such as a single screw extruder shown in FIG. **37**. The active, which may be a taste-masked particulate, may be added to the polymer feed or added to the extruder in a separate feed. The mixture is blended, and warmed and melted in the extruder screw to provide a uniform liquid matrix. The film may be formed by forcing the matrix through rollers or a die. The extrudate may be deposited onto a moving substrate as it leaves the extrusion orifice. Optionally, the speed of the substrate can be faster than the speed of the extrudate leaving the orifice, which stretches the extrudate to a desired film thickness. The film so formed will have a highly uniform distribution of active.

The extruded film composition may then be cooled by any mechanism known to those of ordinary skill in the art. For example, chill rollers, air cooling beds, or water cooling beds may be employed. The cooling step is particularly desirable for these film compositions because PEO tends to hold heat.

Optional Components

A variety of other components and fillers may also be added to the films of the present invention. These may include, without limitation, surfactants; plasticizers which assist in compatibilizing the components within the mixture; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother film surface by releasing oxygen from the film; and thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components.

The variety of additives that can be incorporated into the inventive compositions may provide a variety of different functions. Examples of classes of additives include excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof. These additives may be added with the active ingredient(s).

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragancanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

Such extenders may optionally be added in any desired amount desirably within the range of up to about 80%, desir-

ably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all components.

Further additives may be inorganic fillers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.02% to about 3% by weight and desirably about 0.02% to about 1% based on the weight of all components.

Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5% to about 30%, and desirably ranging from about 0.5% to about 20% based on the weight of the polymer.

There may further be added compounds to improve the flow properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form, especially those which are solid at room temperature. These fats desirably have a melting point of 50° C. or higher. Preferred are tri-glycerides with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantageously added alone or together with mono- and/or di-glycerides or phosphatides, especially lecithin. The mono- and di-glycerides are desirably derived from the types of fats described above, i.e. with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}-fatty acids.

The total amounts used of the fats, mono-, di-glycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5% to about 2% by weight of the total composition

It may be useful to add silicon dioxide, calcium silicate, or titanium dioxide in a concentration of about 0.02% to about 1% by weight of the total composition. These compounds act as texturizing agents.

These additives are to be used in amounts sufficient to achieve their intended purpose. Generally, the combination of certain of these additives will alter the overall release profile of the active ingredient and can be used to modify, i.e. impede or accelerate the release.

Lecithin is one surface active agent for use in the present invention. Lecithin can be included in the feedstock in an amount of from about 0.25% to about 2.00% by weight. Other surface active agents, i.e. surfactants, include, but are not limited to, cetyl alcohol, sodium lauryl sulfate, the Spans™ and Tweens™ which are commercially available from ICI Americas, Inc. Ethoxylated oils, including ethoxylated castor oils, such as Cremophor® EL which is commercially available from BASF, are also useful. Carbowax™ is yet another modifier which is very useful in the present invention. Tweens™ or combinations of surface active agents may be used to achieve the desired hydrophilic-lipophilic balance ("HLB"). The present invention, however, does not require the use of a surfactant and films or film-forming compositions of the present invention may be essentially free of a surfactant while still providing the desirable uniformity features of the present invention.

As additional modifiers which enhance the procedure and product of the present invention are identified, Applicants intend to include all such additional modifiers within the scope of the invention claimed herein.

Other ingredients include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, pregelatinize starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, and polyvinylalcohols.

Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or instable actives may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or instable actives to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

Testing Films for Uniformity

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, color, assay of active ingredients, 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.

A method for testing uniformity in accordance with the present invention includes conveying a film through a manufacturing process. This process may include subjecting the film to drying processes, dividing the film into individual dosage units, and/or packaging the dosages, among others. As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus, it is cut widthwise into at least one portion. The at least one portion has opposing ends that are separate from any other film portion. For instance, if the film is a roll, it may be cut into separate sub-rolls. Cutting the film may be accomplished by a variety of methods, such as with a knife, razor, laser, or any other suitable means for cutting a film.

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). Leaving the middle section intact permits the predominant portion of the film to proceed through the manufacturing process without interrupting the conformity of the film and creating sample-inducted gaps in the film. Accordingly, the concern of missing doses is alleviated as the film is further processed, e.g., packaged. Moreover, maintaining the completeness of cut portions or sub-rolls throughout the process will help to alleviate the possibility of interruptions in further film processing or packaging due to guilty control issues, for example, alarm stoppage due to notice of missing pieces.

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.

Moreover, it may be desirable to repeat the steps of sampling and testing throughout the manufacturing process. Testing at multiple intervals may ensure that uniform film dosages are continuously produced. Alterations to the process can be implemented at any stage to minimize non-uniformity between samples.

The cut portions may be tested for chemical and physical uniformity using any conventional means for examining and testing the film pieces known in the art. For example, visual inspection, conventional or electron microscopy, chemical testing, or use of analytical equipment may be used.

The testing can be used for quality control purposes, for example to assure that the physical and chemical content of the film is uniform and matches desired specifications. Additionally, the testing can be used to assay for desired content of active ingredients. Testing can also be used for other purposes, such as adjusting the manufacturing process to achieve optimum efficiency and appropriate physical and chemical properties and uniformity.

Uses of Thin Films

The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate that the active is released, which may allow for a sustained release delivery system. ln addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal, opthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. lf an adhesive is used, it will desirably be a food grade adhesive that is ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives themselves.

The films may be applied under or to the tongue of the mammal. When this is desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

The films of the present invention are desirably packaged in sealed, air and moisture resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to FlG. **1**, a packaged pharmaceutical dosage unit **10**, includes each film **12** individually wrapped in a pouch or between foil and/or plastic laminate sheets **14**. As depicted in FlG. **2**, the pouches **10**, **10'** can be linked together with tearable or perforated joints **16**. The pouches **10**, **10'** may be packaged in a roll as depicted in FlG. **5** or stacked as shown in FlG. **3** and sold in a dispenser **18** as shown in FlG. **4**. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

The features and advantages of the present invention are more fully shown by the following examples which are provided for purposes of illustration, and are not to be construed as limiting the invention in any way.

EXAMPLES

Preparation of Taste-Masked Pharmaceutically Active Agents

The following drugs were coated with taste masking components and were used in the films of the present invention.

a. Fluidized Bed Coating: A taste-masked particle was prepared having a core material of northindrone (Norlutin®). Northindrone was first sieved through a 60 mesh screen having a 250 micron sieve opening. The resulting particles, i.e., having particles sizes of less than 250 microns, were then coated by the fluidized bed coating procedure in a Verse Glatt Fluidized Bed using a Wurster Column. Accordingly, a 625 grams of 5% methylcellulose and 0.5% Acesulfame® K (a non-caloric sweetener) solution was prepared. The solution was then applied onto 500 grams of the sieved northindrone powder at an air pressure of 40 psi through a Gustav Schlick nozzle model 941. The fluidized bed temperature was heated and maintained at 115° F. during the spraying process. At the end of coating, the resulting particles were further dried therein for 3 minutes. A total of 530 grams taste masked northindrone was obtained.

b. Agglomeration Process: A sweetener solution of 94 grams of 2.5% sodium saccharin and 2.5% Acesulfame® K was prepared. A dry blend of 60 grams of hydroxypropylmethyl cellulose and 40 grams of silica dioxide with 20 grams polythiazide (Renese®) was made. The sweetener solution was then sprayed a little at a time onto the dry blend powder during low-shear mixing. The dry powder was, at this point, being agglomerated through the granulation/absorption process. The wet mixture was then dried in a convection oven at 105° F. for 17 hours. The resulting dried product was ground in a Fitz Hammer Mill grinder and sieved through a 100 mesh screen having a 149 micron sieve opening.

c. Pelletization Process: The following product was made using a model RV02 Mix Pelletizer (made by Eirich Machines Ltd.) at maximum mixing speed. A small of crashed ice was added, slowly through a funnel, to the 40 grams Loratidine®, 40 grams Aspartame®, 10 grams hydroxypropyl cellulose and 5 grams gum arabic powder mix in the mixer while mixing at low settings of both pan rotation and mixing motor. It took 1 to 2 minutes to add the ice. Once the ice addition was completed, both the pan and the rotor mix were turned to high speed to form spherical particles. The end point was determined by examining the particles using a low power microscope. When the end point is not reached after 2

minutes of intense mixing, additional 1 to 2 minutes mixing with or without adding more ice is tried. This procedure is repeated until the end point is reach, i.e., the spherical particles are formed. The wet samples obtained were dried in a tray dryer at 55° C. for about 5 hours. The resulting particles size ranged from 20 to 200 mesh. The particles were then sieved to obtain the desired particle size.

d. Infusion Method: A dry blend of 3.7 grams of Sucralose®, 10 grams fluoxetine HCl (Prozac®), and 1.25 grams polyvinylpyrrolidone were mixed uniformly. Water of 5.0 grams and 2.74 grams of propylene glycol were then added to the mixture and mixed thoroughly. To this mixture, 22 grams of hydroxypropylmethyl cellulose was added and blended under a high shear Stephan Mixer for at least 3 minutes. The resulting particles were sieved through a 100 mesh screen and were ready to be used in film matrix solution.

e. Triglyceride Reduction Formula™ microspheres from Southwest Research Institute were coated with ethylcellulose by a spinning and congealing particle producing process. The coated particles had a particle size of less than 100 microns. The polymer condensed on the drug particles thereby imparting a taste-masked pharmaceutically active agent.

f. Tamoxifen was produced by spray coating 50 to 100 micron sized particles of Eudragit® E100 (cationic methacrylate with dimethylamino ethyl ammonium groups). During fluidized coating, coated particles were isolated using a fractional separation device which insured particles having a size of less than 150 microns. The estimated level of coating was about 15%. The polymer condensed on the drug particles thereby imparting a taste-masked pharmaceutically active agent.

g. Torsemide was coated by a critical fluid process by dissolving torsemide in polyethylene glycol (400 molecular weight) which was added to a flowing stream of supercritical CO_2 by using a sonic spray nozzle. The resulting droplet size was controlled to produce approximated 150 micron sized spherical particles. The particles were then moved to an apparatus used for spraying a polymer coating. The polymer condensed on the drug particles thereby imparting a taste-masked pharmaceutically active agent. The polymer coating used was Eudragit® E100 dissolved in ethanol at 15% solids. The coated product was isolated by lowering the pressure and removal of the CO2 and the ethanol.

h. Felodipine was coated via an emulsion solvent evaporation method using acrylate methacrylate copolymers (Eudragit® RL or Eudragit® PO and Eudragit® RS or Eudragit® PO) as the coating materials. The mean sphere diameter was 12 microns with a drug loading of about 50%.

i. Digoxin was coated with Trappsol® cyclodextrin. A 50% (wt/vol) solution of chemically modified cyclodextrin was produced by mixing it with water at room temperature. A finely ground digoxtin (less than 15 microns) was suspended in the solution with mild stirring. The mix was stirred for 60 minutes and any undissolved drug was removed by centrifugation through a 0.45 micron sized membrane. Spray drying of the solution yielded a dry powder with a 10% drug loading.

Preparation of the Film Forming Composition:

A film-forming composition, Composition A in Table 1, was prepared and mixed under vacuum to remove air bubbles. In further detail, a polymer mix of hydroxypropylmethyl cellulose (Methocel™ E15), polyvinylpyrrolidone and starch and xanthan were added to water with stirring over a short period of time of about 15 minutes. The stirring was set at 350 to 1500 rpm using an axial impeller. Stirring continued for another 45 minutes after combining the components to form a viscous, uniform mix.

To this viscous mix plasticizer (propylene glycol), flavor, antifoam and sweetener were sequentially added. The mixture was stirred for an additional 10 minutes at 500 rpm before the addition of a taste-masked drug.

TABLE 1

Film Forming Polymer Composition Ingredient	Composition A
Hydroxypropylmethyl cellulose	8.5
Polyvinylpyrrolidone	5.5
Starch	5.5
Sweetener	2.4
Flavor (Mint Mix)	3.3
Xanthan Gum	0.3
Plasticizer	3.4
Antifoam agent	0.8
Water	70.4
Total:	100

A taste-masked drug was added to the mixture in about a 5 minute time period. After the addition of the drug the mixture was placed under a vacuum from about 0.1 to about 0.7 torr for about 45 minutes.

Film Compositions with Taste-Masked Pharmaceutically Active Agents:

After removing the vacuum, the product mix was added to a coating pan and filmed using a three-roll coater. The suspension was coated at 250 microns onto siliconized paper substrate and moved through a drying oven heated at 90° C. The composition was dried in accordance with the process set forth in co-pending U.S. application Ser. No. 10/074,272.

The dried product was examined for physical appearance, dissolution in the mouth and bitterness.

The resultant uncut films of inventive composition A with the above-described taste-masked drugs exhibited uniformity in content particularly with respect to the tasted-masked drugs, as well as unit doses of ¾" by 1" by 5-6 mils cut therefrom. The inventive compositions also were observed to have a smooth surface, absent of air bubbles. The films had minimal taste when ingested. All films dissolved in the mouth in less than 15 seconds.

The film produced with the less than 100 micron sized taste-masked triglyceride had a loading of 20 mg per 25 mm^2 piece of film. The film produced with the less than 150 micron sized taste-masked tamoxifen had a loading of 10 mg per 20 mm^2 of film (assuming 85% active). The film produced with the less than 150 micron sized taste-masked torsemide had a loading of 10 mg per 25 mm^2 of film (assuming 90% active). The film produced with the taste-masked digoxin had a loading of 0.5 mg per 15 mm^2 of film (assuming 90% active).

Examples A'-1

Water soluble thin film compositions of the present invention are prepared using the amounts described in Table 1a.

TABLE 1a

Ingredient	Weight (g) A'	B	C	D	E	F	G	H	I
Hydroxypropylmethyl cellulose		1.76		1.63	32.00		3.67		32.00
Peppermint oil		0.90	1.0	1.05		8.0	2.67		
Sweetener	0.15	0.15	0.22	0.10		4.6	1.53	0.15	
Polyvinylpyrrolidone		0.94		1.05		7.0	2.33		
Tween 80[1]	0.5	0.5	2.0	0.65	11.80		1.35	0.5	11.80
Simethicone[2]	0.2	0.2	0.15	0.30	1.80		0.21	0.2	1.80
Listerine[3]	83.35							83.35	
Methylcellulose	6.0								
Cornstarch[4]			1.75						
Agar			1.25						
Water		42.24	93.63	39.22	768.0	280.0	88.24		768.0
Loratadine[5]					19.2				19.2
Pullulan[6]								6.0	
Ibuprofen									38.4

[1]Available from ICI Americas

[2]Available from OSI

[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color

[4]Available from Grain Processing Corporation as Pure Cote B792

[5]Availabel from Schering Corporation as Claritin

[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

The ingredients of inventive compositions A'-I were combined by mixing until a uniform mixture was achieved. The compositions were then formed into a film by reverse roll coating. These films were then dried on the top side of an infrared transparent surface, the bottom side of which was in contact with a heated water bath at approximately 99° C. No external thermal air currents were present above the film. The films were dried to less than about 6% by weight water in about 4 to 6 minutes. The films were flexible, self-supporting and provided a uniform distribution of the components within the film.

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.

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 2

Sample	Additive Weight (g) Trial 1	Trial 2
1	0.04	0.04
2	0.08	0.08
3	0.12	0.12
4	0.16	0.16
5	0.20	0.20
6	0.24	0.24
7	0.28	0.28
8	0.32	0.32

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.

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.

When the films formed from inventive compositions A'-H are placed on the tongue, they rapidly dissolve, releasing the active ingredient. Similarly, when they are placed in water, the films rapidly dissolve which provides a flavored drink when the active is chosen to be a flavoring.

Examples J-L

Thin films that have a controlled degradation time and include combinations of water soluble and water insoluble polymers and water soluble films that allow controlled release of an active are prepared using approximately the amounts described in Table 3.

TABLE 3

Ingredient	Weight (g) J	K	L
Hydroxypropylmethyl cellulose		1.0	1.0
Tween 80[1]	0.7	0.7	0.7
Water			5.0
Aquacoat ECD[2]	17.0	17.0	17.5
Peppermint oil	1.0	0.4	1.1

[1]Available from ICI Americas

[2]A 30% by weight aqueous dispersion of ethyl cellulose available from FMC

The components of inventive compositions J-L were combined and formed into films using the methods for preparing

inventive compositions A'-1 above. These films were also flexible, self-supporting and provided a uniform distribution of active which permits accuracy in dosing.

The uniformity of the films prepared from inventive compositions J-L may also be tested by either visual means measuring the weights of individual dosage films, or by dissolving the films and testing for the amount of active as described above.

Examples M-O

An alternative method of preparing films which provides an accurate dosing may be used for any of inventive compositions A'-1. The method begins with first combining the ingredients with mixing. The combination of ingredients is then divided among individual wells or molds. In such a method, aggregation of the components during drying is prevented by the individual wells.

TABLE 4

	Weight %		
Ingredient	M	N	O
5% Methylcellulose Solution[1]	73.22	44.22	74.22
Raspberry Flavor	3.28	3.28	3.28
Sweetener Blends	1.07	1.07	1.07
Tween-80[2]	2.47	2.47	2.47
Polyvinylpyrrolidone	3.30	3.30	3.30
Ethanol 95%	8.24	8.24	8.24
Propylene Glycol	1.65	1.65	1.65
Calcium Carbonate	4.12	4.12	4.12
Cornstarch[3]	1.65	1.65	1.65
Red Dye[4]	1.00		
Corn Syrup[5]		30.00	

[1]Available from Dow Chemical Co. as Methocel K35
[2]Available from ICI Americas
[3]Available from Grain Processing Corporation as Pure Cote B792
[4]Available from McCormick
[5]Available from Bestfoods, Inc. as Karo Syrup

The ingredients in the above Table 4 were combined and formed into a film by casting the combination of ingredients onto the glass surface and applying heat to the bottom side of the glass. This provided inventive compositions M-O.

The film of composition M was examined both prior to and after drying for variations in the shading provided by the red dye. The film was examined both under sunlight and by incandescent bulb light. No variations in shade or intensity of color were observed.

Further testing of the films of composition M included testing of absorption which is directly related to concentration. The film was cut into segments each measuring 1.0 in. by 0.75 in., which were consecutively assigned numbers. Approximately 40 mg of the scrap material from which the segments were cut was dissolved in about 10 ml of distilled water and then quantitatively transferred to a 25 ml volumetric flask and brought to volume. The solution was centrifuged and scanned at 3 nm intervals from 203-1200 nm. The frequency of maximum absorption was found to be 530 nm. The solution was then re-centrifuged at a higher RPM (for the same length of time) and re-scanned, which demonstrated no change in the % transmission or frequency.

Each of the segments were weighed to 0.1 mg and then dissolved in 10 ml distilled water and transferred quantitatively to a 25 ml volumetric flask and brought to volume with distilled water. Each segment solution was then centrifuged as above, and then scanned, at first from 203-1200 nm and later from only 500 nm to 550 nm at a 1 nm scanning speed. The value recorded was the % transmission at the lowest wave length, which was most frequently 530 nm.

The absorption values are shown in Table 5 below:

TABLE 5

Segment	mg/% A
1-2	1.717
3-4	1.700
5-6	1.774
7*	1.701
9-10	1.721
11-12	1.729
13-14	1.725
15-16	1.713

*segment 8 was lost

The overall average absorption was 1.724. Of the 15 segments tested, the difference between the highest and lowest values was 0.073 units, or 4% based on the average. This shows excellent control over the uniformity of the dye within the composition because the absorption is directly proportional to the concentration of the dye within each segment.

The film of inventive composition N provided a very flexible film. This film was able to be stretched and exhibited a very high tensile strength.

After forming the film of inventive composition O, the film was removed from the glass by very rapidly stripping the length of the glass with a razor. This provided very tightly wound "toothpick-like" dosage forms. Each dosage form consistently weighed 0.02 g. This demonstrates the uniformity of the dosage forms as well as the superior self-supporting properties of the films.

Examples P-W

Compositions P-W were prepared to demonstrate the interaction among various conditions in production of films as they relate to the present invention. The ingredients in the below Table 6 were combined and formed into a film using the process parameters listed in Table 7 below, prepared in a 6 m drying tunnel designed to incorporate bottom drying of the films. Each of the examples shows the effect of different ingredient formulations and processing techniques on the resultant film products.

TABLE 6

	Weight (g)							
Ingredient	P	Q	R	S	T	U	V	W
Hydroxy-propyl-methyl cellulose	320	320	320	320	320	320	345	345
Water	1440	1440	1440	1440		1440	999	999
Sweetener						60	60	45
Mint Flavor						80	80	
Propylene Glycol	50	50	50	100	100	100	100	69.3
Xanthan	22		11	11.23	10	10	10	6.9
Water/ Ethanol (60/40)					1440			
Orange Flavor								42

TABLE 7

	Film Thickness (Micron)	Top[1] v (m/sec)	Bot.[1] v (m/sec)	T[1] (° C.)	Top[2] v (m/sec)
P1	100	0	22	75	0
P2	350	0	22	75	0
P3	350	0	40	75	0
P4	350	0	40	75	0
P5	350	10	40	75	10
Q	350	0	40	75	10
R	350	0	40	85	10
S1	250	0	40	100	0
S2	300	0	40	100	0
S3	350	0	40	100	0
T1	250	0	40	100	0
T2	350	0	40	100	0
U1	300	0	40	100	0
U2	250	0	40	100	0
U3	300	0	40	100	0
V1	300	0	40	100	0
V2	300	0	40	100	0
V3	300	0	40	100	0
W1	300	0	40	93	0
W2	250	0	40	90	0
W3	200	0	40	90	0

	Bot.[2] v (m/sec)	T[2] (° C.)	Film Weight (g)	Coater Speed m/min	% Moisture
P1	23	60	109	5	>20
P2	23	60	n/a	5	>20
P3	40	60	161	3	>20
P4	40	75	191	3	>20
P5	40	75	253	3	>20
Q	40	75	n/a	3	>20
R	0	85		2.5	>20
S1	40	90	163	1.5	<5
S2	40	90	193	1.5	<5
S3	40	90	225	1.5	<5
T1	40	90	64	1.5	<5
T2	40	90	83	1.5	<5
U1	40	90	208	1.5	20
U2	40	90	177	1.5	20
U3	40	90	212	1.3	20
V1	40	90	237	1.3	20
V2	40	100	242	1.3	20
W1	40	90	220	1.3	5
W2	40	90	199	1.3	5
W3	40	90	169	1.3	5

[1]First Heater Section (3 m)
[2]Second Heater Section (3 m)

In Table 7, each of the process parameters contributes to different properties of the films. Film thickness refers to the distance between the blade and the roller in the reverse roll coating apparatus. Bottom velocity and top velocity refer to the speed of air current on the bottom and top sides of the film, respectively. The film weight is a measure of the weight of a circular section of the substrate and the film of 100 cm^2.

Compositions P-R show the effects of visco-elastic properties on the ability to coat the film composition mixture onto the substrate for film formation. Composition P displayed a stringy elastic property. The wet film would not stay level, the coating was uneven, and the film did not dry. In Composition Q, substantially the same formulation as P was used however the xanthan was not included. This product coated the substrate but would not stay level due to the change in the visco-elastic properties of the wet foam. Composition R was prepared using substantially the same formulation, but incorporated one-half of the amount of xanthan of Composition P. This formulation provided a composition that could be evenly coated. Compositions P-Q demonstrate the importance of proper formulation on the ability of the film matrix to conform to a particular coating technique.

The films produced from Composition S contained a large amount of air in the films. This is shown by the dried film thickness which was the same despite that variation in the coated thickness as in Table 7. Microscopic examination of the film revealed a large number of air bubbles in the film. In order to correct for the addition of air in the films, care must be taken in the mixing process to avoid air inclusion.

Composition T included a change in the solvent to 60/40 water ethanol. Composition T was stirred slowly for 45 min. to deaerate the mixture. The dried weight film products T**1** and T**2** were consistent with the increase in solids from T**1** to T**2**. The films dried much faster with less than 5% moisture. With the particular combination of ingredients in Composition T, the substitution of part ethanol for part water allowed the film to dry more quickly. The elimination of air from the film as a result of the slow stirring also contributed to the uniformity of the final film product and the faster drying time.

Only water was used as a solvent in Composition U. The dried weight of the U**1**-U**3** changed consistently in accordance with the change in coating thickness indicating that no air bubbles were present. However, these films contained 20% moisture upon exit from the oven, unlike the films of Composition T, which included part ethanol and dried completely.

The amount of solids was increased and the amount of water was decreased in Compositions V**1** and V**2**. The dried weight was greater than U**1**-U**3** due to the increase in solids, however the films still contained 20% moisture upon exit from the oven, similar to Composition U.

The coating line speed was reduced for Composition V**3**, to prevent premature drying of the exposed top film surface. This film product dried to 6% moisture.

While increasing the amount of solids improved the film weight, longer drying times were required. This was due to the surface of the film sealing preventing easy removal of the water. Therefore, for Compositions W**1**-W**3**, the temperature in the first 3 m section of the dryer was decreased. This prevented the premature drying of the top surface of the films. Even at greater film thicknesses, the films were dried to 5% moisture even at faster coater line speeds.

Examples X-AA

TABLE 8

	Weight (g)			
Ingredient	X	Y	Z	AA
Loratadine	104.69			
Zomig		52.35		
Paxil			104.69	
Hydroxypropyl methylcellulose	320	320	320	150
Sweetener blend	60	60	60	0.4
Simethicone	1.5	1.5	1.5	1.5
Propylene glycol	100	100	100	
Water	1440	1440	1440	790
Cream essence				0.4
Polyvinyl pyrrolidinone				4
Ethanol				40
Cocoa				55.2
Polyoxyl-40-stearate				7

Compositions X, Y and Z of Table 8 were taste mask coated using a Glatt coater and Eudragit E-100 polymethacrylate polymer as the coating. The coating was spray coated at a 20% level. Therefore 10 mg of drug 12.5 mg of the final dry product must be weighed.

The base formula which excluded the drug additive was mixed with care to not incorporate air. After initial mixing the formula was slowly mixed to deaerate over 30 min. During this time the drug was weighed and prepared for addition to the base mix.

For Composition X, the Loratadine (80% drug) was added slowly to the mix with stirring. After 5 min. of stirring, the total mix was added to the pan of a three roll coater set (reverse roll coater) at 30 micron coating thickness.

The process bottom temperature was set at 90° C. with no top heat or air, the bottom air velocity was set at 40 m/sec., and the line speed was set at 1.3 m/min. Total drying time for the film was 4.6 min.

The liquid was coated at 30 microns and dried in the oven in less than 5 min. The film was flexible and a 1"×0.75" piece weighed 70 mg and contained 10 mg of Loratadine.

The experiment was repeated for Compositions Y and Z, Zomig and Paxil, respectively. Both produced flexible films with the target weight of 70 mg containing 5 mg of Zomig and 70 mg containing 10 mg of Paxil, respectively.

The products were sweet without any noticeable drug aftertaste.

The ingredients of Composition AA were mixed in order to reduce air captured in the fluid matrix. After mixing 45 g of loratadine coated at an 80% active level and 20% coating using Eudragit E-100, this mixture was added slowing with mixing until the drug was evenly dispersed, approximately 5 min. The liquid was then deposited into the 3 roll coater (reverse roll coater) and coated at 30 microns at a line speed of 1.3 m/min. The oven temperature was set at 90° C. to apply air and heat to the bottom only, with an air velocity set at 40 m/sec. The dried film was 0.005 inch. thick (5 mil) and was cut into 1 in.×0.75 in. pieces weighing 70 mg+/−0.7 mg, demonstrating the uniformity of the composition of the film. The film was flexible with 5% moisture, free of air bubbles, and had uniform drug distribution as seen under the light microscope, as well as shown by the substantially identical weight measurements of the film pieces.

Examples BA-BI

The incorporation of the anti-foaming/de-foaming agent (i.e., simethicone) provided a film that not only provided a uniform film that substantially reduced or eliminated air bubbles in the film product, but also provided other benefits. The films displayed more desirable organoleptic properties. The films had an improved texture that was less "paper-like" provided a better mouth-feel to the consumer.

The compositions in Table 9 were prepared (including the addition of simethicone in inventive compositions BA-BG) and mixed under vacuum to remove air bubbles.

The resultant uncut films of inventive compositions BA-BG exhibited uniformity in content particularly with respect to the insoluble active, as well as unit doses of ¾" by 1" by 5 mils cut therefrom. The inventive compositions also were observed to have a smooth surface, absent of air bubbles. The significantly higher amounts of simethicone present in inventive compositions BF-BG also provided a very uniform film, but not significantly improved from that of inventive compositions BA-BE.

By contrast, comparative examples BH-BI were observed to have a rougher surface, exhibiting the inclusion of air bubbles in the resultant film which provided a less uniform texture and distribution of the ingredients.

TABLE 9

Ingredient	BA	BB	BC	BD	BE	BF	BG	BH	BI
Hydroxypropylmethyl cellulose	0	3.77	3.70	3.84	0	3.67	0	0	3.84
Peppermint oil	2.94	1.93	2.39	0	0	2.67	2.94	2.67	0
Sweetener	2.20	0.32	0.23	0	0.17	1.53	2.20	1.54	0
Polyvinylpyrrolidone	2.68	2.01	2.39	0	0	2.33	2.68	2.34	0
Tween 80[1]	2.24	1.07	1.48	1.42	0.55	1.35	2.24	0	1.42
Simethicone[2]	0.66	0.42	0.68	0.22	0.22	5.00	2.00	0	0
Listerine[3]	0	0	0	0	92.41	0	0	0	0
Methylcellulose	4.03	0	0	0	0	0	4.03	0	0
Cornstarch[4]	2.68	0	0	0	0	0	2.68	0	0
Water	73.53	90.47	89.14	92.22	0	83.45	72.19	93.46	92.44
Loratadine[5]	4.29	0	0	2.31	0	0	4.29	0	2.31
Pullulan[6]	0	0	0	0	6.65	0	0	0	0
Calcium Carbonate	1.43	0	0	0	0	0	1.43	0	0
Xanthan Gum	0.30	0	0	0	0	0	0.30	0	0
Propylene Glycol	3.02	0	0	0	0	0	3.02	0	0

[1]Available from ICI Americas

[2]Available from OSI

[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color

[4]Available from Grain Processing Corporation as Pure Cote B792

[5]Available from Schering Corporation as Claritin

[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

Examples CA-CC

The following examples of the present invention describe films and film-forming compositions that use an ethoxylated caster oil as a surfactant, or alternatively are free of surfactants, plasticizers and/or polyalcohols. Desirably, the films or film-forming compositions of the present invention are essentially free of surfactants. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of plasticizers. Still furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of polyalcohols. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants and plasticizers. Furthermore, the films or film-forming compositions of the

present invention are desirably formulated to be essentially free of surfactants, plasticizers and polyalcohols.

TABLE 10

Ingredient	(parts by wt.) CA
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
Xanthan Gum	1.14
SURFACTANT[2]:	2.0
PLASTICIZER[3]:	11.67
ANTI-FOAM AGENT[4]	2.44
OTHER	
Spearmint Flavor	10.43
Loratadine (drug)	16.62
Calcium Carbonate	5.54
Sweetener	9.36

[1]Available from Grain Processing Corporation as Pure Cote B792
[2]Ethoxylated caster oil, Cremophor ® EL available from BASF
[3]Propylene Glycol
[4]Silicone Emulsion

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 45 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over 45 min.

After release of the vacuum, 6 grams of the liquid was added to a coating paper using a 200 micron spiral wound rod and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. until about 5% moisture remained. The formula coated and dried to a film thickness of approx. 60 microns and quickly dissolved in the mouth.

TABLE 11

Ingredient	(parts by wt.) CB
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
PLASTICIZER/SOLVENT[2]:	22.1
ANTI-FOAM AGENT[3]	2.44
OTHER	
Raspberry Flavor	0.3
Calcium Carbonate[4]	30.38
Sweetener	8.36

[1]Available from Grain Processing Corporation as Pure Cote B792
[2]Propylene Glycol
[3]Polydimethyl Siloxane Emulsion
[4]Functioned to mimic drug loading

The above ingredients were added to water at 40% until a homogeneous suspension was made. Vacuum was added over 20 min. starting at 500 mm Hg. and ending at 660 mm Hg. until all air was removed from suspension. Film was made as described in prior experiments. The liquid coated the silicone release substrate and dried to a uniform flexible film. The film passed the 180° bend test without cracking and dissolved in the mouth.

TABLE 12

Ingredient	(parts by wt.) CC
POLYMERS:	
Hydroxypropylmethyl cellulose	7.8
Hydroxypropyl cellulose	7.8
ANTI-FOAM AGENT[1]	0.75
OTHER	
Peppermint & Bittermint Flavor	2.25
Tastemasking Flavor[2]	0.3
Calcium Carbonate[3]	15.2
Sweeteners	0.9

[1]Polydimethyl Siloxane Emulsion
[2]Prosweet from Virginia Dave
[3]Functioned to mimic drug loading

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 20 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner up to 760 mm over 35 min.

After release of the vacuum, the liquid was added to a coating paper using a 350 micron smooth bar and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. until about 4% moisture remained. The formula coated and dried to a film. The film had an acceptable taste and quickly dissolved in the mouth. The taste-masking flavor is an ingredient that affects the taste receptors to mask the receptors from registering a different, typical undesirable, taste. The film passed the 180° bend test without cracking and dissolved in the mouth.

Example CD

The following example of the present invention describes films and film-forming compositions that use a taste-masked, pharmaceutically active agent which also contains flavors and taste-masking aids. A taste-masking flavor is an ingredients that effects taste receptors to mask the receptors from registering a different, typically undesirable, taste.

TABLE 13

Ingredient	(grams) CD
Hydroxypropylmethyl cellulose	4.26
Hydroxypropyl cellulose	1.42
Precipitated calcium Carbonate	1.22
Sweetner[1]	0.6
Taste-Masking flavor[2]	0.08
Taste-masked Acetaminophen[3]	5.86
Cinnamon Flavor	0.9
Spearmint Flavor	0.43
Polydimethylsiloxane emulsion	0.23

[1]Sucralose, available from McNeil Nutritionals
[2]Magna Sweet, available from Mafco Worldwide Corp.
[3]Gutte Enteric, coated acetaminophen, Gatte, LLC

The above ingredients, except for the pharmaceutically active agent and flavors, were added at 35 grams water and stirred until polymers were fully hydrated which took about 20 min. Food coloring (7 drops of red food coloring and 1 drop of yellow fool coloring) was also added. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over about 10 to 20 minutes. The

taste-masked Acetaminophen was added to the mix in about 4 minutes was stirring under vacuum. The flavors were then added to the mix in about 4 minutes was stirring under vacuum.

After release of the vacuum, the liquid solution was added to a coating paper using a 350 micron smooth bar. The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90° C. for about 11 minutes until about 3% moisture remained.

The formula coated and dried to a film. The film had an acceptable taste and moderately quickly dissolved in the mouth. The film did not curl on standing. The film passed the 180° bend test without cracking and dissolved in the mouth.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

Examples CE-CF

Thin film compositions of the present invention were prepared using the amounts described in Table 14.

TABLE 14

Component	Weight (g)
Hydroxypropylmethyl cellulose	3.92
Pullulan	3.92
Trehalose[1]	3.5
Precipitated Calcium Carbonate	3.85
Propylene Glycol	1.96
Simethicone[2]	0.35
Bovine Extract[3]	32.5
Water	q.s.

[1]Available from Cargill Inc.
[2]Available from Sentry
[3]Available from Amarillo Biosciences Inc.

The above ingredients were combined by mixing until a uniform mixture was achieved. A sufficient amount of water was present in the film compositions prior to drying, i.e., q.s., which may range between about 200 g to about 1000 g. The bovine extract protein contained in the compositions is a heat sensitive protein. After mixing, the compositions were cast into films on release paper using a K-Control Coater with a 250 micron smooth bar.

In Example CE, the films subsequently were dried in an oven at approximately 80° C. for about 6 minutes. The films were dried to about 4.3 percent moisture. In Example CF, the films were dried in an oven at approximately 60° C. for about 10 minutes. The films were dried to about 5.06 percent moisture. After drying, the protein derived from bovine extract, which was contained in the films, was tested to determine whether or not it remained substantially active. To test the activity, a film dosage unit of this example was administered to a human. After ingesting the dosage, a microarray on the human's blood was conducted. The results, listed in Appendix A which is incorporated by reference herein, and graphically represented in FIG. **32**, demonstrate that the protein was approximately 100 percent active in the final, dried film products of both Examples CE and CF. Therefore, the heat sensitive active did not substantially degrade or denaturize during the drying process.

Example CG

Thin film compositions of the present invention were prepared using the amounts described in Table 15.

TABLE 15

Component	Weight (g unless otherwise indicated) CG	CH
Hydroxypropylmethyl cellulose	4.59	9.18
Hydroxypropyl cellulose	1.53	3.06
Sucralose[1]	0.7	1.4
Magna Sweet[2]	0.09	0.18
Precipitated calcium carbonate	2.0	4
Fat-coated dextromethorphan hydrobromide	5.96	11.93
Orange concentrate flavor	1.05	2.1
Prosweet MM24[3]	0.18	0.35
Propylene glycol	1.22	2.45
Simethicone[4]	0.18	0.35
Water	32.5	65
Red food color		4 drops
Yellow food color		6 drops

[1]Available from McNeil Nutritional
[2]Taste-masking flavor, available from Mafco Worldwide Corp.
[3]Taste-masking flavor, available from Virginia Dare
[4]Available from Sentry

The above ingredients in the amounts listed for CG were combined by mixing, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were subsequently dried according to conventional drying techniques, rather than via the uniform drying process of the present invention. One film was dried in an oven at 80° C. for 9 minutes on a wire rack. The second film was dried in an oven at 80° C. for 9 minutes on a wire screen. Both films were dried to about 2.4 percent moisture.

The resulting dried films showed imprints of the wire rack and screen after drying. These configurations comprise imprints of wire supports typically used in the drying process. Without uniform heat diffusion, the wire supports conducted heat more intensely at the points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The result is increased particle density seen as aggregations at the contact points.

The solution was cast into two more films on release paper using the K-Control Coater with a 350 micron smooth bar. These films were dried by the process of the present invention, under the same time and temperature conditions as above. In particular, the films were dried in an 80° C. air oven for 9 minutes on trays lined with furnace filters, which uniformly disperse heat. The films were dried to about 1.89 percent moisture. The resulting films had no streaks, and were homogenous. Due to uniform heat diffusion throughout the film, no particle aggregations developed.

Example CH

The ingredients in Table 15, in the amounts listed for CH, were combined by mixing, and then cast into three films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for 9 minutes in an 80° C. air oven on trays lined with furnace filters, which uniformly distribute heat. The films were dried to about 2.20 percent moisture. As depicted in FIG. **17**, the dried films **200** had no streaks, and were homogenous, i.e., no particle aggregations developed. The active particles appeared intact in the dried films. The films exhibited adequate strength and passed the 180° bend test without cracking, in which the films are bent in half with pressure.

The mixed solution was cast into three more films on release paper using a K-Control Coater with a 350 micron

smooth bar. These films similarly were dried for 9 minutes in an 80° C. air oven, but by conventional top and bottom drying means. Two of the films were dried on wire racks, while the third was dried on a wire screen. All three films were dried to about 2.65 percent moisture. The dried films showed the imprints of the wire racks and screen, for the reasons described above in Example CG.

More particularly, the dried films **100** exhibited aggregations **110** of particles in both line and diamond configurations, as shown in FIGS. **9-16**. These configurations comprise imprints of wire supports used in the drying process to display the disuniformity in heat transfer which occurs in conventional top and bottom drying. As discussed above, the wire supports conducted heat more intensely at the points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The resulting increased particle density at the contact points is depicted in FIGS. **9-16**.

Moreover, the fat-coated dextromethorphan particles contained within the films of this example were not destroyed by the drying processes. FIGS. **28-31** depict fat-coated dextromethorphan particles **500** prior to any processing, and particularly, their substantially spherical shape. After exposure to drying conditions of 80° C. for 9 minutes, the fat-coated drug particles **500** were found to have remained intact within the films, i.e., maintained their spherical shape, as shown in FIGS. **18-25**. Although the active particles were exposed to potentially deleterious temperatures, they did not degrade. In contrast, fat-coated dextromethorphan particles placed in an evaporating dish and heated in an air oven at 80° C. for 9 minutes substantially degrade. As seen in FIGS. **26** and **27**, the fat-coated dextromethorphan particles appear completely melted after the exposure.

Example C1

Thin film compositions of the present invention were prepared using the amounts described in Table 16.

TABLE 16

Component	Weight (g unless otherwise indicated)
Hydroxypropylcellulose	6.00
Polyethylene oxide	2.00
Sucralose[1]	0.84
Magna sweet[2]	0.09
Mixture of microcrystalline cellulose and sodium carboxymethylcellulose[3]	0.18
Precipitated calcium carbonate	1.55
Sildenafil[4]	2.91
Peppermint & bittermint flavor	1.75
Prosweet[5]	0.44
Masking flavor[6]	1.31
N,2,3-trimethyl-2-isopropylbutanamide[7]	0.075
Simethicone[8]	0.035
Water	32.5
Blue food coloring	3 drops

[1]Available from McNeil Nutritional
[2]Taste-masking flavor, available from Mafco Worldwide Corp.
[3]Avicel CL-611, available from FMC Biopolymer
[4]Available from Pfizer, Inc. as Viagra ®
[5]Taste-masking flavor, available from Virginia Dare
[6]Available from Ungerer and Co.
[7]Cooling agent
[8]Available from Sentry

The above ingredients were combined by mixing until a uniform mixture was achieved, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth bar. One film was dried for 10 minutes in an 80° C. air oven to a moisture level of 3.52%, while the second film was dried for 10 minutes in an 80° C. air oven to a moisture level of 3.95%. The dried films had adequate strength and tear resistance. The films passed the 180° bend test without breaking. The films also dissolved at a moderately fast rate in the mouth and exhibited an acceptable flavor.

As mentioned above, 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. One of the additional advantages of the present invention is that the film composition reaches its viscoelastic state, and even the fully dried state, without exposing the components of the composition to temperatures which will cause them to be altered or unusable for their intended purpose. For example, heat sensitive drugs, proteins, flavors, sweeteners, volatile components, antigens, antibodies and the like, readily decompose at certain temperatures become inactive or denature, making them ineffective for their intended use. In the present invention, due to the combination of a short heat history required to dry, and the controlled non-top-skinning drying process, the film composition never need to attain the oven temperature (or other heat source) to reach the dried state. To demonstrate this, films were made in accordance with the present invention and dried as discussed below. A first thermocouple was placed within the film and a second thermocouple was suspended in the oven in order to measure the temperature differential between the oven environment and the film composition during the drying process.

To measure the temperature differentials, a thermocouple, which was connected to a Microtherma 1 thermometer, was placed within the films, and another thermocouple was suspended in the drying oven. Temperature readings in the films and oven were recorded every 30 seconds during the drying of the films.

The thermocouple results for the first film are listed in Table 17 below, and graphically represented in FIG. **33**. The results for the second film are listed in Table 18 below, and graphically represented in FIG. **34**. The results show that even after 10 minutes of drying, the temperatures of the film were substantially below (at least about 5° C.) the oven environment. Films dried for less than 10 minutes may experience significantly greater temperature differentials. For example, drying for 4 to 6 minutes, which is a particularly desirable time frame for many films of the present invention, produces differentials of about 25° C. to about 30° C. Accordingly, films may be dried at high, potentially deleterious temperatures without harming heat sensitive actives contained within the films.

TABLE 17

Time (Min.)	Probe Temp (° C.)	Oven Temp (° C.)
0	42.7	78
1	48.1	80
2	48.8	81
3	50	80
4	51.6	80
5	53.6	80
6	56.8	80
7	61.4	80

TABLE 17-continued

Time (Min.)	Probe Temp (° C.)	Oven Temp (° C.)
8	66.8	80
9	72.7	80
10	76.1	80

TABLE 18

Time (Min.)	Probe Temp (° C.)	Oven Temp (° C.)
0	44.4	77
1	49.8	81
2	49.2	81
3	49.4	80
4	51	80
5	52	80
6	55	80
7	58.9	80
8	64.5	80
9	69.8	80
10	74.4	80

Example CJ-DB

The following examples describe film compositions of the present invention, which contain water-soluble polymers including polyethylene oxide (PEO) alone or in combination with hydroxypropyl cellulose (HPC) or hydroxypropylmethyl cellulose (HPMC). Thin film compositions were prepared using the polymer amounts listed in Table 19.

TABLE 19

Composition	PEO (g)	HPC (g)	HPMC (g)
CJ		32	8
CK		24	16
CL		16	24
CM		8	32
CN			40
CO	8		32
CP	16		24
CQ	24		16
CR	32		8
CS	40		
CT	4		36
CV	6		34
CV	32	8	
CW	24	16	
CX	16	24	
CY	8	32	
CZ		40	
DA	4	36	
DB	6	34	

The above polymer components were combined with equal amounts of precipitated calcium carbonate (mimics drug loading), simethicone emulsion, and water to form the film compositions. The components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films then were dried for about 9 minutes at 80° C. in accordance with the present invention. The film compositions were tested for various properties, the results of which are described in Table 20 below.

TABLE 20

Composition	Composition of Polymer in Film	Solution Coating Rating	Solution Leveling Rating	% Moisture in Film	180° Bend Test	Dissolution Test (seconds)	Curl Test
CJ	20% HPMC/ 80% HPC	well	well	2.9	Failed at crease	12, 15	Curl
CK	40% HPMC/ 60% HPC	well	well	1.70	Failed at crease	21, 22	Curl
CL	60% HPMC/ 40% HPC	well	well	2.40	Failed at crease	24, 27	Curl
CM	80% HPMC/ 20% HPC	well	well	2.76	Failed at crease	31, 31	Curl
CN	100% HPMC	reasonably well	well	2.66	Failed at crease	35, 38	Curl
CO	10% PEO/ 90% HPMC	some streaking	well	2.27	Failed at crease	31, 32	Curl
CP	15% PEO/ 85% HPMC	well	well	3.31	Failed	24, 27	Curl
CQ	20% PEO/ 80% HPMC	well	well	2.06	Passed	22, 31	Slight curl
CR	40% PEO/ 60% HPMC	well	well	2.01	Passed	13, 12	Slight curl
CS	60% PEO/ 40% HPMC	well	well	1.40	Passed	5, 6	Very slight curl
CT	80% PEO/ 20% HPMC	well	well	1.35	Passed	5, 6	Very slight curl
CU	100% PEO	well	well	0.98	Passed	5, 5	No curl
CV	20% HPC/ 80% PEO	well	well	1.01	Passed	5, 5	No curl
CW	40% HPC/ 60% PEO	well	well	2.00	Passed	6, 6	No curl
CX	60% HPC/ 40% PEO	well	well	0.97	Passed	7, 7	Slight curl
CY	80% HPC/ 20% PEO	well	well	1.41	Passed	12, 12	Very slight curl
CZ	85% HPC/ 15% PEO	well	well	1.86	Failed at crease	13, 14	Curl
DA	90% HPC/ 10% PEO	well	well	1.62	Failed at crease	14, 13	Curl

TABLE 20-continued

Composition	Composition of Polymer in Film	Solution Coating Rating	Solution Leveling Rating	% Moisture in Film	180° Bend Test	Dissolution Test (seconds)	Curl Test
DB	100% HPC	well	well	2.01	Failed at crease	16, 17	Curl

The solution coating rating and solution leveling rating were both based upon panel observations made during casting of the film compositions.

For the 180° bend test, the dried films were placed in a moisture analyzer (HR73 Moisture Analyzer from Mettler Toledo) to obtain percent moisture and to remove any solvent (e.g. water) remaining in the films after drying at 80° C. in accordance with the present invention. The films then were creased to about 180° and observed for break. Films that broke during creasing were considered a failure. lf the film did not break during creasing, a 200 g weight was dropped onto the creased film from a height of about 8.5 mm. Films that broke were considered a failure, and those that did not break were considered a pass. lt should be noted, however, that this flexibility test is an extreme test. Films that failed this test are still considered operable within the scope of the present invention. More specifically, there may be certain applications that do not require such extreme flexibility properties.

The films also were tested for dissolution rate. An approximately 20 mm by 100 mm piece of film, having a 2.85 g weight attached, was lowered into a 32.5° C. water bath to a depth of about 50 mm. The time required for the film to dissolve and separate into two pieces was determined (in seconds).

For the curl test, samples of film (about 35 mm by 35 mm) were placed on a glass plate in a laboratory window ledge. The film samples were allowed to stand in the window ledge at room conditions for two to three days and then were observed for curling.

ln accordance with the present invention, desirable film compositions are flexible, fast dissolving, and not likely to substantially curl. As indicated by the results in Table 20, Compositions CQ-CY performed best, exhibiting good flexibility, dissolution, and curling properties. ln particular, Compositions CQ-CY passed the 180° bend test and dissolved at moderate to fast rates. These compositions also exhibited no or only slight curl. Accordingly, it may be desirable to employ polymer components as in Compositions CQ-CY, particularly about 20% to 100% PEO in the polymer component optionally combined with about 0% to 80% HPC or HPMC.

Examples DC-DG

The following examples of the present invention describe films that include PEO or PEO-polymeric blends and an active component. Thin film compositions with these components were prepared using the amounts described in Table 21.

TABLE 21

	Weight (g unless otherwise indicated)				
Component	DC	DD	DE	DF	DG
PEO[1]	8.75	7	1.75	7	1.75
Sucralose	0.7	0.7	0.7	0.7	0.7

TABLE 21-continued

	Weight (g unless otherwise indicated)				
Component	DC	DD	DE	DF	DG
Precipitated calcium carbonate	3.65	3.65	3.65	3.65	3.65
Orange concentrate flavor	1.05	1.05	1.05	1.05	1.05
Vanilla	0.5	0.5	0.5	0.5	0.5
HPMC		1.75	7.0		
HPC				1.75	7.0
Simethicone[2]	0.35	0.35	0.35	0.35	0.35
Water	32.5	32.5	32.5	32.5	32.5
Loratadine[3]	2.5	2.5	2.5	2.5	2.5
Yellow food coloring	3 drops	3 drops	3 drops	3 drops	3 drops
Red food coloring	2 drops	2 drops	2 drops	2 drops	2 drops

[1]Available from the Dow Chemical Company
[2]Available from Sentry
[3]Available from Schering Corporation as Claritin

The above components for each of Compositions DC through DG were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for about 9 minutes at 80° C. in accordance with the method of the present invention to varying moisture levels.

After drying, the films were tested for various properties, including the 180° bend test, dissolution test, and curl test, as described above in Examples CJ-DB. The films also were tested for resistance to tearing. Tear resistance was measured by a panel test in which members tried to tear the film apart by pulling on opposing ends of the film. Films that tore cleanly received a low grade. Films that stretched a little and began to break received a moderate grade, and films that stretched and were difficult to tear received a high grade.

Composition DC, which included a 100% PEO film base, was dried in accordance with the method of the present invention to about 1.30 percent moisture. The dried film had good strength, and passed the 180° bend test. The film also exhibited good resistance to tearing (high grade). The film dissolved at a fast rate on the tongue, and had a dissolution testing rate of about 3.5 to 4 seconds. The film exhibited no curling.

Composition DD, which included an 80%/20% PEO/HPMC film base, was dried in accordance with the method of the present invention to about 2.30 percent moisture. The dried film exhibited adequate strength, and passed the 180° bend test. The film also exhibited good resistance to tearing. lt dissolved at a moderate to fast rate on the tongue, and had a dissolution testing rate of about 5 seconds. The film exhibited slight curling.

Composition DE, which included a 20%/80% PEO/HPMC film base, was dried in accordance with the method of the

present invention to about 3.0 percent moisture. The film had good strength, and passed the 180° bend test. The film exhibited moderate tear resistance, dissolved on the tongue at a slow rate, and had a dissolution testing rate of 16 seconds. The film exhibited some curling.

Composition DF, which included an 80%/20% PEO/HPC film base, was dried in accordance with the method of the present invention to about 2.52 percent moisture. The film exhibited good strength, passed the 180° bend test, and exhibited high tear resistance. The film also dissolved at a fast rate on the tongue, and had a dissolution rating of 4 seconds. The film exhibited very slight curling.

Composition DG, which included a 20%/80% PEO/HPC film base, was dried in accordance with the method of the present invention to about 2.81 percent moisture. The film had adequate strength, passed the 180° bend test, and exhibited moderate tear resistance. The film dissolved on the tongue at a fast rate, and had a 10 second dissolution testing rate. The film exhibited no curling.

As indicated above, each of Compositions DC-DG contained about 20% to 100% PEO in the polymer component, optionally in combination with varying levels of HPC or HPMC. The results indicate that varying the polymer component achieved different film properties.

Examples DH-DZ

The following examples of the present invention describe films that include PEO or PEO-HPC polymer blends. The film compositions include PEO of varying molecular weights. Thin film compositions with these components were prepared using the amounts described in Table 22 (listed by weight percent of the polymer component).

TABLE 22

Composition	100,000 PEO (wt. %)	200,000 PEO (wt. %)	300,000 PEO (wt. %)	900,000 PEO (wt. %)	HPC (wt. %)
DH			20		80
DI			50		50
DJ			80		20
DK		50			50
DL		67.5			32.5
DM		70			30
DN		75			25
DO		100			
DP	50				50
DQ	100				
DR				10	90
DS				20	80
DT		40		10	50
DU	25			15	60
DV	20	80			
DW		80		20	
DX		80	20		
DY		50	50		
DZ		20	80		

The above polymer components were combined with sucralose, precipitated calcium carbonate (mimics drug loading), orange concentrate flavor, Tween 80 (available from ICI Americas), vanilla flavor, simethicone emulsion, water, and yellow and red food coloring to form the film compositions. The components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The solution coating and leveling properties were observed. The films then were dried for about 9 minutes at 80° C. in accordance with the method of the present invention. The film compositions were tested for various properties to determine the effect of varying the PEO molecular weight and level in the polymer component, the results of which are described in Table 23 below.

TABLE 23

Composition	Film thickness (mils)	% Moisture	Roof of Mouth Tendency	180° Bend Test	Dissolution Test (seconds)	Tear Resistance
DH	3.5	2.5	low	passed	8	poor
DI	3.8	2.01	low	passed	7	moderate
DJ	2.6	2.63	high	passed	3	excellent
DK	3.4	2.35	low	passed	4	poor
DL	3.5	1.74	low	passed	4	good to excellent
DM	3.5	1.68	low	passed	4	good to excellent
DN	3.3	2.33	moderate	passed	3	good to excellent
DO	3.1	2.14	high	passed	4	excellent
DP	4.1	1.33	high	passed	3.5	poor
DQ	3.2	2.07	high	passed	4	good
DR	3.4	1.90	low	passed	10	poor
DS	3.5	2.04	low	passed	10	poor
DT	3.3	2.25	moderate	passed	5	good
DU	3.6	2.84	low to moderate	passed	6	moderate
DV	2.5	3.45	high	passed	2	excellent
DW	2.5	2.83/1.68	high	passed	3-4	excellent
DX	3.5	2.08	high	passed	5	excellent
DY	2.8	1.67	high	passed	3	excellent
DZ	2.5	1.89/0.93	high	passed	3	excellent

The films were tested for various properties, including the 180° bend test, dissolution test, and tear resistance, as described above. The films also were tested for adhesion, i.e., tendency to go to the roof of the mouth. Adhesion was rated by a panel test in which films that did not stick to the roof of the mouth received a low grade, films that stuck somewhat received a moderate grade, and films that stuck completely received a high grade.

As indicated above, the level and molecular weight of PEO in the polymer component were varied to achieve different film properties. In general, the higher the level of PEO in the polymer component, the greater the adhesiveness and tear resistance exhibited by the film. Film compositions containing about 50% or greater levels of PEO attained higher tear resistance ratings than those with less than 50% PEO. The tear resistance of lower levels of PEO, however, was shown to be improved by combining small amounts of higher molecular weight PEOs with the lower molecular weight PEOs (e.g. Compositions DT and DU).

Compositions containing about 20% to 75% PEO performed best with respect to adhesion prevention (lower tendencies to go to the roof of the mouth). Compositions containing higher levels of PEO performed well when adhesion was desired.

As regards dissolution rate, polymer components containing about 50% or higher levels of PEO performed best, providing faster dissolving film compositions. In those films containing combinations of varying molecular weight PEOs, those with about 60% or higher of the lower molecular weight PEOs (100,000 to 300,000) in the PEO combination dissolved faster.

Example EA

The following example of the present invention describes films that include PEO and polyvinyl pyrrolidone (PVP) polymeric blends. Thin film compositions with these components were prepared using the amounts described in Table 24. In particular, the polymer component of the films contained about 80% PEO and 20% PVP, or a ratio of 4:1 PEO to PVP.

TABLE 24

Component	Weight (g unless otherwise noted)
PVP	3.75
PEO	15
Sucralose[1]	1.5
Precipitated calcium carbonate	14.57
Orange concentrate flavor	2.25
Tween 80[2]	0.056
Simethicone[3]	0.38
Water	62.5
Yellow food color	6 drops
Red food color	4 drops

[1]Available from McNeil Nutritionals
[2]Available from Fisher
[3]Available from Sentry

The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for about 9 minutes at 80° C. in accordance with the method of the present invention to a moisture level of about 2.19%. The films exhibited good strength, dissolved in the mouth at a moderate to fast rate, had high tear resistance, a thickness of about 4 mils, good flavor, low tendency to adhere to the roof of the mouth, and passed the 180° bend test. The film had a dissolution rate of 4 seconds, according to the test described above. In addition, the film easily released from the release paper.

Example EB-ED

The following examples of the present invention describe extruded films that include PEO-based polymer components. Film compositions were prepared using the amounts described in Table 25 for Example EC and Table 26 for Example ED.

TABLE 25

COMPONENT	WEIGHT (g unless otherwise noted)
HPC	73.78
Polyethylene oxide	153.22
Sucralose	18.16
Precipitated calcium carbonate	176.38
Orange concentrated flavor	27.24
Tween 80	0.68
Simethicone	4.54
Yellow food coloring	27 drops
Red food coloring	18 drops

TABLE 26

COMPONENT	WEIGHT (g unless otherwise noted)
Polyethylene oxide	227
Sucralose	18.16
Precipitated calcium carbonate	176.38
Orange concentrated flavor	27.24
Tween 80	0.68
Simethicone	4.54
Yellow food coloring	27 drops
Red food coloring	18 drops

The films of Examples EB-ED were extruded using a single screw extruder in accordance with the specifications provided in Table 27 below (temperatures are in ° F.).

TABLE 27

		Temp. Barrel	Temp. Barrel	Temp. Barrel	Temp.	Temp.	Temp.	PSI Pressure		
Composition	RPM	Zn. 1	Zn. 2	Zn. 3	Zn. 4	Die	Melt	P1	P2	Amps
EB	73	175	181	185	190	190	194	600	1250	12
EB	153	177	181	199	211	210	217	175	1070	7.8

TABLE 27-continued

Composition	RPM	Temp. Barrel Zn. 1	Temp. Barrel Zn. 2	Temp. Barrel Zn. 3	Temp. Zn. 4	Temp. Die	Temp. Melt	PSI Pressure P1	PSI Pressure P2	Amps
ED	253	175	181	200	211	210	222	0	761	6.3
ED	109	175	181	200	211	210	207	0	1000	6.0
EC	109	175	181	200	211	210	217	0	875	12.1
EC	149	175	200	226	248	239	258	0	583	7.3

More specifically, for Example EB, two pounds of PEO having a molecular weight of about 200,000 were weighed and placed in a polyethylene plastic bag. This PEO flush was then extruded according to the specifications in Table 27.

For Example EC, a blend of the components listed in Table 25 was prepared. The HPC, PEO, sucralose, and precipitated calcium carbonate were placed in a large electric blender and allowed to mix. A solution of orange concentrate flavor and Tween 80 was added to the blender while mixing, after which a solution of simethicone and the food colors was added to the blender while mixing. The blended composition was extruded in accordance with the specifications in Table 27.

For Example ED, a blend of the components listed in Table 26 was prepared. The PEO, sucralose, and precipitated calcium carbonate were placed in a large electric blender and allowed to mix. A solution of orange concentrate flavor and Tween 80 was added to the blender while mixing, after which a solution of simethicone and the food colors was added to the blender while mixing. The blended composition was extruded in accordance with the specifications in Table 27.

The extruded films did not exhibit stickiness to each other during processing. As such, the resulting film could be rolled or wound onto itself without the need for a backing material.

Examples EE-EH

The following examples of the present invention describe films that include a densifying agent. A thin film composition including PEO-polymeric blends and a densifying agent (simethicone) were prepared using the amounts described in Table 28.

TABLE 28

Component	Weight (g unless otherwise indicated) EE	EF	EG	EH
Hydroxypropylcellulose	3.05	3.05	3.05	3.05
Polyethylene oxide	6.33	6.33	6.33	6.33
Sucralose	0.75	0.75	0.75	0.75
Precipitated calcium carbonate	7.47	7.47	7.09	7.09
Orange concentrate flavor	1.12	1.12	1.12	1.12
Tween 80	0.028	0.028	0.028	0.028
Simethicone	0	0	0.38	0.38
Water	31.25	31.25	31.25	31.25
Yellow food coloring	3 drops	3 drops	3 drops	3 drops
Red food coloring	2 drops	2 drops	2 drops	2 drops

The densities of these thin film compositions were measured, the results of which are shown in Table 29.

TABLE 29

Composition	Average Weight of Film/Density
EE	146.5 mg/1.123
EF	126.5 mg/0.969

TABLE 29-continued

Composition	Average Weight of Film/Density
EG	137 mg/1.057
EH	146 mg/1.119

Vacuum conditions were added to two of the film compositions (EE and EH). Composition EE contained 0% simethicone and vacuum was applied. Composition EF contained 0% simethicone and no vacuum applied. As shown in Table 29 above, the density increased with the addition of vacuum conditions from 0.969 (EF) to 1.123 (EE). Composition EG contained 2% simethicone and no vacuum applied. Composition EH contained 2% simethicone and vacuum was applied. Again, density increased from 1.057 (EG) to 1.119 (EH). Overall, the density of the films increased from 0.969 (EF: no simethicone and no vacuum) to 1.057 (EG: simethicone but no vacuum) to 1.119 (EH: simethicone and vacuum).

Examples E1-EW

The following examples of the present invention describe films that include PEO or PEO-polymeric blends. In particular, PEO was combined with polyvinylpyrrolidone (PVP), starch (pregelatinized modified corn starch), sodium carboxymethyl cellulose (CMC), hydroxypropylcellulose (HPC), hydroxypropylmethyl cellulose (HPMC) or polyvinyl alcohol (PVA) to form the polymer components of the films. Thin film compositions with these components were prepared in accordance with the method of the present invention using the amounts described in FIG. **38**.

In addition to the polymer components listed in FIG. **38**, each of these film compositions included: about 4% sucralose, about 38.85% calcium carbonate, about 6% orange flavor, about 0.15% Tween 80, about 1% simethicone, and food coloring. The PEO included in the polymer component of these examples had a molecular weight of about 200,000.

FIG. **38** also displays certain properties of these films, including: percent solids of solution; viscosity; percent moisture; film thickness; film strength; tear resistance of the film; tendency of the film to go to the roof of the mouth; the 180° bend test; whether molding, or aggregations, are present in the film; dissolution times of the film; rating of dissolution in the mouth; and time in drying oven. Each of these film property tests is described in detail above. The results of these various tests are indicated in FIG. **38**.

Examples EX-FK

The following examples of the present invention describe films that include PEO or PEO-polymeric blends (with HPC) and different active components. Thin film compositions with these components were prepared in accordance with the method of the present invention using the amounts described in Tables 30 and 31.

TABLE 30

	Weight (in g, unless otherwise indicated)						
Component	EX	EY	EZ	FA	FB	FC	FD
HPC	5.68	5.64	6	6.73	6.22	6.22	
PEO	1.89	1.88	2	2.25	1.78	1.78	9.04
Sucralose	0.84	0.84	0.44	0.66	0.84	0.84	0.44
Magna Sweet	0.08	0.08	0.09	0.10	0.09	0.09	
Avicel CL 611[1]	0.18	0.18	0.18	0.20	0.18	0.18	
Precipitated calcium carbonate	0.67		2.2		0.71	3.07	
Dextromethorphan	5.83	6.94					
Caffeine			3.28				
Tadalafil[2]				4.92			
Sildenafil[3]					4.38		
Loperamide[4]						2.8	
Prosweet	0.18	0.18		0.20	0.61	0.18	
Taste Masking Flavor			0.87		1.31	0.89	
Peppermint			0.87				
Peppermint Bittermask flavor			1.07				
Vanilla flavor				0.56			
Watermelon artificial flavor	1.23	1.23			1.22		
Orange flavor				1.18			
Hawaiian punch flavor						1.22	
Strawberry & cream flavor							1.11
WS-23[5]	0.075	0.075	0.075	0.084	0.075	0.075	
WS-3[6]							0.025
Simethicone	0.08	0.08	0.18	0.39	0.09	0.18	46.43
Propylene glycol	0.76	0.38	0.25	0.22			
Water	32.5	32.5	32.5	32.5	32.5	32.5	
Green color	5 drop	5 drop			5 drop		
Red color				2 drop		5 drop	7 drop
Blue color			3 drop				
Yellow color				3 drop			

[1]Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer

[2]Available from Lilly ICOS, LLC, as Cialis ®

[3]Available from Pfizer, Inc. as Viagra ®

[4]Available as Imodium

[5]N-2,3-trimethyl-2-isopropyl butanamide

[6]N-Ethyl-p-menthane-3-carboxamide

TABLE 31

	Weight (in g, unless otherwise indicated)						
Component	FE	FF	FG	FH	FI	FJ	FK
HPC	1.28	3.05	4.5	3.29	2.6	2.92	3.29
PEO	2.66	6.33	3	6.83	5.4	6.08	6.83
Sucralose	0.31	0.9	0.6		0.64		
Magna Sweet		0.09					
Avicel CL 611[1]		0.56	0.45				
Precipitated calcium carbonate	1.07	2.02	0.99	6.05	0.90	2.67	1.39
Meloxicam[2]	1.97						
Risperidone[3]		0.62					
Zyrtec ®[4]			3.75				
Five Grass Powder[5]				2.207			
Tea Tree Oil[6]					4		
Antibacterial concentrate[7]						6.12	
Mite extract[8]							6.87
Prosweet		0.66					
Taste Masking Flavor		1.41					
Peppermint Bittermask flavor		2.81			2.24		
Orange flavor	0.47						
Strawberry & cream flavor			1.5				
WS-3[9]	0.020	0.081	0.038		0.04		
Tween 80	0.012	0.028	0.022		0.024	0.027	
Simethicone	0.08	0.19	0.15	0.37	0.16	0.18	0.37
Water	14.63	31.25	25	31.25	24	22	31.25
Red color	2 drop		5 drop				

TABLE 31-continued

Component	Weight (in g, unless otherwise indicated)						
	FE	FF	FG	FH	FI	FJ	FK
Blue color		3 drop			3 drop		
Yellow color	3 drop						

[1]Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer
[2]Available as Mobic ®
[3]Available as Risperdal ®
[4]Available from Pfizer, Inc.
[5]Allergy treatment
[6]Antibiotic
[7]MegaBac ™, available from Nicrosol Technologies
[8]Allergy treatment
[9]N-Ethyl-p-menthane-3-carboxamide

The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 250 or 350 micron smooth bar. The films were dried for about 9 to 10 minutes at 80° C. in accordance with the method of the present invention resulting in dried films having adequate to good strength.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

The invention claimed is:

1. A drug delivery composition comprising:

(i) a cast film comprising a flowable water-soluble or water swellable film-forming matrix comprising one or more substantially water soluble or water swellable polymers; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate active substantially uniformly stationed in the matrix; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the active;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble or water swellable film-forming matrix is capable of being dried without loss of substantial uniformity in the stationing of said particulate active therein; and

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active.

2. The drug delivery composition of claim **1**, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. The drug delivery composition of claim **1**, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. The drug delivery composition of claim **1**, wherein said taste-masking agent is a thin film coating over portions of said active.

5. The drug delivery composition of claim **1**, wherein the taste-masking agent is a polymer.

6. The drug delivery composition of claim **1**, wherein the taste-masking agent is a water-soluble polymer.

7. The drug delivery composition of claim **6**, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. The drug delivery composition of claim **1**, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. The drug delivery composition of claim **1**, wherein said variation of drug content is less than 5% by weight per film dosage unit.

10. The drug delivery composition of claim **1**, wherein said variation of drug content is less than 2% by weight per film dosage unit.

11. The drug delivery composition of claim **1**, wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

12. The drug delivery composition of claim **1**, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

13. The drug delivery composition of claim **1**, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

14. The drug delivery composition of claim **1**, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

15. The drug delivery composition of claim **1**, wherein said active is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

16. A thin film drug delivery composition comprising:

(a) a cast film comprising an edible water-soluble or water swellable film-forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component substantially uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is substantially uniformly distributed in the film composition; and

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active.

17. The drug delivery composition of claim **16**, wherein said thin film drug delivery composition is extruded.

18. The drug delivery composition of claim **16**, wherein the taste-masking agent is a thin film coating over the particulate active component.

19. The drug delivery composition of claim **16**, wherein the taste-masking agent is a water-soluble polymer.

20. The drug delivery composition of claim **16**, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

21. The drug delivery composition of claim **1**, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

22. The drug delivery composition of claim **1**, wherein said active is selected from the group consisting of ace-inhibitors, antianginal 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, biological response modifiers, 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, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

23. The drug delivery composition of claim **1**, wherein the film forming matrix has the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

24. The drug delivery composition of claim **1**, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

25. The drug delivery composition of claim **1**, wherein said active is an opiate or opiate derivative.

26. The drug delivery composition of claim **16**, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

27. The drug delivery composition of claim **16**, wherein said active is an opiate or opiate derivative.

28. A drug delivery composition comprising:

(i) a cast film comprising a flowable water-soluble or water swellable film-forming matrix comprising one or more substantially water soluble or water swellable polymers; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate active substantially uniformly stationed in the matrix; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the active;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble or water swellable film-forming matrix is capable of being dried without loss of substantial uniformity in the stationing of said particulate active therein;

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active; and

wherein the coated particulate active has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

29. The drug delivery composition of claim **28**, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

30. The drug delivery composition of claim **28**, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

31. The drug delivery composition of claim **28**, wherein said taste-masking agent is a thin film coating over portions of said active.

32. The drug delivery composition of claim **28**, wherein the taste-masking agent is a polymer.

33. The drug delivery composition of claim **28**, wherein the taste-masking agent is a water-soluble polymer.

34. The drug delivery composition of claim **33**, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

35. The drug delivery composition of claim **28**, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

36. The drug delivery composition of claim **28**, wherein said variation of drug content is less than 5% by weight per film dosage unit.

37. The drug delivery composition of claim **28**, wherein said variation of drug content is less than 2% by weight per film dosage unit.

38. The drug delivery composition of claim **28**, wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

39. The drug delivery composition of claim **28**, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

40. The drug delivery composition of claim **28**, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

41. The drug delivery composition of claim **28**, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

42. The drug delivery composition of claim **28**, wherein said active is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, antitussives, decongestants, antihistamines, expectorants, antidiarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

43. The drug delivery composition of claim **28**, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

44. The drug delivery composition of claim **28**, wherein said active is selected from the group consisting of ace-inhibitors, antianginal 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, biological response modifiers, 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, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

45. The drug delivery composition of claim **28**, wherein the film forming matrix has the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

46. The drug delivery composition of claim **28**, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

47. The drug delivery composition of claim **28**, wherein said active is an opiate or opiate derivative.

48. A thin film drug delivery composition comprising:

(a) a cast film comprising an edible water-soluble or water swellable film-forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component substantially uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is substantially uniformly distributed in the film composition;

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active; and

wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

49. The drug delivery composition of claim **48**, wherein said thin film drug delivery composition is extruded.

50. The drug delivery composition of claim **48**, wherein the taste-masking agent is a thin film coating over the particulate active component.

51. The drug delivery composition of claim **48**, wherein the taste-masking agent is a water-soluble polymer.

52. The drug delivery composition of claim **48**, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

53. The drug delivery composition of claim 48, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

54. The drug delivery composition of claim 48, wherein said active is an opiate or opiate derivative.

55. A thin film drug delivery composition comprising:

(a) a cast film comprising an edible water-soluble or water swellable film-forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component substantially uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is substantially uniformly distributed in the film composition;

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active; and

wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

56. The drug delivery composition of claim 55, wherein said thin film drug delivery composition is extruded.

57. The drug delivery composition of claim 55, wherein the taste-masking agent is a thin film coating over the particulate active component.

58. The drug delivery composition of claim 55, wherein the taste-masking agent is a water-soluble polymer.

59. The drug delivery composition of claim 55, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

60. The drug delivery composition of claim 55, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

61. The drug delivery composition of claim 55, wherein said active is an opiate or opiate derivative.

62. A drug delivery composition comprising:

(i) a cast film comprising a flowable water-soluble or water swellable film-forming matrix comprising one or more substantially water soluble or water swellable polymers; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate active substantially uniformly stationed in the matrix; and

(iii) a taste-masking agent selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof to provide taste-masking of the active;

wherein the particulate active has a particle size of 200 microns or less and said flowable water-soluble or water swellable film-forming matrix is capable of being dried without loss of substantial uniformity in the stationing of said particulate active therein; and

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active.

63. The drug delivery composition of claim 62, wherein the particulate active has a particle size of 150 microns or less.

64. The drug delivery composition of claim 62, wherein the particulate active has a particle size of 100 microns or less.

65. The drug delivery composition of claim 62, wherein said variation of drug content is less than 5% by weight per film dosage unit.

66. The drug delivery composition of claim 62, wherein said variation of drug content is less than 2% by weight per film dosage unit.

67. The drug delivery composition of claim 62, wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

68. The drug delivery composition of claim 62, wherein the particulate active has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

69. The drug delivery composition of claim 62, wherein said taste-masking agent is present in the amount of about 0.1-30% by weight of the drug delivery composition.

70. The drug delivery composition of claim 62, wherein said taste-masking agent is present in the amount of about 0.01-10% by weight of the drug delivery composition.

71. The drug delivery composition of claim 62, wherein said active is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, antitussives, decongestants, antihistamines, expectorants, antidiarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

72. The drug delivery composition of claim 62, wherein the film forming matrix has the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

73. The drug delivery composition of claim 62, wherein said active is an opiate or opiate derivative.

74. The drug delivery composition of claim 73, wherein said taste masking agent is peppermint oil.

75. The drug delivery composition of claim 1, wherein said active is an opiate or opiate derivative and said taste masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

76. The drug delivery composition of claim 75, wherein said taste masking agent is peppermint oil.

* * * * *

EXHIBIT E

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP
Confirmation No.	5059	Dated:	December 9, 2010

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Mail Stop Amendment
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Dated: December 9, 2010

Signature: /Marcy Mancuso/

AMENDMENT AND RESPONSE PURSUANT TO 37 C.F.R. §1.111

Sir:

In response to the Office Action dated September 9, 2010, a response to which is due by December 9, 2010, the Applicant responds as follows:

Amendments to the claims begin on page 2 of this submission.

Remarks begin on page 10 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Currently Amended) A drug delivery composition comprising:

(i) a flowable water-soluble film forming matrix;

(ii) a particulate bioeffecting agent uniformly stationed therein; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the bioeffecting agent;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of said particulate bioeffecting agent therein; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.

2. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said bioeffecting agent.

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. (Cancelled)

10. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 5% by weight per film unit.

11. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 2% by weight per film unit.

12. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 0.5% by weight per film unit.

13. (Original) The drug delivery composition of claim 1, wherein the coated particulate bioeffecting agent has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Original) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

18. (Currently Amended) A thin film drug delivery composition comprising:

(a) an edible water-soluble film forming matrix comprising at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and

(b) a coated particulate active component uniformly stationed therein;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a thin film coating over the particulate active component.

21. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

24. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

25. (Withdrawn) A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (Currently amended) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; caragcenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch~~, including tapioca starch, rice starch, corn starch, potato starch, and wheat starch~~; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins~~, such as, gelatin, zein, gluten, soy protein, soy protein isolate, and whey protein~~; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

36. (Previously presented) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of ace-inhibitors, antianginal 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, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholincsterase inhibitors, contraceptives, decongcstants, 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, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Remarks

Claims 1-8 and 10-36 are pending in this application. Claims 25-34 have been withdrawn from consideration by the Examiner. By this Amendment, claim 9 is cancelled and claims 1, 10, 11, 12, 18, and 35 are amended. Support for the amendments to the claims may be found, for example, in the original claims, and the specification. No new matter is added.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Rejection under 35 U.S.C. §112, Second Paragraph

The Office Action rejects claims 1-17 and 35 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Examiner asserts that "Applicant has not particularly pointed out how the combined particulate and taste masking agents can have a particle size of 200 microns or less when they are intimately associated with each other." Moreover, the Examiner asserts that "Applicant has not pointed out if both the particulate bioeffecting agent and the taste masking agent have the claimed particle size or if the particle size is only applicable when the taste masking agent is coated on the particulate bioeffecting agent." *See* Office Action, page 3, second paragraph.

Applicants respectfully disagree with the Examiner and traverse the rejection. Claim 1 clearly recites that "the **combined particulate and taste-masking agent** have a particle size of 200 microns." Accordingly, it would be clear to one skilled in the art that, regardless of whether the combined particulate bioeffecting agent is intimately associated with the taste masking agent or whether the particulate bioeffecting is coated with the taste masking agent, it is the

combination of the particulate bioeffecting agent and the taste masking agent that has a particle size of 200 microns. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner also rejects claim 35 for containing the terms "such as" and "including." Without conceding the propriety of the rejections, claim 35 is amended to more clearly recite various novel features of the claimed invention, with particular attention to the Examiner's comments. Specifically, claim 35 is amended to delete the terms "such as" and "including," thereby obviating the rejection. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. Rejection Under 35 U.S.C. §102

The Office Action rejects claims 1-5, 8-12, 14-19, 22, and 35-36 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 7,067,116 to Bess et al. ("Bess"). Applicants respectfully traverse the rejection.

It is well settled that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *See* MPEP §2131.

Independent claims 1 and 18 require that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit." Bess does not teach or suggest such a feature.

At most Bess teaches that its process involves "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." *See* column 12, lines 13-17.

The instant specification teaches that the ability to achieve the uniformity of content within the claimed range is directly related to Applicants' drying technique. *See* for example paragraphs [0068] and [0069]. Nowhere does Bess teach or suggest the difficulties of achieving uniformity of content in cast films, nor steps or processes to overcome the inherent difficulties in doing so.

Moreover, claim 18 requires "the coating on the particulate active component is a taste-masking agent." Bess fails to teach or suggest such a feature.

Although Bess discloses a presence of a coating, nowhere does Bess teach or suggest a coating that is a taste-masking agent, as claimed.

The Examiner asserts that "the recitation of adsorption complex would necessarily result in a thin film coating over portions of the agent." *See* Office Action, page 4, last paragraph. Applicants respectfully disagree. Although, Bess discloses the taste masking agent as an ion exchange resin, the ion exchange resin does not necessarily form a coating. At most, Bess teaches that "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." *See* column 9, lines 55-60. Nowhere does Bess teach or suggest a taste-masking coating, as required by claim 18 and Bess fails to teach or suggest "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit," as required by claims 1 and 18.

Accordingly Bess does not anticipate independent claims 1 and 18. Claims 2-5, 8-12, 14-17, 19, 22, and 35-36 variously depend from claims 1 and 18 and, thus, also are not anticipated by Bess. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. Rejections Under 35 U.S.C. §103

A. Chen in view of Ghana

The Office Action rejects claims 1–12, 17, and 35-36 under 35 U.S.C. §103(a) over PCT Publication No. WO 00/42992 to Chen et al. ("Chen") in view of U.S. Patent No. 5,653,993 to Ghana et al. ("Ghana"). Applicants respectfully traverse the rejection.

Chen is cited for its alleged disclosure of water soluble hydrocolloid, mucosal coating, an effective dose of agent. The Examiner acknowledges that Chen fails to teach or suggest the particle size of the encapsulated active agents. *See* Office Action, page 7, line 12. Nevertheless, the Examiner cites Ghana as allegedly curing the deficiencies of Chen.

By this Amendment, independent claim 1 is amended to recite that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit." Chen and Ghana, whether considered independently or combined, fail to teach or suggest such features.

Neither Chen nor Ghana disclose the difficulties of achieving uniformity of content in cast films, nor steps or processes to overcome the inherent difficulties in doing so. Thus, the Examiner has not provided any rationale to modify Chen or Ghana in order to arrive at the presently claimed invention.

The claimed invention is directed to solving the problems associated with achieving a taste-masked drug which is uniformly distributed throughout a film, such that individual dosage units cut from the film will have the same amount of drug in them and will be pleasant tasting.

There are several problems addressed by the present invention. One such problem is the delivery of bad-tasting actives in a dosage form which inherently exposes a high degree of the active to the taste buds. This is because most films are relatively thin by nature with planar surfaces and such the active is readily exposed to the taste buds as the film is dissolved. Thus, in view of the relatively large surface area of exposure, determining the proper size of the taste-masked particles was an important finding. Drug delivery films are not only relatively thin, but often dimensionally small. Thus, the smaller particles allow for a more uniform distribution to be readily achieved. Particles which are too large may self aggregate and cause a loss of uniformity of drug content per unit volume of film. Particles which are too large will also require more taste-masking material to effectively cover the active. Additionally, particles larger than 200 microns will present a gritty mouth feel and may be thicker than the film per se.

In short, the claimed invention solves the problems associated with effective delivery of a uniform amount of taste masked drug in a film dosage unit.

In particular, self aggregation or conglomeration of particles leads to **non-uniformity** of distribution of the drug in the film. The failure to achieve a high degree of accuracy with respect to the amount of active ingredient in dosage cut from the film can be harmful to the patient and may not meet the stringent governmental or agency standards relating to variation of active in dosage forms.

Self aggregation in film containing a pharmaceutical active increases the probability of perception of an unpleasant tasting film, as well as destroys the uniformity of the pharmaceutical agent in the film.

The claimed invention introduces a composition and processes as a solution that overcomes the above-mentioned problems.

Such a solution includes specific features such as particle size; maintaining the uniform distribution of active components by locking-in or substantially preventing migration of the active components within the visco-elastic film and resulting film product; and particular taste-masking agents.

Although Chen discloses the use of taste-modifying agents in a film dosage form, Chen merely mixes taste modifying agents into the film-forming mix without recognizing the problem of separation or aggregation of the taste-modifying agents from the unpleasant tasting pharmaceutical agents. Therefore, Chen does not recognize the problem to be solved by the claimed invention, i.e. attaining low adjuvant content, high-taste-masked pharmaceutical active content films which have enhanced flexibility, structural integrity and **uniformity** (emphasis added). *See* page 3, lines 20-22.

Uniformity is important in oral film products, particularly products intended for delivery of pharmaceutical actives such that regulatory approval of the product may be obtained. As further explained on page 22 of the present application, the films prepared in accordance with the present invention have a "high degree of uniformity of the components of the film [which] makes them particularly well suited for incorporating pharmaceuticals". (lines 26-29). Specifically, the film products have:

> 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.
>
> (page 38, lines 16-20).

In contrast, Chen fails to teach or suggest and has absolutely no appreciation for the need to achieve dried films that are uniform in content.

As further evidence that Chen completely fails to appreciate uniformity, Chen merely discloses conventional hot air oven drying. Chen describes that the film is "dried under aeration at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation." (page 15, lines 28-29). Chen, however, does not disclose or even contemplate using the specific controlled, bottom-drying methods presently claimed. The only means of drying disclosed in the cited reference is the method of drying that the present application specifically seeks to avoid (uncontrolled air drying).

Ghana is cited for its alleged disclosure of a diameter ranges from about 25 to 600 microns. Ghana is directed to preparation of individual taste-masked microcapsules. Nowhere does Ghana teach or suggest film that is uniform in content, as required by the claims. Therefore, Ghana fails to cure the deficiencies of Chen. Therefore, Chen and Ghana, whether considered independent or combines fails to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit."

Moreover, the Supreme Court addressed the standard for obviousness in its decision of *KSR International Co. v. Teleflex Inc.*, et al., 550 U.S. 389; 127 S.Ct. 1727; 167 L.Ed.2d 705; 82 U.S.P.Q.2d 1385 (2007). In order for an examiner to establish a prima facie case of obviousness

after KSR, some degree of predictability is necessary. (82 U.S.P.Q.2d at 1395-97). *Takeda Chemical Industries Ltd. V. Alphapharm Pty. Ltd.*, 83 USPQ.2d 1169 (Fed. Cir. 2007) is a post KSR decision in which the Federal Circuit articulated standards for establishing non-obviousness which again includes predictability of success. (83 USPQ.2d at 1176-79). Further, Section 2143.02 (II) of the MPEP states that "Obviousness does not require absolute predictability, however, at least some degree of predictability is required."

Clearly, the disclosure of Chen and Ghana does not provide sufficient predictability or expectation to support a prima facie case of obviousness as it fails to disclose, teach or suggest the drug delivery composition of the present invention.

Accordingly, the Examiner has not presented a prima facie case of obviousness as the examiner fails to present, inter alia, any evidence that the drug delivery composition contains the elements and properties, as claimed, nor has the Examiner presented any rationale to modify the cited references to arrive at the claimed composition.

Thus, claim 1 would not have been rendered obvious by Chen and Ghana. Claims 2–12, 17, and 35-36 depend from claim 1 and, thus, also would not have been rendered obvious by Chen and Ghana. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Schiraldi in view of Grass

The Office Action rejects claims 1–4, 9-13, 17-20, and 22-23 under 35 U.S.C. §103(a) over U.S. Patent No. 4,713,243 to Schiraldi et al. ("Schiraldi") in view of U.S. Patent No. U.S. Patent No. 3,237,596 to Grass et al. ("Grass"). Applicants respectfully traverse the rejection.

The Examiner acknowledges that Schiraldi does not teach all the limitations provided by the claims, but alleges that Grass remedies the deficiencies of Schiraldi. The Examiner asserts that Grass teaches a method of coating discrete solids that have a particle size of 5 to 200 microns thus is easily combinable with Schiraldi. Applicants respectfully disagree.

Applicants wish to remind the Examiner of the "*Basic Requirements of a Prima Facie Case of Obviousness*", which can be found in M.P.E.P. §2143. According to these requirements, the following are necessary to establish a prima facie case of obviousness: (1) a reference or combination of references must provide some suggestion or motivation to modify the reference or to combine the teachings; (2) there must be a reasonable expectation of success; and (3) there must be a teaching or suggestion of all claim limitations.

Schiraldi is directed to a bioadhesive extruded film. Schiraldi describes a process for obtaining their bioadhesive extruded films. The components are all described as "powders" that are blended and then extruded by passing them through heated stainless steel rollers. Nowhere in Schiraldi is it disclosed or suggested that the components are uniformly distributed throughout the final end product. As the Examiner notes, the components are merely blended together.

The Examiner has not provided any teaching to suggest that the extruded film of the present invention is uniform. Nothing in the reference suggests that simply blending components guarantees uniformity. Furthermore, a liquid plasticizer is added to the powder blend during the blending process. According to Schiraldi, the purpose of the plasticizer is to "...improve polymer melt processing by reducing the polymer melt viscosity and to impart flexibility to the final product."

Thus, the films of Schiraldi must be extruded, and Schiraldi teaches away from a casted film product. "The film of the present invention has the advantage of being an extruded film,

rather than a cast film." (Schiraldi, col. 3, ll. 64-65). Accordingly, one of skill in the art would not find that the components utilized by Schiraldi would provide a casted film.

Grass is cited for its alleged disclosure of the particle size of about 5 to about 200 microns. Grass is directed to a method of coating discrete solids having a particular particle size. Nowhere does Grass teach or suggest film that is uniform in content, as required by the claims. Therefore, Grass fails to cure the deficiencies of Schiraldi.

Moreover, there is no rationale suggested in Schrialdi that the extruded film should be modified to be a casted film. Furthermore, there is no rationale suggested by Grass that its method can be used in a casted film product. In addition, there is no level of predictability in the teaching of Schiraldi that their components could be used in a casted film. There is also no level of predictability in the teachings of Grass that their formulations would be useful in a casted film product.

There is no rationale in Schiraldi or Grass to modify their teachings, in order to arrive at the claimed invention. Furthermore, there is no predictability in the teachings of Schiraldi or Grass to lead one of skill in the art to arrive at the present invention with any expectation of success. Moreover, the combination of Schiraldi and Grass does not teach all the claim limitations.

Therefore, independent claims 1 and 18 would not have been rendered obvious by Schiraldi and Grass. Claims 2–4, 9-13, 17, 19, 20, 22, and 23 variously depend from claims 1 and 18 and, thus, also would not have been rendered obvious by Schiraldi and Grass. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Schiraldi in view of Thakur

The Office Action rejects claims 18-21 and 23-24 under 35 U.S.C. §103(a) over Schiraldi in view of U.S. Patent No. U.S. Publication No. 2004/0156901 to Thakur e al. ("Thakur").

The Examiner acknowledges that Schiraldi fails to teach or suggest that the medicament is coated with a taste-masking water soluble polymer. *See* Office Action, page 9, 3rd paragraph. Nevertheless, the Examiner cites Thakur as allegedly curing Schiraldi's deficiencies. Applicants respectfully traverse the rejection.

For at least the reasons mentioned above, Schiraldi fails to teach or suggest all the features of claims 1 and 18. Thakur is cited for its alleged teaching particulate cores of actives agents coated with taste-masking polymer. Thakur's disclosure is directed to "a solid dosage formulation of topiramate intended primarily for use by pediatric patients, or for patients who have difficulty swallowing tablets." *See* Abstract. Nowhere does Thakur teach or suggest film that is uniform in content, as required by the claims. Therefore, Thakur fails to cure the deficiencies of Schiraldi. Therefore, Schiraldi and Thakur, whether considered independent or combines fails to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit."

Moreover, similar to the arguments stated above in regards to Grass, there is no rationale in Schiraldi or Thakur to modify their teachings. Furthermore, there is no predictability in the teachings of Schiraldi or Thakur to lead one of skill in the art to arrive at the present invention with any expectation of success. Moreover, the combination of Schiraldi and Thakur does not teach all the claim limitations. Applicants therefore respectfully request reconsideration and withdrawal of the Section 103 rejection based thereon.

IV. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

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Julie Tabarovsky
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Electronic Acknowledgement Receipt

EFS ID:	9002680
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Julie Tabarovsky/Marcy Mancuso
Filer Authorized By:	Julie Tabarovsky
Attorney Docket Number:	1199-4B CIP
Receipt Date:	09-DEC-2010
Filing Date:	10-JUL-2007
Time Stamp:	15:52:16
Application Type:	Utility under 35 USC 111(a)

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		Amendment_and_Response.pdf	164555 13388a2192b087f5d60f0afeaf619d79714a0d45	yes	21

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	21
Warnings:			
Information:			
	Total Files Size (in bytes):	164555	

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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.

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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/775,484	07/10/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 12/09/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 35	Minus	** 36	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/AMANDA FORD/

EXHIBIT F

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP
Confirmation No.	5059	Dated:	April 4, 2011

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

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Alexandria, Virginia 22313-1450

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Dated: April 4, 2011

Signature: Shannon Farischon/Shannon Farischon/

AMENDMENT AND RESPONSE PURSUANT TO 37 C.F.R. §1.116

Sir:

This is in response to the final Office Action dated February 2, 2011, a reply to which is due April 4, 2011 under the weekend rule.

Amendments to the Claims as reflected in the listing of claims; and

Remarks begin on page 12 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Currently Amended) A drug delivery composition comprising:

(i) a flowable water-soluble or water swellable film forming matrix comprising two or more substantially water soluble or water swellable polymers; said matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate bioeffecting agent uniformly stationed ~~therein~~ in the matrix; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the bioeffecting agent;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble or water swellable film forming matrix is capable of being dried without loss of uniformity in the stationing of said particulate bioeffecting agent therein; and

wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film dosage unit.

2. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said bioeffecting agent.

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. (Cancelled)

10. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 5% by weight per film unit.

11. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 2% by weight per film unit.

12. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 0.5% by weight per film unit.

13. (Original) The drug delivery composition of claim 1, wherein the coated particulate bioeffecting agent has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Original) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists,

proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

18. (Currently Amended) A thin film drug delivery composition comprising:

(a) an edible water-soluble or water swellable film forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; said matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component uniformly stationed ~~therein~~ in the matrix; wherein the coating on the particulate active component is a taste-masking agent,

and

wherein the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film dosage unit.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a thin film coating over the particulate active component.

21. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

24. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

25. (Withdrawn) A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (Previously presented) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone;

poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

36. (Previously presented) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of ace-inhibitors, antianginal 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, biological response modifiers, 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, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

37. (New) The drug delivery composition of claim 1, wherein the two or more water soluble or water swellable polymers have the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

Remarks

Claims 1-8 and 10-37 are pending in this application. Claims 25-34 have been withdrawn from consideration by the Examiner. By this Amendment, claims 1 and18 are amended and new claim 37 is added. Support for the amendments to the claims and the new claim may be found, for example, in the original claims, and the specification at paragraph [0160]. No new matter is added.

Entry of the amendments is proper under 37 CFR §1.116 because the amendments: (a) place the application in condition for allowance for the reasons discussed herein; (b) do not raise any new issue requiring further search and/or consideration as the amendments amplify issues previously discussed throughout prosecution; (c) satisfy a requirement of form asserted in the previous Office Action; and (d) place the application in better form for appeal, should an appeal be necessary. The amendments are necessary and were not earlier presented because they are made in response to arguments raised in the final rejection. Entry of the amendments is thus respectfully requested.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Rejection Under 35 U.S.C. §102

The Office Action rejects claims 1-5, 8-12, 14-19, 22, and 35-36 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 7,067,116 to Bess et al. ("Bess"). Applicants respectfully traverse the rejection.

By this Amendment, the independent claims are amended to recite that the "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix; (ii) a particulate bioeffecting agent uniformly stationed in the matrix." Nowhere does Bess teach or suggest such features.

In particular, Bess fails to teach or suggest a matrix that comprises at least two water soluble or water swellable polymers and that the active present in the matrix is capable of being maintained with the aid of particular viscosity.

Nowhere does Bess teach or suggest that specific viscosity can be used to aid in maintaining non-self aggregating uniformity of the active in the matrix. At most Bess discloses that "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." However, Bess fails to teach or suggest a "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix," as Bess does not appreciate the need for specific uniformity, as claimed.

The Office Action acknowledges that "Bess does not disclose the active component is uniformly distributed in the film composition; and wherein the infirmity is determined by the composition having a variation of drug content of less than 10% per film unit." *See* Office Action page 5, 3rd and 4th paragraphs.

Nonetheless, the Office Action asserts that because "Bess does disclose the composition is thoroughly mixed prior to casting into a film. Bess additionally discloses the composition the same components prepared as a film,...one skilled in the art would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient." *See* Office Action page 5 last paragraph through page 6, 1st paragraph. Applicants respectfully disagree.

As is well settled:

> 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 a given set of circumstances is not sufficient.'

In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). In other words, it must be clear to one of ordinary skill in the art that the film matrix discussed in Bess **necessarily** possesses all of the properties and characteristics of the film matrix recited in the independent claims to support an inherency rejection. As will be discussed below, evidence found, e.g., in the instant specification precludes such a determination.

The Examples and Comparative Example found of the instant specification illustrate how films having compositions recited in the independent claims, but are manufactured by two different processes, can exhibit different properties. *See* pages 22-37 of the published specification.

The missing elements of Bess cannot be inherent because the processes Bess uses to make its composition is clearly different from the novel process disclosed in the present application.

The ability to achieve the uniformity of content within the claimed range is directly related to Applicants' drying technique which is disclosed in must be carefully controlled. Conventional drying of cast films in ovens will not preserve uniformity.

As described in the present invention, a number of techniques are employed to avoid bubbles and provide uniform heterogeneity. In particular, the present specification obtains, "a composition mixture with substantially no air bubble formation in the final product" by utilizing "anti-foaming or surface-tension reducing agents" and controlling the speed of the mixture to prevent cavitation and "allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film". (Instant specification, paragraph [0075]) (emphasis added).

Bess fail to disclose the difficulties of achieving uniformity of content in cast films, nor steps or processes to overcome the inherent difficulties in doing so.

Applicants' process forms a visco-elastic matrix rapidly to "lock-in" the uniformity of the flowable matrix during the drying process. Bess merely recites air drying or drying under warm air, without any suggestion or even hint of the problem relating to uniformity. Uniformity, as recited by Applicants is clearly not taught nor suggested, nor is it at all predictable.

The film of Bess is dried using one of the "conventional" drying techniques, i.e. air-dried or dried under warm air. The method of drying as described by Bess would trap moisture inside the film. (Bess, col. 8, lines 47-50). Once the trapped moisture begins to evaporate, the surface of the film will rip open and reform. As such, a film that includes uniform heterogeneity is not expected in films that are dried according to the methods described in Bess. Uniform distribution of actives within the final film would not be expected with Bess's process. In fact, conventional processing does not produce films with uniformity of content, as further described below.

In contrast, the present specification utilizes a controlled drying process that avoids the formation of bubbles and a rippling effect by evaporating or removing at least a portion of the liquid carrier in a faster drying time than those conventionally used in the art. The faster drying time encourages uniform distribution of the actives because viscosity of the film increases at a quicker rate utilizing this method.

For at least the reasons mentioned, Bess fails to teach or suggest all the features of the independent claims. Accordingly Bess does not anticipate independent claims 1 and 18. Claims 2-5, 8-12, 14-17, 19, 22, and 35-36 variously depend from claims 1 and 18 and, thus, also are not anticipated by Bess. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. Rejections Under 35 U.S.C. §103

A. Chen in view of Ghana

The Office Action rejects claims 1–8, 10-12, 17, and 35-36 under 35 U.S.C. §103(a) over PCT Publication No. WO 00/42992 to Chen et al. ("Chen") in view of U.S. Patent No. 5,653,993 to Ghana et al. ("Ghana").

Without conceding the propriety of the rejection, the independent claims are amended to recite that the "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix; (ii) a particulate bioeffecting agent uniformly stationed in the matrix." Nowhere does Chen teach or suggest such features. Ghana fails to cure the deficiencies of Chen, as it also fails to teach or suggest such features.

Whether considered independently or combined, Chen and Ghana fail to teach or suggest that specific viscosity can be used to aid in maintaining non-self aggregating uniformity of the active in the matrix and that uniformity is determined by the composition having a variation of drug content of less than 10% per film dosage unit, as claimed.

The Office Action acknowledges that Chen and Ghana do not disclose the drug content uniformity but asserts that because "Chen and Ghana are both drawn to the preparation of films, and disclose the solution is mixed to provide a uniform solution prior to film preparation....the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient." *See* Office Action page 9, 2nd paragraph.

As mentioned above, in order to support an inherency rejection, it must be clear to one of ordinary skill in the art that the film matrix discussed in Chen and Ghana **necessarily** possesses all of the properties and characteristics of the film matrix recited in the independent claims to support an inherency rejection. As will be discussed below, evidence found, e.g., in the instant specification precludes such a determination.

The Examples and Comparative Example found of the instant specification illustrate how films having compositions recited in the independent claims, but are manufactured by two different processes, can exhibit different properties. *See* pages 22-37 of the published specification.

The claimed invention is directed to solving the problems associated with achieving a taste-masked drug which is uniformly distributed throughout a film, such that individual dosage units cut from the film will have the same amount of drug in them and will be pleasant tasting.

As described in the present invention, "the products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film." *See* paragraph [0160].

Although Chen discloses the use of taste-modifying agents in a film dosage form, Chen merely mixes taste modifying agents into the film-forming mix without recognizing the problem of separation or aggregation of the taste-modifying agents from the unpleasant tasting pharmaceutical agents. Therefore, Chen does not recognize the problem to be solved by the claimed invention, i.e. attaining low adjuvant content, high-taste-masked pharmaceutical active content films which have enhanced flexibility, structural integrity and **uniformity** (emphasis added). *See* page 3, lines 20-22.

As further evidence that Chen completely fails to appreciate uniformity, Chen merely discloses conventional hot air oven drying. Chen describes that the film is "dried under aeration at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation." (page 15, lines 28-29). Chen, however, does not disclose or even contemplate

using the specific controlled, bottom-drying methods presently claimed. The only means of drying disclosed in the cited reference is the method of drying that the present application specifically seeks to avoid (uncontrolled air drying).

Ghana is cited for its alleged disclosure of a diameter ranges from about 25 to 600 microns. Ghana is directed to preparation of individual taste-masked microcapsules. Nowhere does Ghana teach or suggest film that is uniform in content, as required by the claims. Therefore, Ghana fails to cure the deficiencies of Chen. Therefore, Chen and Ghana, whether considered independent or combines fails to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit" and a "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix."

Thus, claim 1 would not have been rendered obvious by Chen and Ghana. Claims 2–12, 17, and 35-36 depend from claim 1 and, thus, also would not have been rendered obvious by Chen and Ghana. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Schiraldi in view of Grass

The Office Action rejects claims 1- 4, 10-13, 17-20, and 22-23 under 35 U.S.C. §103(a) over U.S. Patent No. 4,713,243 to Schiraldi et al. ("Schiraldi") in view of U.S. Patent No. U.S. Patent No. 3,237,596 to Grass et al. ("Grass"). Applicants respectfully traverse the rejection.

The Examiner acknowledges that Schiraldi does not teach all the limitations provided by the claims, but alleges that Grass remedies the deficiencies of Schiraldi. The Examiner asserts that Grass teaches a method of coating discrete solids that have a particle size of 5 to 200 microns thus is easily combinable with Schiraldi. Applicants respectfully disagree.

Without conceding the propriety of the rejection, the independent claims are amended to recite that the "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix; (ii) a particulate bioeffecting agent uniformly stationed in the matrix." Nowhere does Schiraldi teach or suggest such features. Grass fails to cure the deficiencies of Schiraldi, as it also fails to teach or suggest such features.

In particular, Schiraldi and Grass fail to teach or suggest a matrix that comprises at least two water soluble or water swellable polymers and that the active present in the matrix is capable of being maintained with the aid of particular viscosity. At most Schiraldi discloses that "for the uses for the present invention contemplated here, the plasticizer should be non-toxic. The purpose of the plasticizer is to improve polymer melt processing by reducing the polymer melt viscosity and to impart flexibility to the final product." However, Schiraldi fails to teach or suggest a "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix," as Schiraldi does not appreciate the need for specific uniformity, as claimed.

As described in the present invention, "the products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film." *See* paragraph [0160].

Schiraldi describes a process for obtaining their bioadhesive extruded films. The components are all described as "powders" that are blended and then extruded by passing them through heated stainless steel rollers. Nothing in the reference suggests that simply blending components guarantees uniformity to any level. Nowhere in Schiraldi is it disclosed or suggested that the components are uniformly distributed throughout the final product, let alone that the final product has a uniformity that is no more than 10% variance per unit area nor that

the matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix."

As mentioned above, in order to support an inherency rejection, it must be clear to one of ordinary skill in the art that the film matrix discussed in Schiraldi and Grass **necessarily** possesses all of the properties and characteristics of the film matrix recited in the independent claims to support an inherency rejection.

As mentioned in the previous response, the Examiner has not provided any teaching to suggest that the extruded film of the Schiraldi is uniform. Nothing in the references suggests that simply blending components guarantees uniformity.

Grass is merely cited for its alleged disclosure of the particle size of about 5 to about 200 microns. Grass is directed to a method of coating discrete solids having a particular particle size. Nowhere does Grass teach or suggest film that is uniform in content nor does it teach a matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix," as required by the claims. Therefore, Grass fails to cure the deficiencies of Schiraldi.

Accordingly, independent claims 1 and 18 would not have been rendered obvious by Schiraldi and Grass. Claims 2–4, 9-13, 17, 19, 20, 22, and 23 variously depend from claims 1 and 18 and, thus, also would not have been rendered obvious by Schiraldi and Grass. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Schiraldi in view of Thakur

The Office Action rejects claims 18-21 and 23-24 under 35 U.S.C. §103(a) over Schiraldi in view of U.S. Patent No. U.S. Publication No. 2004/0156901 to Thakur e al. ("Thakur").

The Examiner acknowledges that Schiraldi fails to teach or suggest that the medicament is coated with a taste-masking water soluble polymer. *See* Office Action, page 11 last paragraph. Nevertheless, the Examiner cites Thakur as allegedly curing Schiraldi's deficiencies. Applicants respectfully traverse the rejection.

For at least the reasons mentioned above, Schiraldi fails to teach or suggest all the features of claims 1 and 18. Thakur is cited for its alleged teaching particulate cores of actives agents coated with taste-masking polymer. Thakur's disclosure is directed to "a solid dosage formulation of topiramate intended primarily for use by pediatric patients, or for patients who have difficulty swallowing tablets." *See* Abstract. Nowhere does Thakur teach or suggest film that is uniform in content and a matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix," as required by the claims. Therefore, Thakur fails to cure the deficiencies of Schiraldi. Therefore, Schiraldi and Thakur, whether considered independent or combined fail to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit" and a "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix."

Moreover, similar to the arguments stated above in regards to Grass, there is no rationale in Schiraldi or Thakur to modify their teachings. Furthermore, there is no predictability in the teachings of Schiraldi or Thakur to lead one of skill in the art to arrive at the present invention with any expectation of success. Moreover, the combination of Schiraldi and Thakur does not teach all the claim limitations. Applicants therefore respectfully request reconsideration and withdrawal of the Section 103 rejection based thereon.

III. New Claim

By this Amendment, new claim 37 is presented. New claim 37 depends from claim 1 and, thus, distinguishes over the applied references for at least the reasons discussed above with respect to claim 1. Prompt examination and allowance of new claim 37 are respectfully requested.

IV. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

/Julie Tabarovsky/
Julie Tabarovsky
Registration No. 60,808

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Electronic Acknowledgement Receipt

EFS ID:	9803973
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Julie Tabarovsky/Shannon Farischon
Filer Authorized By:	Julie Tabarovsky
Attorney Docket Number:	1199-4B CIP
Receipt Date:	04-APR-2011
Filing Date:	10-JUL-2007
Time Stamp:	16:19:40
Application Type:	Utility under 35 USC 111(a)

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		1199-4B_CIP_Amendment_Response_04_04_11.pdf	156414 [illegible]	yes	22

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Claims	2	11
	Applicant Arguments/Remarks Made in an Amendment	12	22
Warnings:			
Information:			
	Total Files Size (in bytes):	156414	

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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.

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.

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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number	Filing Date	To be Mailed
11/775,484	07/10/2007	☐

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT 04/04/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 37	Minus	** 36	= 1	X $26 =	26	OR	X $ =	
Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	26	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/TINA J. BARDEN/

Document code: WFEE

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP
Confirmation No.	5059	Dated:	December 9, 2010

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

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Dated: December 9, 2010

Signature: /Marcy Mancuso/

AMENDMENT AND RESPONSE PURSUANT TO 37 C.F.R. §1.111

Sir:

In response to the Office Action dated September 9, 2010, a response to which is due by December 9, 2010, the Applicant responds as follows:

Amendments to the claims begin on page 2 of this submission.

Remarks begin on page 10 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Currently Amended) A drug delivery composition comprising:

(i) a flowable water-soluble film forming matrix;

(ii) a particulate bioeffecting agent uniformly stationed therein; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the bioeffecting agent;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of said particulate bioeffecting agent therein; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.

2. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said bioeffecting agent.

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. (Cancelled)

10. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 5% by weight per film unit.

11. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 2% by weight per film unit.

12. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 0.5% by weight per film unit.

13. (Original) The drug delivery composition of claim 1, wherein the coated particulate bioeffecting agent has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Original) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

18. (Currently Amended) A thin film drug delivery composition comprising:

(a) an edible water-soluble film forming matrix comprising at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and

(b) a coated particulate active component uniformly stationed therein;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a thin film coating over the particulate active component.

21. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

24. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

25. (Withdrawn) A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (Currently amended) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; caragecnan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch~~, including tapioca starch, rice starch, corn starch, potato starch, and wheat starch~~; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins~~, such as, gelatin, zein, gluten, soy protein, soy protein isolate, and whey protein~~; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

36. (Previously presented) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of ace-inhibitors, antianginal 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, biological response modifiers, 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, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Remarks

Claims 1-8 and 10-36 are pending in this application. Claims 25-34 have been withdrawn from consideration by the Examiner. By this Amendment, claim 9 is cancelled and claims 1, 10, 11, 12, 18, and 35 are amended. Support for the amendments to the claims may be found, for example, in the original claims, and the specification. No new matter is added.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Rejection under 35 U.S.C. §112, Second Paragraph

The Office Action rejects claims 1-17 and 35 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Examiner asserts that "Applicant has not particularly pointed out how the combined particulate and taste masking agents can have a particle size of 200 microns or less when they are intimately associated with each other." Moreover, the Examiner asserts that "Applicant has not pointed out if both the particulate bioeffecting agent and the taste masking agent have the claimed particle size or if the particle size is only applicable when the taste masking agent is coated on the particulate bioeffecting agent." *See* Office Action, page 3, second paragraph.

Applicants respectfully disagree with the Examiner and traverse the rejection. Claim 1 clearly recites that "the **combined particulate and taste-masking agent** have a particle size of 200 microns." Accordingly, it would be clear to one skilled in the art that, regardless of whether the combined particulate bioeffecting agent is intimately associated with the taste masking agent or whether the particulate bioeffecting is coated with the taste masking agent, it is the

combination of the particulate bioeffecting agent and the taste masking agent that has a particle size of 200 microns. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner also rejects claim 35 for containing the terms "such as" and "including." Without conceding the propriety of the rejections, claim 35 is amended to more clearly recite various novel features of the claimed invention, with particular attention to the Examiner's comments. Specifically, claim 35 is amended to delete the terms "such as" and "including," thereby obviating the rejection. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. Rejection Under 35 U.S.C. §102

The Office Action rejects claims 1-5, 8-12, 14-19, 22, and 35-36 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 7,067,116 to Bess et al. ("Bess"). Applicants respectfully traverse the rejection.

It is well settled that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *See* MPEP §2131.

Independent claims 1 and 18 require that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit." Bess does not teach or suggest such a feature.

At most Bess teaches that its process involves "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." *See* column 12, lines 13-17.

The instant specification teaches that the ability to achieve the uniformity of content within the claimed range is directly related to Applicants' drying technique. *See* for example paragraphs [0068] and [0069]. Nowhere does Bess teach or suggest the difficulties of achieving uniformity of content in cast films, nor steps or processes to overcome the inherent difficulties in doing so.

Moreover, claim 18 requires "the coating on the particulate active component is a taste-masking agent." Bess fails to teach or suggest such a feature.

Although Bess discloses a presence of a coating, nowhere does Bess teach or suggest a coating that is a taste-masking agent, as claimed.

The Examiner asserts that "the recitation of adsorption complex would necessarily result in a thin film coating over portions of the agent." *See* Office Action, page 4, last paragraph. Applicants respectfully disagree. Although, Bess discloses the taste masking agent as an ion exchange resin, the ion exchange resin does not necessarily form a coating. At most, Bess teaches that "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." *See* column 9, lines 55-60. Nowhere does Bess teach or suggest a taste-masking coating, as required by claim 18 and Bess fails to teach or suggest "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit," as required by claims 1 and 18.

Accordingly Bess does not anticipate independent claims 1 and 18. Claims 2-5, 8-12, 14-17, 19, 22, and 35-36 variously depend from claims 1 and 18 and, thus, also are not anticipated by Bess. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. Rejections Under 35 U.S.C. §103

A. Chen in view of Ghana

The Office Action rejects claims 1–12, 17, and 35-36 under 35 U.S.C. §103(a) over PCT Publication No. WO 00/42992 to Chen et al. ("Chen") in view of U.S. Patent No. 5,653,993 to Ghana et al. ("Ghana"). Applicants respectfully traverse the rejection.

Chen is cited for its alleged disclosure of water soluble hydrocolloid, mucosal coating, an effective dose of agent. The Examiner acknowledges that Chen fails to teach or suggest the particle size of the encapsulated active agents. *See* Office Action, page 7, line 12. Nevertheless, the Examiner cites Ghana as allegedly curing the deficiencies of Chen.

By this Amendment, independent claim 1 is amended to recite that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit." Chen and Ghana, whether considered independently or combined, fail to teach or suggest such features.

Neither Chen nor Ghana disclose the difficulties of achieving uniformity of content in cast films, nor steps or processes to overcome the inherent difficulties in doing so. Thus, the Examiner has not provided any rationale to modify Chen or Ghana in order to arrive at the presently claimed invention.

The claimed invention is directed to solving the problems associated with achieving a taste-masked drug which is uniformly distributed throughout a film, such that individual dosage units cut from the film will have the same amount of drug in them and will be pleasant tasting.

There are several problems addressed by the present invention. One such problem is the delivery of bad-tasting actives in a dosage form which inherently exposes a high degree of the active to the taste buds. This is because most films are relatively thin by nature with planar surfaces and such the active is readily exposed to the taste buds as the film is dissolved. Thus, in view of the relatively large surface area of exposure, determining the proper size of the taste-masked particles was an important finding. Drug delivery films are not only relatively thin, but often dimensionally small. Thus, the smaller particles allow for a more uniform distribution to be readily achieved. Particles which are too large may self aggregate and cause a loss of uniformity of drug content per unit volume of film. Particles which are too large will also require more taste-masking material to effectively cover the active. Additionally, particles larger than 200 microns will present a gritty mouth feel and may be thicker than the film per se.

In short, the claimed invention solves the problems associated with effective delivery of a uniform amount of taste masked drug in a film dosage unit.

In particular, self aggregation or conglomeration of particles leads to **non-uniformity** of distribution of the drug in the film. The failure to achieve a high degree of accuracy with respect to the amount of active ingredient in dosage cut from the film can be harmful to the patient and may not meet the stringent governmental or agency standards relating to variation of active in dosage forms.

Self aggregation in film containing a pharmaceutical active increases the probability of perception of an unpleasant tasting film, as well as destroys the uniformity of the pharmaceutical agent in the film.

The claimed invention introduces a composition and processes as a solution that overcomes the above-mentioned problems.

Such a solution includes specific features such as particle size; maintaining the uniform distribution of active components by locking-in or substantially preventing migration of the active components within the visco-elastic film and resulting film product; and particular taste-masking agents.

Although Chen discloses the use of taste-modifying agents in a film dosage form, Chen merely mixes taste modifying agents into the film-forming mix without recognizing the problem of separation or aggregation of the taste-modifying agents from the unpleasant tasting pharmaceutical agents. Therefore, Chen does not recognize the problem to be solved by the claimed invention, i.e. attaining low adjuvant content, high-taste-masked pharmaceutical active content films which have enhanced flexibility, structural integrity and **uniformity** (emphasis added). *See* page 3, lines 20-22.

Uniformity is important in oral film products, particularly products intended for delivery of pharmaceutical actives such that regulatory approval of the product may be obtained. As further explained on page 22 of the present application, the films prepared in accordance with the present invention have a "high degree of uniformity of the components of the film [which] makes them particularly well suited for incorporating pharmaceuticals". (lines 26-29). Specifically, the film products have:

> 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.
>
> (page 38, lines 16-20).

In contrast, Chen fails to teach or suggest and has absolutely no appreciation for the need to achieve dried films that are uniform in content.

As further evidence that Chen completely fails to appreciate uniformity, Chen merely discloses conventional hot air oven drying. Chen describes that the film is "dried under aeration at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation." (page 15, lines 28-29). Chen, however, does not disclose or even contemplate using the specific controlled, bottom-drying methods presently claimed. The only means of drying disclosed in the cited reference is the method of drying that the present application specifically seeks to avoid (uncontrolled air drying).

Ghana is cited for its alleged disclosure of a diameter ranges from about 25 to 600 microns. Ghana is directed to preparation of individual taste-masked microcapsules. Nowhere does Ghana teach or suggest film that is uniform in content, as required by the claims. Therefore, Ghana fails to cure the deficiencies of Chen. Therefore, Chen and Ghana, whether considered independent or combines fails to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit."

Moreover, the Supreme Court addressed the standard for obviousness in its decision of *KSR International Co. v. Teleflex Inc.*, et al., 550 U.S. 389; 127 S.Ct. 1727; 167 L.Ed.2d 705; 82 U.S.P.Q.2d 1385 (2007). In order for an examiner to establish a prima facie case of obviousness

after KSR, some degree of predictability is necessary. (82 U.S.P.Q.2d at 1395-97). *Takeda Chemical Industries Ltd. V. Alphapharm Pty. Ltd.*, 83 USPQ.2d 1169 (Fed. Cir. 2007) is a post KSR decision in which the Federal Circuit articulated standards for establishing non-obviousness which again includes predictability of success. (83 USPQ.2d at 1176-79). Further, Section 2143.02 (II) of the MPEP states that "Obviousness does not require absolute predictability, however, at least some degree of predictability is required."

Clearly, the disclosure of Chen and Ghana does not provide sufficient predictability or expectation to support a prima facie case of obviousness as it fails to disclose, teach or suggest the drug delivery composition of the present invention.

Accordingly, the Examiner has not presented a prima facie case of obviousness as the examiner fails to present, inter alia, any evidence that the drug delivery composition contains the elements and properties, as claimed, nor has the Examiner presented any rationale to modify the cited references to arrive at the claimed composition.

Thus, claim 1 would not have been rendered obvious by Chen and Ghana. Claims 2–12, 17, and 35-36 depend from claim 1 and, thus, also would not have been rendered obvious by Chen and Ghana. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Schiraldi in view of Grass

The Office Action rejects claims 1–4, 9-13, 17-20, and 22-23 under 35 U.S.C. §103(a) over U.S. Patent No. 4,713,243 to Schiraldi et al. ("Schiraldi") in view of U.S. Patent No. U.S. Patent No. 3,237,596 to Grass et al. ("Grass"). Applicants respectfully traverse the rejection.

The Examiner acknowledges that Schiraldi does not teach all the limitations provided by the claims, but alleges that Grass remedies the deficiencies of Schiraldi. The Examiner asserts that Grass teaches a method of coating discrete solids that have a particle size of 5 to 200 microns thus is easily combinable with Schiraldi. Applicants respectfully disagree.

Applicants wish to remind the Examiner of the "*Basic Requirements of a Prima Facie Case of Obviousness*", which can be found in M.P.E.P. §2143. According to these requirements, the following are necessary to establish a prima facie case of obviousness: (1) a reference or combination of references must provide some suggestion or motivation to modify the reference or to combine the teachings; (2) there must be a reasonable expectation of success; and (3) there must be a teaching or suggestion of all claim limitations.

Schiraldi is directed to a bioadhesive extruded film. Schiraldi describes a process for obtaining their bioadhesive extruded films. The components are all described as "powders" that are blended and then extruded by passing them through heated stainless steel rollers. Nowhere in Schiraldi is it disclosed or suggested that the components are uniformly distributed throughout the final end product. As the Examiner notes, the components are merely blended together.

The Examiner has not provided any teaching to suggest that the extruded film of the present invention is uniform. Nothing in the reference suggests that simply blending components guarantees uniformity. Furthermore, a liquid plasticizer is added to the powder blend during the blending process. According to Schiraldi, the purpose of the plasticizer is to "...improve polymer melt processing by reducing the polymer melt viscosity and to impart flexibility to the final product."

Thus, the films of Schiraldi must be extruded, and Schiraldi teaches away from a casted film product. "The film of the present invention has the advantage of being an extruded film,

rather than a cast film." (Schiraldi, col. 3, ll. 64-65). Accordingly, one of skill in the art would not find that the components utilized by Schiraldi would provide a casted film.

Grass is cited for its alleged disclosure of the particle size of about 5 to about 200 microns. Grass is directed to a method of coating discrete solids having a particular particle size. Nowhere does Grass teach or suggest film that is uniform in content, as required by the claims. Therefore, Grass fails to cure the deficiencies of Schiraldi.

Moreover, there is no rationale suggested in Schrialdi that the extruded film should be modified to be a casted film. Furthermore, there is no rationale suggested by Grass that its method can be used in a casted film product. In addition, there is no level of predictability in the teaching of Schiraldi that their components could be used in a casted film. There is also no level of predictability in the teachings of Grass that their formulations would be useful in a casted film product.

There is no rationale in Schiraldi or Grass to modify their teachings, in order to arrive at the claimed invention. Furthermore, there is no predictability in the teachings of Schiraldi or Grass to lead one of skill in the art to arrive at the present invention with any expectation of success. Moreover, the combination of Schiraldi and Grass does not teach all the claim limitations.

Therefore, independent claims 1 and 18 would not have been rendered obvious by Schiraldi and Grass. Claims 2–4, 9-13, 17, 19, 20, 22, and 23 variously depend from claims 1 and 18 and, thus, also would not have been rendered obvious by Schiraldi and Grass. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. **Schiraldi in view of Thakur**

The Office Action rejects claims 18-21 and 23-24 under 35 U.S.C. §103(a) over Schiraldi in view of U.S. Patent No. U.S. Publication No. 2004/0156901 to Thakur e al. ("Thakur").

The Examiner acknowledges that Schiraldi fails to teach or suggest that the medicament is coated with a taste-masking water soluble polymer. *See* Office Action, page 9, 3rd paragraph. Nevertheless, the Examiner cites Thakur as allegedly curing Schiraldi's deficiencies. Applicants respectfully traverse the rejection.

For at least the reasons mentioned above, Schiraldi fails to teach or suggest all the features of claims 1 and 18. Thakur is cited for its alleged teaching particulate cores of actives agents coated with taste-masking polymer. Thakur's disclosure is directed to "a solid dosage formulation of topiramate intended primarily for use by pediatric patients, or for patients who have difficulty swallowing tablets." *See* Abstract. Nowhere does Thakur teach or suggest film that is uniform in content, as required by the claims. Therefore, Thakur fails to cure the deficiencies of Schiraldi. Therefore, Schiraldi and Thakur, whether considered independent or combines fails to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit."

Moreover, similar to the arguments stated above in regards to Grass, there is no rationale in Schiraldi or Thakur to modify their teachings. Furthermore, there is no predictability in the teachings of Schiraldi or Thakur to lead one of skill in the art to arrive at the present invention with any expectation of success. Moreover, the combination of Schiraldi and Thakur does not teach all the claim limitations. Applicants therefore respectfully request reconsideration and withdrawal of the Section 103 rejection based thereon.

IV. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

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Electronic Acknowledgement Receipt

EFS ID:	9002680
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Julie Tabarovsky/Marcy Mancuso
Filer Authorized By:	Julie Tabarovsky
Attorney Docket Number:	1199-4B ClP
Receipt Date:	09-DEC-2010
Filing Date:	10-JUL-2007
Time Stamp:	15:52:16
Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amendment_and_Response.pdf	164555 13388a2192b087f5d60f0afeaf619d79714a0d45	yes	21

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	21
Warnings:			
Information:			
	Total Files Size (in bytes):	164555	

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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.

PTO/SB/06 (07-06)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/775,484	Filing Date 07/10/2007	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT 12/09/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 35	Minus	** 36	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/AMANDA FORD/

EXHIBIT G

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Garry L. Myers	Examiner:	Janet L. Epps-Smith
Application No.:	12/537,571	Group Art Unit:	1633
Confirmation No:	5630	Docket:	1199-82
Filed:	August 7, 2009	Dated:	February 29, 2012
For:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS		

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
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Dated: February 29, 2012
Signature: Christine Briscoe/cbriscoe/

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Sir:

In fulfillment of the requirements of candor and good faith set forth in 37 C.F.R. §1.56, Applicants submit herewith the following Supplemental Information Disclosure Statement in accordance with the provisions of 37 C.F.R. §1.97 and §1.98. It is understood that the information provided herein is solely for the purpose of fulfilling Applicants' obligations under the law and should not be construed as, nor is it intended to be, an admission of prior art.

Copies of the U.S. patent documents listed on the Form PTO/SB/08a which is being submitted herewith are not provided as the United States Patent and Trademark Office has

waived the requirement for paper submission of U.S. patent documents. A copy of the listed foreign patent document is being submitted herewith.

The fee of $180 pursuant to 37 C.F.R. § 1.17(p) is being submitted herewith. If any additional fees are deemed due, please charge any such fees to Deposit Account No. 08-2461. The Commissioner also is hereby authorized to credit any over payment to Deposit Account No. 08-2461.

Should the Examiner have any questions or comments concerning the above, the Examiner is respectfully invited to contact the undersigned at the telephone number given below.

Respectfully submitted,

/Jon A. Chiodo/
Jon A. Chiodo
Registration No.: 52,739

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. 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	12537571
Filing Date	2009-08-07
First Named Inventor	Myers et al
Art Unit	1614
Examiner Name	
Attorney Docket Number	1199-82

U.S.PATENTS Remove

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	4582835		1986-04-15	Lewis et al	
	2	5800832		1998-09-01	Tapolsky et al	
	3	6159498		2000-12-12	Tapolsky et al	
	4	6264981	B1	2001-07-24	Zhang et al	

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	1	20030069263	A1	2003-04-10	Breder et al	
	2	20050147658	A1	2005-07-07	Tapolsky et al	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12537571
	Filing Date	2009-08-07
	First Named Inventor	Myers et al
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	1199-82

	3	20050048102	A1	2005-03-03	Tapolsky et al	
	4	20060281775	A1	2006-12-14	Kelly, II et al	
	5	20070148097	A1	2007-06-28	Finn et al	
	6	20080254105	A1	2008-10-16	Tapolsky et al	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	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	9817251	WO		1998-04-30	Virotex Corporation		☐
	2	9955312	WO		1999-11-04	Virotex Corporation		☐
	3	2007070632	WO	A2	2007-06-21	Biodelivery Sciences Int., Inc.		☐
	4	2008011194	WO	A2	2008-01-24	Biodelivery Sciences Int., Inc.		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12537571
	Filing Date	2009-08-07
	First Named Inventor	Myers et al
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	1199-82

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]
	1	Abeer M. Al-Ghananeem et al., "Effect of pH on Sublingual Absorption of Oxycodone Hydrochloride." AAPS PharmSciTech 2006; 7(1) Article 23 (http://www.aapspharmscitech.org)	☐
	2	Mahmood et al., "A limited sampling method for the estimation of AUC and Cmax of carbamazepine and carbamazepine epoxide following a single and multiple dose of a sustained-release product." BrJ Clin Pharmacol 1998; 45: pp 241-246	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[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	12537571
	Filing Date	2009-08-07
	First Named Inventor	Myers et al
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	1199-82

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

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ 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	/Jon A. Chiodo Reg. No. 52,739/	Date (YYYY-MM-DD)	2009-09-03
Name/Print	Jon A. Chiodo	Registration Number	52,739

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.**

Electronic Acknowledgement Receipt

EFS ID:	6007104
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Jon Anthony Chiodo/Jillian Romeo
Filer Authorized By:	Jon Anthony Chiodo
Attorney Docket Number:	1199-82
Receipt Date:	03-SEP-2009
Filing Date:	07-AUG-2009
Time Stamp:	10:05:40
Application Type:	Utility under 35 USC 111(a)

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	Information Disclosure Statement (IDS) Filed (SB/08)	1199-82_IDS.pdf	1729811 0e2e7fc514abd1957cf866076e6e48090e7c2412	no	5
Warnings:					
Information:					

2	Foreign Reference	WO1998017251.pdf	1861033 e8ae1a77043d2fbf71d4ba8894028a4e858108de	no	42
Warnings:					
Information:					
3	Foreign Reference	WO1999055312.pdf	2200901 fc5c27e73d1b16db65bd770f411f4fa7218741ab	no	51
Warnings:					
Information:					
4	Foreign Reference	WO2007070632.pdf	2361148 34ee6fa53f80f1224499ac22d2c1e2ff9f360c81	no	42
Warnings:					
Information:					
5	Foreign Reference	WO2008011194.pdf	2726713 613b5ffd421695cb22802db80f3339199b56d175	no	53
Warnings:					
Information:					
6	NPL Documents	Abber_et_al.pdf	132665 b72f12212d217df9b2b6683c7d26ced4169d3264	no	5
Warnings:					
Information:					
7	NPL Documents	Mahmood.pdf	414863 f5b1bb19cc080c669078bc3992cb1b78106b9d83	no	6
Warnings:					
Information:					
		Total Files Size (in bytes):	11427134		

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.

EXHIBIT H

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Myers et al.	Examiner:	Janet L. Epps-Smith
Serial No.:	12/537,571	Group Art Unit:	1633
Confirmation No.:	5630	Docket:	1199-82
Filed:	August 7, 2009	Dated:	February 29, 2012
For:	Sublingual and Buccal Film Compositions		

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
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Dated: February 29, 2012

Signature: Christine Briscoe/cbriscoe/

AMENDMENT AND RESPONSE

Sir:

In response to the office action dated August 31, 2011, a response to which is due by February 29, 2012 in view of the concurrently filed petition for three month extension of time, please amend the application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 7 of this paper.

Amendments to the Claims:

This listing of claims shall replace all previous listings in this application:

1. (Currently Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffer in an amount to provide a local pH ~~of~~ for said composition of a value sufficient to optimize absorption of said buprenorphine, wherein said local pH is from about 2 to about 3.5 in the presence of saliva.
2. (Canceled).
3. (Currently Amended) The composition of claim 1 ~~2~~, wherein the local pH of said composition is from about 3 to about 3.5 [[4]].
4. (Original) The composition of claim 1, wherein said film dosage composition provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
5. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one polymer in an amount of at least 25% by weight of said composition.
6. (Original) The composition of claim 1, wherein said buffer is present in an amount of from about 2:1 to about 1:5 by weight of buffer to buprenorphine.
7. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one self-supporting film forming polymer.
8. (Original) The film dosage composition of claim 1, wherein said buprenorphine is present in an amount of from about 2 mg to about 16 mg per dosage.
9. (Original) The film dosage composition of claim 1, wherein said buffer comprises sodium citrate, citric acid, and combinations thereof.

10. (Original) The film dosage composition of claim 1, wherein said buffer comprises acetic acid, sodium acetate, and combinations thereof.
11. (Currently Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffer in an amount sufficient to inhibit the absorption of said naloxone, while also optimizing absorption of said buprenorphine when administered orally.
12. (Currently Amended) The composition of claim 11, wherein said composition has a local pH of about 2 to about 3.5 [[4]].
13. (Currently Amended) The composition of claim 11, wherein said composition has a local pH of about 3 to about 3.5 ~~said buffer is present in an amount sufficient to provide a therapeutically adequate absorption of buprenorphine~~.
14. (Currently Amended) The composition of claim 13, wherein ~~a therapeutically adequate absorption of buprenorphine comprises~~ said buffer is present in an amount sufficient to provide a bioequivalent level of absorption of buprenorphine as a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
15. (Currently Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffering system;

    wherein said buffering system comprises a buffer capacity sufficient to maintain the ionization of naloxone during the time which said composition is in the oral

cavity of a user, and also sufficient to optimize the absorption of said buprenorphine.

16. (Currently Amended) The composition of claim 15, wherein said composition has a local pH of about 2 to about 3.5 [[4]].

17. (Currently Amended) A method of treating narcotic dependence of a user, comprising the steps of:

    a. providing a composition comprising:

        i. A polymeric carrier matrix;

        ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;

        iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and

        iv. A buffer in an amount to provide a local pH of about 2 to about 3.5 for said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and

    b. administering said composition to the oral cavity of a user.

18. (Original) The composition of claim 17, wherein said method provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.

19. (Currently Amended) The method of claim 17, wherein said composition has a local pH of about 3 [[2]] to about 3.5 [[4]].

20. (Original) The method of claim 17, wherein said film dosage composition is administered to the user through buccal administration, sublingual administration, and combinations thereof.

21. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of at least 1 minute.

22. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of between about 1 and 1.5 minutes.

23. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of up to 3 minutes.
24. (Currently Amended) A process of forming a film dosage composition comprising the steps of:
    a. casting a film-forming composition, said film-forming composition comprising:
        i. A polymeric carrier matrix;
        ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
        iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
        iv. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and
    b. drying said film-forming composition to form a self-supporting film dosage composition.
25. (Currently Amended) The process of claim 24, wherein said composition has a local pH of about 2 to about 3.5 [[4]].
26. (Currently Amended) A film dosage composition comprising a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, said film dosage composition having a bioequivalent release profile as a tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof, and wherein said composition provides a local pH of from about 2 to about 3.5.
27. (Original) An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.

28. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 5.431 hr.ng/ml to about 56.238 hr.ng/ml for buprenorphine.
29. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 102.88 hr.pg/ml to about 812.00 hr.pg/ml for naloxone.
30. (Original) The formulation of claim 27, wherein said formulation comprises about 2 to about 16 mg of buprenorphine or a salt thereof.
31. (Original) The formulation of claim 27, wherein said formulation comprises about 0.5 to about 4 mg of naloxone or a salt thereof.

REMARKS

The present application has been amended. Specifically, the claims have been amended to recite a particular local pH value and/or to recite that the buffer optimizes absorption of buprenorphine while also inhibiting absorption of the naloxone. Support for these amendments may be found, for example, at paragraphs [0013-17] and in the claims of the application as filed. It is noted that terms such as "optimize" and "inhibit" are defined in the application. No new matter is introduced through this Amendment.

Brief Description of the Invention

To aid the Examiner's understanding, the Applicant believes that it is beneficial to provide a concise explanation of the invention. Delivery of compounds such as buprenorphine and naloxone was previously known, however, the previously-accepted form of the delivery is in the form of a tablet (e.g., a Suboxone® tablet). The present invention is directed to the formation of a suitable film product that provides a certain release profile and in some embodiments, is bioequivalent result to, for example, a Suboxone® tablet. The desired result is a product that provides a Cmax that is 80-125% the level provided by, for example, the Suboxone® tablet at the same dosage levels of the buprenorphine and the naloxone.

The desired film product includes the delivery of buprenorphine and naloxone together. The film is either a single-layered film or a multi-layered film. In either case, it is desired to provide a product that is cognizant of both the buprenorphine and naloxone. That is, the absorption of the buprenorphine should be "optimized" (as defined at paragraph [0019] of the application) to provide a desired level of absorption, but at the same time the absorption of the naloxone should be inhibited to provide a minimal, if any, level of absorption. As explained in detail throughout the application, the present applicants have discovered that the film product should include a buffer that provides a specific buffer capacity to the film in order to achieve the desired result.

As set forth in the application as filed, according to pH partition theory, one would expect that saliva (which has a local pH of about 6.5) would maximize the absorption of both actives, given their respective pKa levels. See, for example, the Examples in the application

as filed. As generally understood, absorption of an active depends on the available unionized form of the active. Thus, as the local pH of the surrounding environment is lowered, basic actives will be more ionized, and less will be available for absorption.

Thus, it would be contrary to think of lowering the pH from 6.5 to pH 5.5, and especially to pH 3.5, given the above-mentioned theory. However, as explained in the application as filed, the absorption of the buprenorphine was increased by dropping the pH from 6.5 to 5.5. The absorption at a pH of 5.5 was, however, higher than desired (i.e., it was "maximized", not "optimized"). Extrapolating this further, it was surprising to find that the absorption for the buprenorphine decreased to a desirable level upon further lowering of the pH. As explained in the application as filed and in the Examples, controlling the local pH by providing a buffer having a specific buffer capacity in the film compositions of the present invention provides a system in which the desired release and/or absorption of the components is achieved.

For film products including both buprenorphine and naloxone, it was particularly surprising to find that both may be included in one film by providing a buffer having a pH of from about 2 to about 3.5. At this buffer capacity, it was found that the absorption of the buprenorphine may be optimized to a desirable level, while at the same time the absorption of the naloxone may be inhibited to a desirable level.

The present applicants have discovered that following pH partition theory actually does not result in a suitable product. This discovery was completely surprising and was not known prior to the invention. The claims have been amended where applicable to reflect the essence of the invention.

Response to Rejection

In the Office Action, the Examiner rejected claims 1, 4, 5, 7-10, 15, 17 and 20-24 under 35 U.S.C. §102(b) as allegedly anticipated by Oksche (WO 2008/025791, counterpart US 2010/0087470). The Examiner alleged that Oksche discloses the use of modified cellulose materials to administer buprenorphine and naloxone orally. The Examiner also pointed to the use of citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid.

The applicant respectfully traverses the instant rejection, and notes that the claims recite that the buffering system is sufficient to "optimize" the absorption of buprenorphine. To clarify the claims, the Applicant has amended claim 1 to recite that the pH for the buprenorphine is from 2 to 3.5. This pH allows for absorption of buprenorphine, but, in the case where naloxone is present, its absorption is minimized. The naloxone is included in the formulation, for example, as an antagonistic component if the product is injected or snorted by a product abuser, but its effect is minimized when the product is taken as intended, such as orally. As explained above, a pH of about 5.5 may be useful in maximizing absorption, however, not "optimizing" the absorption as defined in the application as filed. Even further, for the other claims as pending, the claims recite the use of a buffer that is suitable to not only optimize the absorption of buprenorphine, but also at the same time to inhibit the absorption of the naloxone.

The mere disclosure of the use of a pH modifier, for example, citric acid, is not the same as providing a buffer system that is sufficient to provide a buffer capacity suitable to optimize the absorption of the buprenorphine, let alone inhibit the absorption of the naloxone. Oksche completely fails to acknowledge that the pH of the system plays any role in the optimization or inhibition of the actives to be administered. Oksche merely discloses the inclusion of "suitable pH modifiers", without providing any discussion as to their use, their amount, the resulting pH levels, or their relation to the absorption of the buprenorphine. Oksche completely failed to recognize that providing a particular buffer capacity would be beneficial or important in the absorption of the buprenorphine. Oksche does not disclose any particular buffer capacity, either expressly or implicitly. Oksche only generally discloses flavoring agents, pH modifiers, and taste masking agents, each of which may have a pronounced effect on the pH of the material.

The present application is based upon the discovery that the delivery and absorption of buprenorphine can be optimized to a desired level through administration via a film if the pH is balanced appropriately.

Since Oksche fails to disclose the present limitation of a buffer capacity suitable to optimize the absorption of the buprenorphine, it cannot anticipate the claims as pending.

Next, in the Office Action, claims 1-31 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Oksche. The Examiner acknowledged that the reference fails to disclose the specific range of pH in the claims. However, the Examiner alleged that it would have been obvious to identify the optimal pH in an effort to provide optimal absorption of both the buprenorphine and the naloxone. In short, the Examiner alleged that the pH range would be a matter of routine experimentation.

The Applicant respectfully traverses the instant rejection and notes that the general disclosure in Oksche of a buffer is not sufficient to establish a *prima facie* case of obviousness. As an initial matter, it appears that the Examiner has set forth an "obvious to try" rejection. In order to establish that it would have been obvious to try certain variations, there must be a "finite number" of choices to choose from, which provide predictable results. Here, there are a significant number of pH ranges to choose from, ranging from 1-14 and including all fractions thereof. In addition, there are a significantly high number of potential buffers from which to choose, including acids, bases, and combinations thereof. Oksche provides absolutely no teaching as to what a suitable buffer that can provide a suitable buffer capacity is, nor is there simply a finite number of choices available.

Even further, for reasons stated in detail in the application, the proper buffering capacity is not one of routine experimentation nor is it one that can be predictably selected by one of ordinary skill in the art. Those skilled in the art would have simply relied upon pH partition theory and selected a buffering capacity that follows this theory – for example, a pH commensurate with the pKa of the active. However, as explained in the application, following pH partition theory did not result in a suitable product and the proper buffer capacity actually varied from that expected by the theory. Thus, the buffer capacity suitable to optimize the absorption of the buprenorphine and, at the same time, to inhibit the absorption of the naloxone, is not predictable.

The present inventors have undertaken significant experimentation to determine the conditions to effectively and efficiently deliver a suitable dosage of buprenorphine and, at the same time, to effectively and efficiently inhibit the absorption of naloxone. The inventors have determined that the buffer selected and the buffer capacity used in the film has a significant and dramatic affect on the absorption of actives. However, the arrival at this

invention is not simply limited to mere selection of pH ranges, and must take into account the Cmax and AUC values for the product.

As can be seen, one must consider a number of variables and consider many different features in order to consider the absorption of the buprenorphine "optimized", as presently claimed, so as to provide a bioequivalent release level as that of a Suboxone® tablet having similar levels of buprenorphine. The particular buffering levels and amount play a critical role in determining the effectiveness of the composition. The buffer capacity must be considered so as to provide the desired absorption levels of both actives. The discovery of the desirable buffer capacity was certainly not contemplated in Oksche and would not have been predictable.

The claims include both components to be together in a single film, with a buffer capacity that is suitable for both. The inventors have found that the two components may be used together with a single buffer capacity that optimizes the absorption of the buprenorphine but concurrently inhibits the absorption of the naloxone. This discovery was certainly not disclosed or contemplated in Oksche.

Oksche fails to disclose or suggest any buffering capacity and, in fact, fails to even acknowledge that buffering capacity can play a role in the relative absorptions of the components. Oksche merely states that buffers can be used, but includes nothing further. This general disclosure of a buffer is not sufficient to render obvious claims that require a particular buffer capacity to optimize the absorption of buprenorphine and inhibit the absorption of naloxone.

The Examiner alleged that modification of the pH values would be obvious. However, the Applicant respectfully disagrees and notes that there has been undertaken a significant course of experimentation to determine how pH can have an effect on the absorption (which is summarized in the application as filed). Oksche merely discloses that certain additives may be used, including acids as well as bases. One of ordinary skill in the art would therefore be led to believe that any particular pH value, whether neutral, acidic or basic, would be acceptable based upon the disclosure of Oksche. Further, there is no reason to believe, based upon the teachings of Oksche, that pH would even play any role in the effectiveness of the composition.

Some of the claims recite a particular Cmax value for both the buprenorphine and the naloxone – which is not disclosed or even suggested in Oksche. Oksche is completely silent as to the Cmax for the naloxone, and merely discusses values for the buprenorphine. Summarizing the invention, the present invention includes embodiments that provide a bioequivalent release and absorption as that of a Suboxone® tablet, both for the buprenorphine and the naloxone, which is not disclosed in Oksche.

At best, Oksche generally discloses that acids and bases may be used in the system, but does not even consider the pH effect on the absorption, let alone varying pH values in one composition.

As explained above, the present applicants have discovered that the suitable buffer capacity actually differs from that which would be expected from pH partition theory. For example, the buffer capacity for a product including both the buprenorphine and naloxone would be one that minimizes the absorption of the naloxone but optimizes the absorption of the buprenorphine – a concept not disclosed nor considered by Oksche. For example, the present inventors have discovered that at a pH of about 2-3.5, the relative absorptions can be controlled effectively. Alternatively, if the pH of the formulation is 2-3.5, the desired absorption profile may be achieved for buprenorphine while minimizing absorption of the naloxone.

One of ordinary skill in the art reading Oksche would not be led to believe that pH would play any role in the absorption. Even further, with respect to those claims including buprenorphine and naloxone, one of ordinary skill in the art certainly would not believe that varying local pH values would have any determinable or noticeable effect. There is no rational basis to modify Oksche to arrive at the presently claimed invention, and it would not be predictable to one of ordinary skill in the art to arrive at the claimed invention. For these reasons, these claims including the dual-region composition are allowable over Oksche.

There is no rational basis to arrive at the presently claimed invention based upon Oksche. Further, based upon the experimentation undertaken by the Applicants, and summarized in the application, the results obtained were certainly not predictable. Oksche

states nothing about the buffer capacity playing any role whatsoever in the optimum absorption, and one of ordinary skill in the art would not think it plays any role. There would be no reason to modify Oksche to arrive at any of these specific limitations as presently claimed. As such, claims 1-31 are not obvious over Oksche for a multitude of reasons.

Information Disclosure Statement

The Applicant is submitting herewith an Information Disclosure Statement, citing several references. Included in this submission is the citation of U.S. Publication No. 2011/0262522, which specifically claims pH ranges that are outside those presently claimed. In fact, based upon the disclosure of this reference, it would not be obvious to those of ordinary skill in the art to make or use the presently-claimed invention.

Conclusion

The fees for a three month extension of time is also due with this submission, to be charged to Deposit Account No. 08-2461. In addition, the fee for a late filed IDS may also be charged to the same Deposit Account. If any additional fees are due, the Commissioner is hereby authorized to charge payment any fees associated with this communication, or credit any overpayment, to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. § 1.136.

If there are any questions or if additional information is required, the Examiner is respectfully requested to contact Applicant's attorney at the number listed below.

Respectfully submitted,

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EXHIBIT I

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Myers et al.	Examiner:	Janet L. Epps-Smith
Serial No.:	12/537,571	Group Art Unit:	1633
Confirmation No.:	5630	Docket:	1199-82
Filed:	August 7, 2009	Dated:	October 22, 2012
For:	Sublingual and Buccal Film Compositions		

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P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: October 22, 2012

Signature: /Jane Callahan/Jane Callahan

AMENDMENT AND RESPONSE
AFTER FINAL OFFICE ACTION

Madam:

In response to the Final Office Action dated May 2, 2012, a response to which is due by August 2, 2012, please amend the application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 7 of this paper.

Amendments to the Claims:

This listing of claims shall replace all previous listings in this application:

1. (Previously Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffer in an amount to provide a local pH for said composition of a value sufficient to optimize absorption of said buprenorphine, wherein said local pH is from about 2 to about 3.5 in the presence of saliva.
2. (Canceled).
3. (Previously Amended) The composition of claim 1, wherein the local pH of said composition is from about 3 to about 3.5.
4. (Original) The composition of claim 1, wherein said film dosage composition provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
5. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one polymer in an amount of at least 25% by weight of said composition.
6. (Original) The composition of claim 1, wherein said buffer is present in an amount of from about 2:1 to about 1:5 by weight of buffer to buprenorphine.
7. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one self-supporting film forming polymer.
8. (Original) The film dosage composition of claim 1, wherein said buprenorphine is present in an amount of from about 2 mg to about 16 mg per dosage.

9. (Original) The film dosage composition of claim 1, wherein said buffer comprises sodium citrate, citric acid, and combinations thereof.
10. (Original) The film dosage composition of claim 1, wherein said buffer comprises acetic acid, sodium acetate, and combinations thereof.
11. (Previously Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffer in an amount sufficient to inhibit the absorption of said naloxone, while also optimizing absorption of said buprenorphine when administered orally.
12. (Previously Amended) The composition of claim 11, wherein said composition has a local pH of about 2 to about 3.5.
13. (Previously Amended) The composition of claim 11, wherein said composition has a local pH of about 3 to about 3.5.
14. (Previously Amended) The composition of claim 13, wherein said buffer is present in an amount sufficient to provide-a bioequivalent level of absorption of buprenorphine as a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
15. (Previously Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffering system;

wherein said buffering system comprises a buffer capacity sufficient to maintain the ionization of naloxone during the time which said composition is in the oral cavity of a user, and also sufficient to optimize the absorption of said buprenorphine.

16. (Previously Amended) The composition of claim 15, wherein said composition has a local pH of about 2 to about 3.5.

17. (Previously Amended) A method of treating narcotic dependence of a user, comprising the steps of:

    a. providing a composition comprising:

        i. A polymeric carrier matrix;

        ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;

        iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and

        iv. A buffer in an amount to provide a local pH of about 2 to about 3.5 for said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and

    b. administering said composition to the oral cavity of a user.

18. (Original) The composition of claim 17, wherein said method provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.

19. (Previously Amended) The method of claim 17, wherein said composition has a local pH of about 3 to about 3.5.

20. (Original) The method of claim 17, wherein said film dosage composition is administered to the user through buccal administration, sublingual administration, and combinations thereof.

21. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of at least 1 minute.

22. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of between about 1 and 1.5 minutes.
23. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of up to 3 minutes.
24. (Previously Amended) A process of forming a film dosage composition comprising the steps of:
    a. casting a film-forming composition, said film-forming composition comprising:
        i. A polymeric carrier matrix;
        ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
        iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
        iv. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and
    b. drying said film-forming composition to form a self-supporting film dosage composition.
25. (Previously Amended) The process of claim 24, wherein said composition has a local pH of about 2 to about 3.5.
26. (Previously Amended) A film dosage composition comprising a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, said film dosage composition having a bioequivalent release profile as a tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof, and wherein said composition provides a local pH of from about 2 to about 3.5.
27. (Original) An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a Cmax

of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.

28. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 5.431 hr.ng/ml to about 56.238 hr.ng/ml for buprenorphine.
29. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 102.88 hr.pg/ml to about 812.00 hr.pg/ml for naloxone.
30. (Original) The formulation of claim 27, wherein said formulation comprises about 2 to about 16 mg of buprenorphine or a salt thereof.
31. (Original) The formulation of claim 27, wherein said formulation comprises about 0.5 to about 4 mg of naloxone or a salt thereof.

REMARKS

Claims 1 and 3-31 are pending in this office action.

Rejection Under 35 U.S.C. §112

In the Office Action, the Examiner rejected claims 1-3, 13-14, 16-23, and 25-26 under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. The Examiner stated that the amendments to the pH from about 2 to about 3.5 for buprenorphine was not in the specification. The Examiner pointed to paragraph [0016] which discusses the pH that inhibits naloxone, but alleged that there was no support in the specification for the pH with regard to buprenorphine.

The Applicant respectfully traverses this rejection and directs the Examiner to paragraph [0064], for example. This paragraph states, in relevant part:

> In such combination films [including buprenorphine and naloxone], it has been discovered that the local pH of the film composition should preferably be in the range of about 2 to about 4, and more preferably about 3 to about 4... Most preferably the local pH of the film composition is about 3.5. At this local pH level, absorption of the buprenorphine is optimized while absorption of the naloxone is inhibited.

There is clear and literal support in the application as filed for the local pH of a combination film (e.g., including buprenorphine and naloxone) being from about 2 to about 3.5. Additional support for the pH being about 3.5 may be found in additional paragraphs, including, for example, paragraphs [0067] and [0087], as well as Example 8, which is directly related to an Analysis of *In Vivo* Absorption of a Film Having a Ph of From 3-3.5 (paragraphs [0097]-[0101].

In view of the significant literal support for this pH range in the application as filed, the Applicant respectfully traverses the rejection. There is ample support in the application for the claimed limitations, and thus the rejection should be withdrawn.

Rejection under 35 U.S.C. §103

In the Office Action, the Examiner rejected claims 1 and 3-31 under 35 U.S.C. §103(a) as allegedly obvious over Oksche (WO 2008/025791, counterpart US 2010/0087470). The Examiner stated that, although Oksche fails to disclose pH values, the determination of a suitable pH range would have been obvious and routine experimentation. The Examiner stated that Oksche discloses a Suboxone tablet, and thus it would have been obvious to modify Oksche accordingly. Finally, the Examiner stated that the "open range" of the pH in the claims (i.e., using the term "about") further demonstrates its obviousness.

Applicant's Response

The Applicant respectfully traverses the instant rejection, noting that the reference cited would simply not direct one of ordinary skill in the art to using a pH range that is clearly claimed. In fact, there is no direction in Oksche that one of ordinary skill in the art could follow and come up with the claimed invention. Finally, the Applicant has demonstrated through the examples shown in the application that the presently claimed range demonstrates unexpected and significant improvements, particularly when compared to that of the prior art and when compared to what one of ordinary skill in the art would have been led to believe (i.e., through partition theory, as explained in the application as filed at paragraph [0100]).

In addition, the Applicant traverses the Examiner's opinion that the term "optimize" is not limiting. The Examiner stated that limitations from the specification are not read into the claims, which is correct, however, the term "optimize" is expressly and unequivocally defined in the specification. The Applicant is permitted to be its own lexicographer, and terms that are given definition in the specification are defined as such in the claims. (**CITE**).

The claims specifically identify a particular pH range, which is sufficient to achieve the goals of optimizing the absorption of one component (buprenorphine) and minimizing the absorption of a second component (naloxone). There is absolutely no identified pH range in Oksche, and thus no direction whatsoever to allow one of ordinary skill in the art to come up

with the claimed invention. There is simply no predictability in modifying the pH of Oksche to the claimed level and expecting to achieve the significant results claimed.

Even further, as explained in detail in the application as filed and in the previous response, one of ordinary skill in the art would have expected that a product would follow pH partition theory. According to pH partition theory, one would expect that saliva (which has a pH of about 6.5) would maximize the absorption of both actives. However, it has been surprisingly discovered by the Applicant that by buffering the dosage to a particular pH level, the optimum levels of absorption of the buprenorphine and the naloxone may be achieved. It has been discovered that the desirable local pH of a composition including buprenorphine and naloxone is between about 2 to about 3.5. At this local pH level, the desired absorption of the buprenorphine and the naloxone is achieved. As described in the application as filed and in the Examples (discussed below), controlling the local pH of the film compositions of the present invention provides a system in which the desired release and/or absorption of the components is achieved.

As such, if one of ordinary skill in the art was to simply modify the pH, that person would have followed pH partition theory and used a pH of about 6.5. This is far outside the claimed range.

Experimental Results

The present inventors have undertaken significant experimentation to determine the conditions to effectively and efficiently deliver a suitable dosage of buprenorphine and, in appropriate circumstances, to effectively and efficiently inhibit the absorption of naloxone. The inventors have determined that the buffer selected and the buffer capacity used in the film has a significant and dramatic affect on the absorption of actives. However, the arrival at this invention is not simply limited to mere selection of pH ranges, and must take into account the Cmax and AUC values for the product.

The Examples are set forth in the application as filed, and as can be seen, the Applicant discovered that optimized values can be achieved when the pH of the film falls within the claimed range. These results are surprising, particularly in view of pH partition

theory, which would be understood that a pH of about 6.5 would be successful in achieving the desired balance between drug solubility and ionization.

The tests conducted by the Applicant demonstrate surprising and very effective results at the claimed pH levels. Again, these levels are certainly not obvious over Oksche's general disclosure (including lack of any pH range) and the present examples demonstrate the surprising effect that is achieved.

In particular, the Examples show the significant benefits when a pH of about 3.5 is used as compared to a pH of 6.5 and 5.5. See, for example, Example 8, which tested products at a pH of from 3.0-3.5.

As has previously been explained, the present applicants have discovered that the suitable buffer capacity actually differs from that which would be expected from pH partition theory. For example, the buffer capacity for a product including both the buprenorphine and naloxone would be one that minimizes the absorption of the naloxone but optimizes the absorption of the buprenorphine – a concept not disclosed nor considered by Oksche. For example, the present inventors have discovered that at a pH of about 2-3.5, the relative absorptions can be controlled effectively.

Conclusion

The fees for a three month extension of time is also due with this submission, to be charged to Deposit Account No. 08-2461. If any additional fees are due, the Commissioner is hereby authorized to charge payment any fees associated with this communication, or credit any overpayment, to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. § 1.136.

If there are any questions or if additional information is required, the Examiner is respectfully requested to contact Applicant's attorney at the number listed below.

Respectfully submitted,

/Stephen J. Brown /
Stephen J. Brown
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Attorney for Applicant(s)

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Electronic Patent Application Fee Transmittal

Application Number:	12537571
Filing Date:	07-Aug-2009
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Filer:	Stephen J. Brown/Jane Callahan
Attorney Docket Number:	1199-82

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1290	1290

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**1290**

Electronic Acknowledgement Receipt	
EFS ID:	14040836
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Stephen J. Brown/Jane Callahan
Filer Authorized By:	Stephen J. Brown
Attorney Docket Number:	1199-82
Receipt Date:	22-OCT-2012
Filing Date:	07-AUG-2009
Time Stamp:	14:06:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1290
RAM confirmation Number	390
Deposit Account	082461
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) 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	Extension of Time	1199-82_Petition_for_Extension_of_Time.PDF	83250 9b443c049d40812e7780a20a68877f3c4a3dc697	no	2
Warnings:					
Information:					
2		1199-82_amendment_and_response_dated_10-22-12.PDF	42569 4ae585c88011487370 11b24fae291bc3312bdb95	yes	11

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment After Final	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	11

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30341 abab3a9e6ad62bd647c7510140fbc592381bd0e4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	156160		

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.

PTO/SB/22 (10-12)
Approved for use through 1/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 1199-82

Application Number: 12/537,571

Filed: August 7, 2009

For: Sublingual and Buccal Film Compositions

Art Unit: 1633

Examiner: Janet L. Epps-Smith

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$150	$75	$
☐ Two months (37 CFR 1.17(a)(2))	$570	$285	$
☒ Three months (37 CFR 1.17(a)(3))	$1,290	$645	$ 1,290
☐ Four months (37 CFR 1.17(a)(4))	$2,010	$1,005	$
☐ Five months (37 CFR 1.17(a)(5))	$2,730	$1,365	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 08-2461.

☐ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration number 43,519.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Stephen J. Brown/ — Signature

October 22, 2012 — Date

Stephen J. Brown — Typed or printed name

973-331-1700 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☒ * Total of 1 forms are submitted.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/537,571	08/07/2009	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 10/22/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 30	Minus	** 31	= 0	X $ =		OR	X $62=	0
Independent (37 CFR 1.16(h))	* 7	Minus	***7	= 0	X $ =		OR	X $250=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/YOLANDA CHADWICK/

EXHIBIT J

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12537571	Filing Date	2009-08-07	Docket Number (if applicable)	1199-82 RCE	Art Unit	1633
First Named Inventor	Garry L. Myers			Examiner Name	Epps-Smith, Janet L.		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 082461

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Stephen J. Brown/	Date (YYYY-MM-DD)	2013-04-30
Name	Stephen J. Brown	Registration Number	43519

This collection of information is required by 37 CFR 1.114. 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 1.11 and 1.14. This collection is estimated to take 12 minutes 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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/22 (03-13)
Approved for use through 3/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 1199-82 RCE
Application Number 12537571	Filed August 7, 2009
For SUBLINGUAL AND BUCCAL FILM COMPOSITIONS	
Art Unit 1633	Examiner Epps-Smith, Janet L.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☑	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$ 200
☐	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☐	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 082461.

☐ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration number 43,519.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Stephen J. Brown/ — Signature

April 30, 2013 — Date

Stephen J. Brown — Typed or printed name

973-331-1700 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Myers et al.	Examiner:	Janet L. Epps-Smith
Serial No.:	12/537,571	Group Art Unit:	1633
Confirmation No.:	5630	Docket:	1199-82 RCE
Filed:	August 7, 2009	Dated:	April 30, 2013
For:	Sublingual and Buccal Film Compositions		

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: April 30, 2013

Signature: Stephen J. Brown \Stephen J. Brown\

AMENDMENT AND RESPONSE WITH REQUEST FOR CONTINUED EXAMINATION

Madam:

In response to the Final Office Action dated May 2, 2012, and Advisory Action dated November 2, 2012, Applications make the following amendments and remarks. This communication is filed concurrently with a Request for Continued Examination.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

Amendments to the Claims:

This listing of claims shall replace all previous listings in this application:

1. (Currently Amended) A film dosage composition comprising:
   a. A polymeric carrier matrix;
   b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
   c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
   d. A buffer in an amount to provide a local pH for said composition of a value sufficient to optimize absorption of said buprenorphine, wherein said local pH is from about 3 [[2]] to about 3.5 in the presence of saliva.
2. (Canceled).
3. (Cancelled).
4. (Original) The composition of claim 1, wherein said film dosage composition provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
5. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one polymer in an amount of at least 25% by weight of said composition.
6. (Original) The composition of claim 1, wherein said buffer is present in an amount of from about 2:1 to about 1:5 by weight of buffer to buprenorphine.
7. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one self-supporting film forming polymer.
8. (Original) The film dosage composition of claim 1, wherein said buprenorphine is present in an amount of from about 2 mg to about 16 mg per dosage.
9. (Original) The film dosage composition of claim 1, wherein said buffer comprises sodium citrate, citric acid, and combinations thereof.
10. (Original) The film dosage composition of claim 1, wherein said buffer comprises acetic acid, sodium acetate, and combinations thereof.

11. (Cancelled).
12. (Cancelled).
13. (Cancelled).
14. (Cancelled).
15. (Cancelled).
16. (Cancelled).
17. (Currently Amended) A method of treating narcotic dependence of a user, comprising the steps of:
    a. providing a composition comprising:
        i. A polymeric carrier matrix;
        ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
        iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
        iv. A buffer in an amount to provide a local pH of about 3 [[2]] to about 3.5 for said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and
    b. administering said composition to the oral cavity of a user.
18. (Original) The composition of claim 17, wherein said method provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
19. (Cancelled).
20. (Original) The method of claim 17, wherein said film dosage composition is administered to the user through buccal administration, sublingual administration, and combinations thereof.
21. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of at least 1 minute.
22. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of between about 1 and 1.5 minutes.

23. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of up to 3 minutes.
24. (Cancelled).
25. (Cancelled).
26. (Cancelled).
27. (Original) An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.
28. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 5.431 hr.ng/ml to about 56.238 hr.ng/ml for buprenorphine.
29. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 102.88 hr.pg/ml to about 812.00 hr.pg/ml for naloxone.
30. (Original) The formulation of claim 27, wherein said formulation comprises about 2 to about 16 mg of buprenorphine or a salt thereof.
31. (Original) The formulation of claim 27, wherein said formulation comprises about 0.5 to about 4 mg of naloxone or a salt thereof.

REMARKS

Independent claims 1 and 17 have been amended to recite a local pH range of about 3 to about 3.5. This limitation was previously claimed in claims 3 and 19, respectively. Accordingly, no new matter has been added.

Claims 3, 11-16, 19, and 24-26 have been cancelled without prejudice.

Claims 1, 4-10, 17-18, 20-23, and 27-31 are pending.

Rejection under 35 U.S.C. §103

In the Office Action, the Examiner rejected claims 1 and 3-31 under 35 U.S.C. §103(a) as allegedly obvious over Oksche (WO 2008/025791, counterpart U.S. Patent Application Publication No. 2010/0087470). The Examiner stated that, although Oksche fails to disclose pH values, the determination of a suitable pH range would have been obvious and routine experimentation. The Examiner stated that Oksche discloses a Suboxone tablet, and thus it would have been obvious to modify Oksche accordingly. Finally, the Examiner stated that the "open range" of the pH in the claims (i.e., using the term "about") further demonstrates its obviousness. Applicants respectfully traverse this rejection.

Although believed unnecessary, claims 3, 11-17, 19, and 24-26 have been cancelled to further prosecution. The rejection of these claims has been rendered moot and withdrawal is respectfully requested.

Claims 1, 4-10, 17-18, and 20-23:

Independent claims 1 and 17 have been amended to recite a local pH range of about 3 to about 3.5. Claims 4-10 and 18 and 20-23 depend from claims 1 and 17, respectively.

As previously argued, the claimed pH range achieves the goals of optimizing the absorption of one component (buprenorphine) and minimizing the absorption of a second component (naloxone). The Applicants have repeatedly shown that Oksche is completely devoid of any recitation of any pH range. Thus, there is absolutely no direction in Oksche to allow one of ordinary skill in the art to come up with the claimed invention. And, assuming arguendo that Oksche disclosed a pH, there is simply no predictability in modifying that pH to the claimed level and expecting to achieve the significant results claimed.

Moreover, Applicants have repeated demonstrated that experimental results in the specification show that the claimed pH range has unexpected benefits. A detailed discussion of these results is presented below for completeness. To briefly summarize, , the present applicants have discovered that the suitable buffer capacity actually differs from that which would be expected from pH partition theory. For example, the buffer capacity for a product including both the buprenorphine and naloxone would be one that minimizes the absorption of the naloxone but optimizes the absorption of the buprenorphine – a concept not disclosed nor considered by Oksche. For example, the present inventors have discovered that at a pH of about 3-3.5, the relative absorptions can be controlled effectively.

In response, to these experimental results and argument, the Examiner has essentially conceded that they are sufficient to overcome the rejection over Oksche, but that the claims are not commensurate in scope to the data:

> Applicant's argument that the Examples show significant benefits when a pH of about 3.5 is used is used as compared to a pH of 6.5 and 5.5, Example 8 tested products at a pH of ***from 3.0-3.5*** is not sufficient to provide evidence of unexpected or significant benefits associated with the full scope of the claimed invention, which recites a "local pH of ***about 2 to about 3.5 in the presence of saliva***." Applicant showing is not commensurate in scope with the claimed invention.

(Advisory Action at 2-3 (emphasis original).) Applicants note that the Examiner has not alleged that the experimental results are to be expected or otherwise rebutted the demonstration of unexpected results.

Accordingly, although believed unnecessary and only to further prosecution, Applicants have amended independent claims 1 and 17 to recite the local pH range of about 3 to about 3.5 to provide a scope that is fully and expressly supported by the experimental results. In view of the claims amendments, the Examiner's comments, and the experimental results Applicants submit that the alleged *prima facie* obviousness has been rebutted. For this reason alone, reconsideration and withdrawal of the rejection are respectfully solicited for claims 1, 4-10, 17-18, and 20-23.

As discussed above, previously described in the earlier responses, and as supported throughout the specification, the Applicant has surprisingly identified that the optimized

adsorption of buprenorphine and the optimized limited adsorption of naloxone do not follow traditional or expected adsorption profiles. Both compounds are conjugate organic acids with pKa's at approximately 8, and yet as the pH of the film for delivering the agents decreases, one compound undergoes a optimum adsorption, but the other compound surprisingly trends the opposite direction and is inhibited at the same lower pH levels. This divergence allows the Applicant to produce a film which delivers buprenorphine to the bloodstream and passes the naloxone to the gut where it is ineffective, thus providing a treatment regime for buprenorphine. At the same time, the film is protected from abuse, because if a patient diverts the dosage, the naloxone inhibits the opioid effect when injected, snorted or otherwise administered in a drug abuse attempt.

To counter the experimental evidence and surprising results, the Examiner has offered only a single reference, *Oksche,* in an obviousness rejection. *Oksche* is completely silent regarding adjusting pH to optimize the adsorption of buprenorphine and minimize the adsorption of naloxone. The only evidence offered by the Examiner for such a conclusion is that *Oksche* mentions pH modifiers such as "citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid" in the context of "secondary components such as preservatives, anti-oxidants, surfactants, viscosity enhancers, colouring agents, flavouring agents, pH modifiers, sweeteners or taste-masking agents [that] may be incorporated into the composition." *Oksche*, [0072]. Thus, the Examiner concludes that optimizing the pH is obvious in view of *Oksche* because pH modifiers are mentioned in passing. The Examiner relies on MPEP 2144.05 and asserts that "it would have been obvious to the ordinary skilled artisan... to modify their teachings so as to identify the optimal range of pH/dosage in an effort to identify formulations that would provide optimal adsorption of both agonist and antagonist. As per MPEP 2144.05, ... identification of the optimal pH/dosage appears to be a matter of routine experimentation." *Advisory Action* dated November 6, 2012, p. 4.

Applicant submits that the Examiner's arguments are misplaced for at least two reasons. First, MPEP 2144.05 applies for "Obviousness of Ranges," yet nothing within the disclosure of *Oksche* describes any range of pH. *Oksche* is completely silent regarding any amounts of acids, bases, buffers or anything substantive beyond the passing mention of "secondary components." Thus, the Examiner's conclusion that it would be obvious to

provide a specific range of pH for controlling adsorption of one active and inhibiting the adsorption of a similar active cannot be supported by that disclosure. Therefore, the Examiner is impermissibly relying on Applicant's own discovery of the significance of pH ranges in optimizing adsorption.

Second, even accepting for the sake of argument that MPEP 2144.05 applied because *Oksche* somehow provides some concept of pH, the instructions within that section of the MPEP again leads to the conclusion that reliance on *Oksche* is not proper. "A particular parameter must first be recognized as a result-effective variable, i.e. a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." MPEP 2144.05(II)(B) (citing *In re Antonie*, 559 F.2d 618 (CCPA 1977)) (emphasis added.) Here, *Oksche* is completely silent regarding the necessity of adding an acid or buffer. *Oksche* treats such components in the same manner as a flavoring agent, coloring agent, taste masking agent, or any number of other secondary components. *Oksche* does not indicate that the pH of 2-3.5 would lead to an optimized buprenorphine adsorption AND a minimized naloxone adsorption. *Oksche* never identifies nor understands the criticality of pH, and therefore cannot be asserted for the conclusion that it's merely a results effective variable that can be modified.

Moreover, based on the disclosure of Oksche one of skill in the art would have had a no rationale to use pH to modify absorption. Significantly, Oksche actually discusses enhancing absorption of buprenorphine over the mucosa. However, this discussion has nothing to do with pH, but rather points to permeation enhancers:

> In order **to allow absorption of buprenorphine over the mucosa of the mouth**, and particularly sublingually, in one embodiment **the dosage forms may additionally use agents that enhance absorption of the active agent, i.e. so-called permeation enhancers**.
>
> Such permeation enhancers may be selected from the group comprising propandiol, dexpanthenol, and oleic acid. The permeation enhancers may also be selected from the group comprising saturated or unsaturated fatty acids, hydrocarbons, linear or branched fatty alcohols, dimethylsulfoxide, propylene glycol, decanol, dodecanol, 2-octyldodecanol, glycerine, ethanol or other alcohols.

(¶ 0085-86 (emphasis added).) None of these would be considered to modify pH or act as buffers.

Furthermore, this is but one of many variables and ingredients that could be considered to effect absorption of the active ingredients. Accordingly, one of skill in the art with knowledge of the absorption of the actives from a tablet at pH 6.5, would have had no rationale to turn to pH out of all parameters to optimize absorption, much less to drastically reduce the pH to 3 to 3.5 and expect optimum results.

In sum, the rejection is completely devoid of any evidence or reasoning sufficient to demonstrate that one of skill in the art would have had any rationale to modify Oksche to arrive at the claimed invention.

For these additional reasons, the rejection falls short of providing a *prima facie* case for the obviousness of the claims. Reconsideration and withdrawal are respectfully solicited.

As noted above, the previous discussion of the experimental results is included here for completeness:

Experimental Results

Even further, as explained in detail in the application as filed and in the previous response, one of ordinary skill in the art would have expected that a product would follow pH partition theory. According to pH partition theory, one would expect that saliva (which has a pH of about 6.5) would maximize the absorption of both actives. However, it has been surprisingly discovered by the Applicant that by buffering the dosage to a particular pH level, the optimum levels of absorption of the buprenorphine and the naloxone may be achieved. It has been discovered that the desirable local pH of a composition including buprenorphine and naloxone is between about 2 to about 3.5. At this local pH level, the desired absorption of the buprenorphine and the naloxone is achieved. As described in the application as filed and in the Examples (discussed below), controlling the local pH of the film compositions of the present invention provides a system in which the desired release and/or absorption of the components is achieved.

As such, if one of ordinary skill in the art was to simply modify the pH, that person would have followed pH partition theory and used a pH of about 6.5.

The present inventors have undertaken significant experimentation to determine the conditions to effectively and efficiently deliver a suitable dosage of buprenorphine and, in appropriate circumstances, to effectively and efficiently inhibit the absorption of naloxone. The inventors have determined that the buffer selected and the buffer capacity used in the film has a significant and dramatic effect on the absorption of actives. However, the arrival at this invention is not simply limited to mere selection of pH ranges, and must take into account the Cmax and AUC values for the product.

The Examples are set forth in the application as filed, and as can be seen, the Applicant discovered that optimized values can be achieved when the pH of the film falls within the claimed range. These results are surprising, particularly in view of pH partition theory, which would be understood that a pH of about 6.5 would be successful in achieving the desired balance between drug solubility and ionization.

The tests conducted by the Applicant demonstrate surprising and very effective results at the claimed pH levels. Again, these levels are certainly not obvious over Oksche's general disclosure (including lack of any pH range) and the present examples demonstrate the surprising effect that is achieved.

In particular, the Examples show the significant benefits when a pH of about 3.5 is used as compared to a pH of 6.5 and 5.5. See, for example, Example 8, which tested products at a pH of from 3.0-3.5.

As has previously been explained, the present applicants have discovered that the suitable buffer capacity actually differs from that which would be expected from pH partition theory. For example, the buffer capacity for a product including both the buprenorphine and naloxone would be one that minimizes the absorption of the naloxone but optimizes the absorption of the buprenorphine – a concept not disclosed nor considered by Oksche. For example, the present inventors have discovered that at a pH of about 2-3.5, the relative absorptions can be controlled effectively.

Claims 27-31:

Independent claim 27 recites that the "formulation provides an in vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone." Claims 28-31 depend from claim 27.

These claims have not been addressed in any of the art rejections, except by number. Thus, the limitations of these claims have never been addressed by the Examiner. Accordingly, these claims have not been rejected on any grounds.

Moreover, while Oksche does discuss the Cmax for buprenorphine, it is completely silent as to the Cmax for naloxone. Thus, even if the Examiner had applied the reference to the claims 27-31, Oksche would fall far short of supporting a rejection of claims 27-31 as obvious.

For these reasons, the rejection does not present a *prima facie* case for the obviousness of claims 27-31. Reconsideration and withdrawal of the rejection as to these claims are respectfully solicited.

Conclusion

In view of the foregoing, it is submitted that rejection has been met and the claims are in condition for allowance. Prompt entry of the amendments and allowance of the application are respectfully solicited.

The fees for a one month extension of time is also due with this submission, to be charged to Deposit Account No. 08-2461. If any additional fees are due, the Commissioner is hereby authorized to charge payment any fees associated with this communication, or credit any overpayment, to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. § 1.136.

If there are any questions or if additional information is required, the Examiner is respectfully requested to contact Applicant's attorney at the number listed below.

Respectfully submitted,

/Stephen J. Brown/
Stephen J. Brown
Registration No.: 43,519
Attorney for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
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Electronic Patent Application Fee Transmittal

Application Number:	12537571
Filing Date:	07-Aug-2009
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Filer:	Stephen J. Brown
Attorney Docket Number:	1199-82

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
OTHER PUBLICATION PROCESSING FEE	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	200	200
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**5530**

Electronic Acknowledgement Receipt	
EFS ID:	15654992
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	1199-82
Receipt Date:	30-APR-2013
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	TrackOne Request	1199-82_RCE_Request_for_Prioritized_Examination.pdf	153663 ee4f91c40fd9ddc0ad86f251e4c9881effe822a	no	2
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	1199-82_RCE_RCE.PDF	797915 a7c54b2ac9cf49a55534c6828aa3a5a0c68dce78	no	3
Warnings:					
Information:					
3	Extension of Time	1199-82_REC_EOT.PDF	187110 29906b3a636d6faf05ea3d86ede1f820fb249d04	no	2
Warnings:					
Information:					
4		1199-82_RCE_Amendment.pdf	54837 c67e87326a16acf2539f25971bfc05dae282c839	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment Submitted/Entered with Filing of CPA/RCE	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	12

Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	35221 d04be5f037b18e98ed20801e81be1e650e7ed3ed	no	2
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Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-13)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Garry L. Myers	Nonprovisional Application Number (if known):	12537571
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. The executed inventor's oath or declaration is filed with the application. (37 CFR 1.63 and 1.64)

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Stephen J. Brown, Reg. No. 43,519/	Date April 30, 2013
Name (Print/Typed) Stephen J. Brown	Practitioner Registration Number 43519

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *Total of _____ forms are submitted.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/537,571	Filing Date 08/07/2009	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 = *		X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 = *		X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **04/30/2013**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 19	Minus	** 31	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***7	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
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Exhibit K

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
95/001,753	09/12/2011	7,824,588	117744-00016	6620

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Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

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DIAMOND, ALAN D	
ART UNIT	PAPER NUMBER
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04/17/2014	PAPER

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The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE PATENT TRIAL AND APPEAL BOARD

BIODELIVERY SCIENCES INTERNATIONAL, INC.
Requester

v.

MONOSOL RX, LLC
Patent Owner and Appellant

Appeal 2014-000547
Reexamination Control 95/001,753
Patent 7,824,588 B2
Technology Center 3900

Before CHUNG K. PAK, JEFFREY B. ROBERTSON, and RAE LYNN P. GUEST, *Administrative Patent Judges*.

GUEST, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal by the Patent Owner from the Patent Examiner's decision to reject pending claims in an *inter partes* reexamination of U.S. Patent 7,824,588 B2 (herein after the "'588 patent").[1]

[1] The '588 patent issued November 2, 2010, to Robert K. Yang, et al.

wherein the resulting self-supporting film maintains the substantially uniform content of therapeutic active composition per unit of film.

REJECTIONS OF CLAIMS BASED ON SECTION 112

Claims 1-24, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 106, 111-132, 177, 178, 183, 186, 189, 192 and 193 stand rejected under 35 U.S.C. § 112, first and second paragraphs as indefinite, lacking in written description support, and lacking an enabling disclosure.

Claim 1 was amended during reexamination to recite a self-supporting therapeutic active-containing film in which there is "a substantially uniform content of therapeutic active composition" in both the wet film and maintained in the resulting self-supporting film "per unit of film." Claims 192 and 193 are new claims and have similar language to that added to claim 1.

The Examiner found that "[i]t is not clear exactly what is encompassed by a substantially uniform content of therapeutic active composition, and the '588 patent does not provide a definition for a substantially uniform content of therapeutic active composition." RAN at 9. The Examiner thus rejects the claim as being indefinite under 35 U.S.C. § 112, second paragraph, and as lacking adequate written descriptive support and lacking an enabling disclosure in the '588 patent under 35 U.S.C. § 112, first paragraph. *Id.* at 9-10. The Examiner further explains that "it is not clear how close to being uniform the product must be in order to be considered 'substantially uniform'. 'Substantially uniform' is not defined in the '588 patent." *Id.* at 68-69.

Patent Owner argues that the phrase "substantially uniform content of therapeutic active composition" means "a film having a degree of uniformity of ± 10% from the FDA label amount for the active per dosage unit." App. Br. 20.[2] In other words, the Patent Owner is arguing that the substantially uniform content must be defined with respect to a particular active content recognized and labeled by the FDA as a proper "dosage."

In support of this meaning, the Patent Owner points to the background of the '588 patent where the process of Fuchs is discussed as follows:

> 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.

'588 patent, col. 2, ll. 25-44.

We disagree with the Patent Owner's interpretation of the phrase "substantially uniform content of therapeutic active composition." The

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[2] *Cf.* App. Br. 24 (defining the phrase as "a degree of uniformity sufficient to maintain the amount of active in each dosage unit within 10% of the FDA amount of active."); App. Br. 15 (defining only the term *uniformity* as "the amount of active present may not vary more than 10% from amount of the active set by the FDA, for example, in a unit dose (per unit of film, i.e. in a film unit)"); Patent Owner's Rebuttal Brief 3, dated September 9, 2013 (hereinafter "Reb. Br.") (defining the phrase as "a degree of uniformity consistent with FDA pharmaceutical products and must include the limited variation such that the amount of active present may not vary more than 10% from the amount of the active set by the FDA per unit of film, i. e. per therapeutic dosage unit.").

FDA standard identified by Patent Owner in the portion of the '588 patent reproduced supra, is not again referenced. In the remaining parts of the '588 patent, uniformity is characterized not with respect to an FDA recognized dosage, but with respect to the lack of agglomeration of active material in any part of the film. For example, the '588 patent states that the active material is "evenly distributed throughout the film," which is "achieved by . . . the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure." '588 patent, col. 1, ll. 37-42. An objective of the process is "a substantially non-self-aggregating uniform heterogeneity throughout the area of the films." *Id.* at col. 4, ll. 5-9. The '588 patent further describes "a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods." *Id.*, col. 6, ll. 25-32. The process of the '588 patent provides "uniform distribution of components *for any given area in the film*." *Id.* at col. 7, ll. 26-29 (emphasis added).

Requiring a particular film to have an amount of active relative to a FDA recognized dosage considers the active amount in each individual "dosage unit" as compared to a particularly preferred or desired dosage. Patent Owner's interpretation disregards whether or not the active is agglomerated within the film and considers only a total amount of active material per dosage sized film rather than uniformity at *any given area in the film*, be it a small selected area, an area of the film consistent with a particular dosage, or an entire roll of film. Accordingly, the sentence relied

upon by the Patent Owner, stating that uniformity is "virtually mandated" by FDA requirements that the actual dosage be within a range of the labeled dosage, does not provide a definition of what would be considered "uniform," in light of the description of the '588 patent.

Further, the '588 patent describes three tests for determining uniformity. The first test was a visual inspection 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." *Id.* at col. 28, ll. 1-9. This first test is not consistent with the Patent Owner's interpretation because the test does not measure the active content with respect to any particular desired dosage. Further, Patent Owner's interpretation does not exclude the presence of agglomerated particles, which is the purpose of the visual appearance test.

The second test involved cutting out "dosage forms" "from random locations throughout the film" and additively weighing the randomly selected dosage forms. *Id.* at col. 28, ll. 10-16. Table 2 shows that with each additional dosage form, the weight increased by exactly 0.04g. *Id.* at col. 28, ll. 19-65. The '588 patent explains 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." *Id.* at col. 29, ll. 3-9. This second test also is not consistent with the Patent Owner's interpretation because the test does not measure the active content with respect to any particular

desired dosage. Rather, the second test is directed towards comparing the active content at various locations on the same film.

The third test involved dissolving "individual doses" and testing for the amount of active in films of particular size. *Id.* at col. 29, ll. 10-12. The '588 patent states that "[t]his demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active." *Id.* at col. 29, ll. 13-15. Although the third test determines the actual amount of active within a dosage sized film, the third test also is not consistent with Patent Owner's interpretation because the test does not measure the active content with respect to any particular desired dosage. Rather, the third test is directed towards comparing the active content at various locations on the same film.

Accordingly, we conclude that the term "uniform" in the claims is not directed to uniformity as compared to a particular FDA dosage as proposed by Patent Owner, but rather non-agglomerated and evenly dispersed active content for any area of a given film.

This claim interpretation is more consistent with the Examiner's interpretation of the phrase "unit of film," with which the Patent Owner agrees. App. Br. 17. The Examiner determined that the phrase "unit of film" was broad, but definite, and indicated that "[i]t could be a roll of finished film, it could be a standard area of dried film before being cut, or it could be a dosage unit. Any size can be a unit." RAN 11.

Further, we agree with the Examiner that, while the term "uniform" appears definite in light of the '588 patent, we are not instructed as to the scope to which a film may be "substantially uniform." We are not provided

a degree of agglomeration or an amount of unevenly dispersed active material for which the film would still be acceptable. Considering that the second, additive-weight-based test shows only complete uniformity, with no additional films weighing more or less than exactly 0.04g, we are not instructed as to what deviation in weight would be considered "substantially uniform." Further, we are not provided the results of the dissolution test as evidence of a range of acceptable uniformity.

Words of degree may lack precision, but they do not necessarily render a claim indefinite. *Seattle Box Co., Inc. v. Indus. Crating & Packing, Inc.*, 731 F.2d 818, 826 (Fed. Cir. 1984) (A term of degree is definite if the specification "provides some standard for measuring that degree. . . . that is, whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification."). As discussed above, under the proper interpretation of the term "uniform," the '588 patent provides no standard or guidance by which the term "substantially" can be measured or determined. Nor is there any intrinsic and/or extrinsic evidence relied upon by Patent Owner to show that such term has a known meaning in the art. Thus, we agree with the Examiner that such relative expression, amenable to any number of plausible claim constructions, is deemed indefinite within the meaning of 35 U.S.C. § 112, second paragraph. *Ex parte Miyazaki*, 89 USPQ2d 1207, 1211 (BPAI 2008) ("[During prosecution of a patent application,] if a claim is amenable to two or more plausible claim constructions [upon giving it the broadest reasonable interpretation consistent with the Specification], the USPTO is justified in requiring the applicant to more precisely define the metes and bounds of the

claimed invention by holding the claim unpatentable under 35 U.S.C. § 112, second paragraph, as indefinite."); *see also In re Morris*, 127 F.3d 1048, 1056 (Fed. Cir. 1997) ("It is the applicants' burden to precisely define the invention, not the PTO's. *See* 35 U.S.C. § 112, ¶ 2 . . . . [T]his section puts the burden of precise claim drafting squarely on the applicant.").

Since we are unable to determine an acceptable degree of agglomeration or degree of uniformity for any area of a given film to be considered "substantially uniform," we decline to reach the question of whether the '588 patent provides written descriptive support and an enabling disclosure under 35 U.S.C. § 112, first paragraph. *In re Wilson*, 424, F.2d 1382, 1385 (CCPA 1970); *In re Steele*, 305 F.2d 859, 862 (CCPA 1962). However, we will address the propriety of the certain prior art rejections maintained by the Examiner for the sake of administrative and judicial efficiency because we need not understand the exact scope of "substantially uniform" to resolve certain prior art rejections and/or can give a certain conditional interpretation of "substantially uniform" to resolve certain prior art rejections as is readily apparent from the discussions below. *See, e.g., Ex parte Saceman*, 27 USPQ2d 1472, 1474 (Bd. Pat. App. & Int. 1993); *Ex parte Ionescu*, 222 USPQ 537, 540 (Bd. Pat. App. & Int. 1984).

REJECTIONS BASED ON CHEN

Claims 192 and 193 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Chen.[3] Claim 1 and the claims that depend therefrom stand

[3] WO 00/42992, published July 27, 2000, naming Li-Lan Chen et al. as inventors.

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, either alone or view of additional prior art.[4] Patent Owner does not argue for the separate patentability of any dependent claims. Accordingly, the dependent claims stand or fall with claim 1.

Patent Owner contends that Chen fails to disclose a step of removing the polar solvent "by exposing the matrix to a temperature greater than the degradation temperature of said therapeutic active composition," as recited in claim 1.[5] Patent Owner argues that Chen teaches away from drying a film at a temperature above the degradation temperature of the therapeutic active composition. PO App. Br. 25-27. Patent Owner relies on the statement in Chen that the film is "dried under aeration at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation." *Id.* at 27; Chen, p. 15, ll. 19-29. Patent Owner argues that by this statement "Chen says such temperatures should be avoided" and that "Chen is concerned about keeping the temperature low to avoid destabilizing active agents." App. Br. 26 and 27.

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[4] Other additional art combined with Chen includes Le Person (Le Person, et al., "Near infrared drying of pharmaceutical thin films: experimental analysis of internal mass transport," Chem. Eng. Processing, Vol. 37, pp. 257-263 (1998)), Bernstein (US 5,656,297, issued August 12, 1997), Staab (US 5,393,528, issued February 28, 1995) and Hijiya (US 4,562,020, issued December 31, 1985).

[5] Patent Owner does not present separate the arguments with respect to claims 1, 192, and 193. However, only claim 1 includes a requirement that the temperature be greater than the degradation temperature of the therapeutic active composition.

We disagree with Patent Owner that Chen's statement suggests that higher temperatures "should be avoided" or "keeping the temperature low." Rather, Chen teaches a temperature range in order "to avoid destabilizing the agents contained within the formulation." Chen, p. 15, ll. 28-29. We disagree with Patent Owner that this statement would have suggested the skilled artisan limit the drying temperature to any particular temperature within the recited range of 40-100°C, provided that the film does not, in fact, result in degraded active ingredients. Thus, we find this statement in Chen consistent with the '588 patent. *See* '588 patent, col. 12, ll. 33-43.

Moreover, we agree with the Examiner that the skilled artisan would "have optimized Chen's drying step by using as high a drying temperature as possible within Chen's disclosed the range of 40-100°C without destabilizing the active agent because temperature is a results-effective variable with respect to active agent destabilization as taught by Chen; and so as to dry Chen's film as quickly as possible." RAN 28-29 and 74. We note that the example in Chen of drying for only 9 minutes (Chen, p. 17, ll. 13-15) is consistent with the description in the '588 patent of "drying the film within about 10 minutes or fewer." '588 patent, col. 7, ll. 33-35; *see* RAN 74. Patent Owner has not persuasively rebutted the Examiner's rationale as to the skilled artisan's reasonable optimization of temperatures within the range disclosed in Chen.

With respect to all of the claims on appeal, Patent Owner contends that Chen fails to disclose a film having a "substantially uniform content of therapeutic active composition per unit of film." According to Patent Owner, Chen does "not indicate or establish that the substantially uniform

content of the components is such that, for example, the amount of the active in individual dosage units varies by no more than 10% with respect to the desired/label amount for a particular film." App. Br. 28. Patent Owner argues that "[t]he actual degree of uniformity must be established through a determination of the actual amount of therapeutic active in at least samples of dosage units, which Chen does not disclose." *Id.* at 28 and 31-32. Patent Owner further argues that Figure 5 of Chen demonstrates that "in six instances the amount of active released from Chen's films is greater than 110% of the expected/desired amount." *Id.* at 30; Reb. Br. 5-6.

Initially, we note that Patent Owner's arguments substantially rely on Patent Owner's proposed claim interpretation which emphasizes uniformity with respect to a FDA-recognized dosage. For example, Patent Owner emphasizes a lack of evidence to support that the films of Chen are inherently within 10% of a recognized FDA dosage. Reb. Br. 5-6 Also, Patent Owner's arguments with respect to Figure 5 are exclusively related to release of an amount of active being more than 110% of "an expected/desired amount of pharmaceutical active for that drug." Reb. Br. 5.

We did not adopt the Patent Owner's proposed claim interpretation for the reasons discussed above and determine that the term "uniform content of therapeutic active composition" means non-agglomerated and evenly dispersed active content for any area of a given film, with the qualifier "substantially" expanding the scope to encompass some undefined agglomeration or some undefined degree of unevenly dispersed active material to also be acceptable. Accordingly, we do not find Patent Owner's arguments, including those regarding the release data over time in Figure 5

of Chen, to be compelling of a lack of uniformity. Figure 5 does not suggest agglomerated or unevenly dispersed active content for any area of a given film. Figure 5 merely indicates that different amounts of active material releases from the Chen films at various times, which is not shown to be an indicator that the active material is agglomerated or unevenly dispersed.

We agree with the Examiner that there is sufficient evidence to find that Chen inherently discloses a film with a substantially uniform content of therapeutic active composition per unit of film. RAN 21, 69-73, and 75.

In a case such as this where patentability rests upon a property of the claimed material not disclosed within the art, the PTO has no reasonable method of determining whether there is, in fact, a patentable difference between the prior art materials and the claimed material. Therefore, where the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily possess the characteristics of his claimed product. *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990); *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). However, the initial burden of presenting a case of unpatentability remains with the Requester and Examiner. If that burden is met, only then does the burden of coming forward with evidence or argument shift to the Patent Owner. *See In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

Although Patent Owner argues that the drying process of Chen is a conventional drying method that is distinguishable from the drying process of the '588 patent (App. Br. 29; Reb. Br. 14-15), we find that Chen describes

a substantially identical process to that described in the '588 patent. RAN 70 and 75.

Claim 1 does not recite any particular film drying steps. The evidence does not support Patent Owner's contention that the processes disclosed in Chen and in the '588 patent are clearly distinguishable. The '588 patent describes its drying process generally and does not clearly identify how a drying step can vary from a conventional drying process and avoid agglomerations of the active ingredients. For example, the '588 patent states that agglomerations form from "conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment." However, the description of non-agglomerating drying methods in the '588 patent does not clearly distinguish such drying equipment. *See* col. 14, ll. 13-14 ("the inventive process is not limited to any particular apparatus for the above-described desirable drying."). The '588 patent is not limited to any particular drying methods but rather includes a variety of drying methods. *Id.* col. 7, ll. 6-25; col. 25, ll. 15-16 ("When a controlled or rapid drying process is desired, this may be through a variety of methods."). The only process clearly distinguished by the '588 patent is "uncontrolled air currents, either above or below the film" which "can create non-uniformity in the final film product." *Id.*, col. 7, ll. 19-21; *see also* col. 6, ll. 50-61; col. 12, ll. 47-57 ("The films are Controllably dried to prevent aggregation and migration of components, as well as preventing heat build up within."); col. 10, l. 67-col. 11, l. 4; col. 13, ll. 13-15; col. 25, ll. 2-8. The '588 patent does not exclude top air flow (*id.* at col. 11, ll. 6-23) nor does the '588 patent require bottom directed

drying, since it only describes this process as either exemplary or preferable. *See id.* at col. 6, ll. 53-58; col. 7, ll. 6-8; col. 12, ll. 56-57; col. 25, ll. 22-23.

Chen describes a process in which a film is dried in a "drying oven with aeration controller" as illustrated in Figure 2. Chen, p. 6, l. 2. Figure 2 is reproduced below.

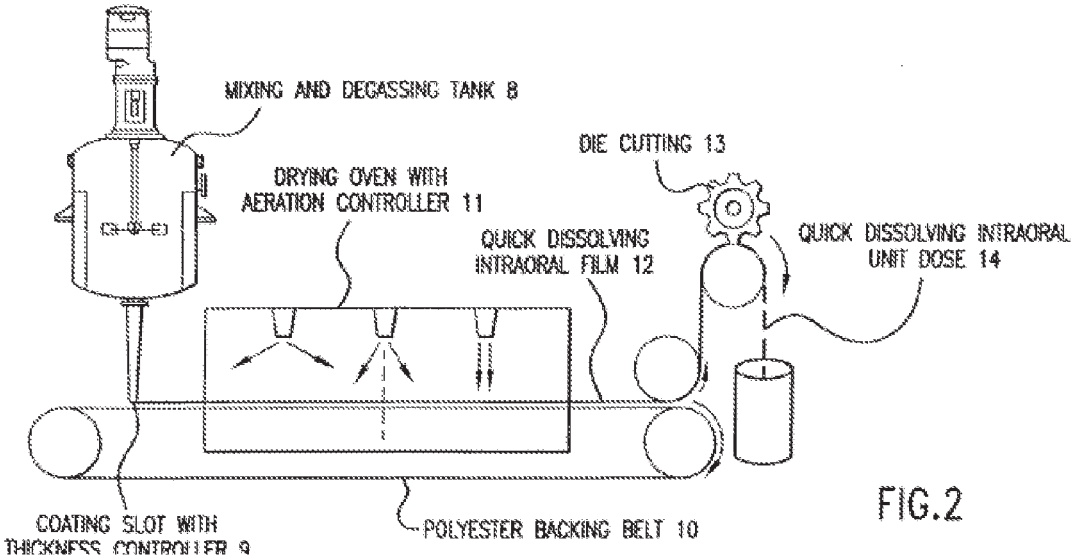

Figure 2 depicts a schematic of a manufacturing process for a dosage unit. Chen, p. 5, l. 31-p. 6, l. 3.

Figure 2 shows that at the initial drying stage, air currents are not directed onto the top of the film. Thus, we find that Chen teaches controlled drying and avoiding air currents directed onto the top surface of a film. The drying process of Chen is not sufficiently distinguished from the general drying method of the '588 patent.

Patent Owner's position is supported by the testimony of Dr. Rounds,[6] who testifies that Chen uses "a high presence of air flowing over the surface(s) of the wet film product" and that "uneven air currents flow[ing] over the wet film surface . . . can cause disruption of the fluid matrix and the components held therein, causing compositional non-uniformity of active content in the final, resulting film product." Rounds Decl. ¶ 16. We give little weight to Dr. Rounds' testimony because neither the "hot air circulating oven" nor the controlled air flow of Chen is distinguished from the equipment of the '588 patent. Dr. Rounds does not address Figure 2 which appears to show air diverted from the wet film surface consistent with the requirement for "controlled drying" in the '588 patent.

Moreover, the Examiner also finds that Chen's Table 4 describes weight per dosage film, thickness, density and water content measurements with minimal deviation as evidence that substantially uniform content of therapeutic active is inherent in the films described by Chen. RAN 15 and 71; *see* Chen p. 20, Table 4. The measured weight per dosage film as described in Chen is consistent with the additive weight test described in the '588 patent for determining uniformity. Specifically, the '588 patent states: "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." '588 patent, col. 29, ll. 4-9. Because the claims require only a "substantially uniform" film, which is broader than complete uniformity, but

[6] Declaration of Rhyta S. Rounds, dated January 9, 2012 and entered into the record on January 10, 2012 with Patent Owner's Response (hereinafter "Rounds Declaration" or "Rounds Decl.").

indefinite as to the degree of agglomeration or unevenly dispersed active material that would still be considered substantially uniform, for the purpose of applying art to the claims, we find that a weight deviation of ± 0.001 satisfies the limitation of "substantially uniform" active content. This amount is well within the less than 10% variation of active content per film unit requirement of claim 3.[7] Patent Owner does not persuasively show a distinction between the additive weight test of the '588 patent and the consistent weight measurements of Chen.

Accordingly, the Examiner's finding of inherency based on the processes of Chen and the '588 patent being "substantially identical" is supported by the evidence of record, as well as the Examiner's finding that Chen teaches films with consistent weight per unit film. Accordingly, the burden was properly shifted to Patent Owner to demonstrate that the process of Chen does not, in fact, teach a film having a substantially uniform content of therapeutic active composition per unit of film.

REJECTIONS BASED ON PEH

Claims 192 and 193 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Peh,[8] either alone or in view of additional prior art.[9]

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[7] While Patent Owner does not clearly argue the limitation of claim 3 separately from independent claims 1, 192 and 193, we note that Patent Owner refers to claim 3 in distinguishing the scope over that of claim 1. App. Br. 23; Reb. Br. 3.

[8] Kok Khiang Peh et al., "Polymeric Films as Vehicle for Buccal Delivery: Swelling, Mechanical, and Bioadhesive Properties," J. Pharm. Pharmaceut. Sci., Vol. 2, No. 2, pp. 53-61 (1999).

§ 41.81. *See also* MPEP § 2682 (8th ed., Rev. 7, July 2008). In the event neither party files a request for rehearing within the time provided in 37 C.F.R. § 41.79, and this decision becomes final and appealable under 37 C.F.R. § 41.81, a party seeking judicial review must timely serve notice on the Director of the United States Patent and Trademark Office. *See* 37 C.F.R. §§ 90.1 and 1.983.

AFFIRMED

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