PTO/SB/14 (06-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-4B CIP
	Application Number	
Title of Invention	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Robert	K.	Yang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Flushing	State/Province	NY	Country of Residence i	US

Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

Address 1	138-10 Franklin Avenue, Apt. 2C		
Address 2			
City	Flushing	State/Province	NY
Postal Code	11355	Country i	US

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Richard	C.	Fuisz	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	McLean	State/Province	VA	Country of Residence i	US

Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

Address 1	1127 Langley Lane		
Address 2			
City	McLean	State/Province	VA
Postal Code	22101	Country i	US

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Garry	L.	Myers	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Kingsport	State/Province	TN	Country of Residence i	US

PTO/SB/14 (06-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-4B CIP
	Application Number	
Title of Invention	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS	

Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	908 Colfax Avenue				
Address 2					
City	Kingsport	**State/Province**	TN		
Postal Code	37660	**Country**i	US		

Applicant 4 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Joseph	M.	Fuisz	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Washington	**State/Province**	DC	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	1200 23rd Street, Apt. 905				
Address 2					
City	Washington	**State/Province**	DC		
Postal Code	20037	**Country**i	US		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	23869		
Email Address	jlarmann@hoffmannbaron.com	Add Email	Remove Email

Application Information:

Title of the Invention	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS		
Attorney Docket Number	1199-4B CIP	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	34	**Suggested Figure for Publication (if any)**	1

PTO/SB/14 (06-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-4B CIP
	Application Number	
Title of Invention	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS	

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recongnition (37 CFR 11.9)
Customer Number	23869		

Domestic Benefit Information:

This section allows for the applicant to claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c). Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation in part of	10768809	2004-01-30
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10768809	non provisional of	60443741	2003-01-30
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10768809	Continuation in part of	PCT/US02/32575	2002-10-11
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32575	non provisional of	60386937	2002-06-07
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32575	non provisional of	10074272	2002-02-14
Prior Application Status	Expired		Remove

PTO/SB/14 (06-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-4B CIP
	Application Number	
Title of Invention	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60328868	2001-10-12
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10768809	Continuation in part of	PCT/US02/32594	2002-10-11
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32594	non provisional of	60414276	2002-09-27
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32594	non provisional of	60386937	2002-06-07
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32594	non provisional of	10074272	2002-02-14
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60328868	2001-10-12
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10768809	Continuation in part of	PCT/US02/32542	2002-10-11
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32542	non provisional of	60386937	2002-06-07
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32542	non provisional of	60371940	2002-04-11
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32542	non provisional of	10074272	2002-02-14
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60328868	2001-10-12
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation in part of	10856176	2004-05-28
Prior Application Status	Expired		Remove

PTO/SB/14 (06-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-4B CIP
	Application Number	
Title of Invention	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10856176	non provisional of	60473902	2003-05-28
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10856176	Continuation in part of	10768809	2004-01-30
Additional Domestic Priority Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			◉ Yes ○ No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

If the Assignee is an Organization check here. ☒

Organization Name	MonoSolRx LLC		
Mailing Address Information:			
Address 1	6560 Melton Road		
Address 2			
City	Portage	**State/Province**	IN
Country [i]	US	Postal Code	46368
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button. Add

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Jamie M. Larmann/			Date (YYYY-MM-DD)	2007-07-10
First Name	Jamie	Last Name	Larmann	Registration Number	48623

PTO/SB/14 (06-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-4B CIP
	Application Number	
Title of Invention	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS	

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

1199-4B CIP

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

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Application No. 10/768,809, filed January 30, 2004, which claims benefit to U.S. Provisional Application No. 60/443,741 filed January 30, 2003; U.S. Application No. 10/768,809 is also a continuation-in-part of PCT/US02/32575, filed October 11, 2002, which claims priority to U.S. Provisional Application No. 60/386,937, filed June 7, 2002, and U.S. Application No. 10/074,272, filed February 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed October 12, 2001; U.S. Application No. 10/768,809 is also a continuation-in-part of PCT/US02/32594, filed October 11, 2002, which claims priority to U.S. Provisional Application No. 60/414,276, filed September 27, 2002, U.S. Provisional Application No. 60/386,937, filed June 7, 2002, and U.S. Application No. 10/074,272, filed February 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed October 12, 2001; and U.S. Application No. 10/768,809 is also a continuation-in-part of PCT/US02/32542, filed October 11, 2002, which claims priority to U.S. Provisional Application No. 60/386,937, filed June 7, 2002, U.S. Provisional Application No. 60/371,940, filed April 11, 2002, and U.S. Application No. 10/074,272, filed February 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed October 12, 2001; this application is also a continuation-in-part of U.S. Application 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 No. 10/856,176 is also a continuation-in-part of U.S. Application No. 10/768,809; the contents all of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] 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

[0003] 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.

[0004] 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.

[0005] Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Patent 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.

[0006] 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.

[0007] 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.

[0008] The problems of self-aggregation leading to non-uniformity of a film were addressed in U.S. Patent 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.

[0009] 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. Patent 5,629,003 to Horstmann et al. and U.S. Patent 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.

[0010] 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.

[0011] 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.

[0012] 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.

[0013] 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

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] 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.

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] 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.

[0027] 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.

[0028] 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.

[0029] 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

[0030] Figure 1 shows a side view of a package containing a unit dosage film of the present invention.

[0031] Figure 2 shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

[0032] Figure 3 shows a side view of the adjacently coupled packages of Figure 2 arranged in a stacked configuration.

[0033] Figure 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.

[0034] Figure 5 is a schematic view of a roll of coupled unit dose packages of the present invention.

[0035] Figure 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.

[0036] Figure 7 is a schematic view of an apparatus suitable for drying the films of the present invention.

[0037] Figure 8 is a sequential representation of the drying process of the present invention.

[0038] Figure 9 is a photographic representation of a film dried by conventional drying processes.

[0039] Figure 10 is a photographic representation of a film dried by conventional drying processes.

[0040] Figure 11 is a photographic representation of a film dried by conventional drying processes.

[0041] Figure 12 is a photographic representation of a film dried by conventional drying processes.

[0042] Figure 13 is a photographic representation of a film dried by conventional drying processes.

[0043] Figure 14 is a photographic representation of a film dried by conventional drying processes.

[0044] Figure 15 is a photographic representation of a film dried by conventional drying processes.

[0045] Figure 16 is a photographic representation of a film dried by conventional drying processes.

[0046] Figure 17 is a photographic representation of a film dried by the inventive drying process.

[0047] Figure 18 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0048] Figure 19 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0049] Figure 20 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0050] Figure 21 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0051] Figure 22 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0052] Figure 23 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0053] Figure 24 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0054] Figure 25 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0055] Figure 26 is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80°C.

[0056] Figure 27 is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80°C.

[0057] Figure 28 is a photomicrographic representation of fat coated particles at room temperature prior to processing.

[0058] Figure 29 is a photomicrographic representation of fat coated particles at room temperature prior to processing.

[0059] Figure 30 is a photomicrographic representation of fat coated particles at room temperature prior to processing.

[0060] Figure 31 is a photomicrographic representation of fat coated particles at room temperature prior to processing.

[0061] Figure 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.

[0062] Figure 33 is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

[0063] Figure 34 is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

[0064] Figure 35 is a schematic representation of a continuously-linked zone drying apparatus in accordance with the present invention.

[0065] Figure 36 is a schematic representation of a separate zone drying apparatus in accordance with the present invention.

[0066] Figure 37 is a schematic representation of a single screw extrusion apparatus for use in producing films of the present invention.

[0067] Figure 38 is a table providing examples of thin film compositions of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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

[0076] 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

[0077] 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.

[0078] 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.

[0079] Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Delaware 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 100L, believed to be 100% lactide having a melting point within the range of 338°-347°F (170°-175°C); lactide/glycolide 100L, 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).

[0080] The Biodel materials represent a family of various polyanhydrides which differ chemically.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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 1mg to about 200mg.

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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

[0094] 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.

[0095] 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.

[0096] 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.

[0097] 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.

[0098] 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.

[0099] 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 September 27, 2003, attorney docket No. 1199-15P) the entire subject matter of which is incorporated by reference herein. Taste-masking of actives, as disclosed therein, is described herein below.

Particle Formation

[0100] 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 pharmacueuticals. 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.

[0101] The taste-masked or controlled-release particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof.

[0102] Useful organoleptic agents include flavors and sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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.

[0107] 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.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] 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.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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.

[0119] 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.

[0120] 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. Patent 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.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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.

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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

[0131] 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

[0132] 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.

[0133] 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.

[0134] Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin®), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

[0135] 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.

[0136] 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®).

[0137] 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®, vardenafils, apomorphines, such as Uprima®, yohimbine hydrochlorides such as Aphrodyne®, and alprostadils such as Caverject®.

[0138] 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.

[0139] 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.

[0140] Anti-inflammatory agents include steroidal anti-inflammatory drugs, such as cortisone, triamcinalone, prednisone, prednisolone, and the like.

Other Actives

[0141] 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.

[0142] An anti-oxidant may also be added to the film to prevent the degradation of an active, especially where the active is photosensitive.

[0143] 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

[0144] 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 300mg, desirably up to about 150mg or as low as the microgram range, or any amount therebetween.

[0145] 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

[0146] 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.

[0147] 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 (cinnamon); citral, i.e., alpha citral (lemon, lime); neral, i.e. beta citral(lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream);heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors);

butyraldehyde (butter, cheese);valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal(citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits);aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla);12,6-dimethyl- 5-heptenal, i.e. melonal (melon); 2 dimethyloctanal (greenfruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

[0148] 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.

[0149] 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. In general, amounts of about 0.1 to about 30 wt% are useful with the practice of the present invention.

Sweeteners

[0150] 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 I and II).

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

[0151] In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with the sweetener selected. This amount will normally be 0.01 % to about 10 % by weight of the composition. 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

[0152] 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.

[0153] 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.

Film Forming Processes

[0154] 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.

[0155] Desirably, the thickness of the film is less than about 380 microns, for example, less than about 250 microns.

Wet-Cast Films

[0156] In 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. Patent 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).

[0157] 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 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. 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.

[0158] 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.

[0159] 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.

[0160] 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.

[0161] 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:

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

[0162] 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.

[0163] 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:

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

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.

[0164] 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

$$\mu/\mu_o = 1 + 2.5\varphi + C_1\varphi^2 + C_2\varphi^3 + ...$$

where C is a constant.

[0165] 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.

[0166] 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., <500μm. 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.

[0167] 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.

[0168] 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.

[0169] 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.

[0170] 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

[0171] 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.

[0172] 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.

[0173] Figure 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 Figure 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**.

[0174] 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.

[0175] 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.

[0176] 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.

[0177] 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.

[0178] 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.

[0179] Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

[0180] 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.

[0181] 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.

[0182] 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 pre-mix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

[0183] 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.

[0184] 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.

[0185] 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.

[0186] 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.

[0187] 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

[0188] 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.

[0189] 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.

[0190] 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.

[0191] 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.

[0192] 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

[0193] 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 figure 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.

[0194] 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.

[0195] 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 (4th 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.

[0196] 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.

[0197] 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. Patent No. 6,281,337 to Cannon-Carlson, et al., which in incorporated herein in its entirety.

[0198] 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.

[0199] 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.

[0200] 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.

[0201] 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.

[0202] 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.

[0203] 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.

[0204] 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.

[0205] 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 Figure 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 Figure 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.

[0206] 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.

[0207] In one embodiment, a specific example of an appropriate drying method is that disclosed by Magoon in U.S. Patent 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.

[0208] 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.

[0209] 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.

[0210] 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.

[0211] 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.

[0212] 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.

[0213] 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 0.1mils to about 10mils. 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

[0214] 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.

[0215] 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.

[0216] 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.

[0217] 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.

[0218] 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.

[0219] 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

[0220] 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.

[0221] 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).

[0222] 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.

[0223] 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.

[0224] 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.

[0225] 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.

[0226] 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.

[0227] 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

[0228] 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.

[0229] 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.

[0230] 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.

[0231] 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.

[0232] 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.

[0233] 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

[0234] 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.

[0235] 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.

[0236] 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.

[0237] 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.

[0238] 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.

[0239] 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.

[0240] 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

[0241] 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, ophthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

[0242] 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.

[0243] 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.

[0244] 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 Figure 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 Figure 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 Figure 5 or stacked as shown in Figure 3 and sold in a dispenser **18** as shown in Figure 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.

[0245] 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.

[0246] 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:

[0247] 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:

[0248] 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.

[0249] 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	**Composition**
Ingredient	**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

[0250] 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:

[0251] 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 No. 10/074,272.

[0252] The dried product was examined for physical appearance, dissolution in the mouth and bitterness.

[0253] 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.

[0254] 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'-I:

[0255] Water soluble thin film compositions of the present invention are prepared using the amounts described in Table 1a.

TABLE 1a

	Weight (g)								
Ingredient	**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

[0256] 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.

[0257] 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.

[0258] 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

[0259] The individual dosages were consistently 0.04gm, 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.

[0260] 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.

[0261] 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:

[0262] 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

	Weight (g)		
Ingredient	**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

[0263] 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.

[0264] 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:

[0265] 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

	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

[0266] 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.

[0267] 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.

[0268] 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 3nm intervals from 203-1200nm. The frequency of maximum absorption was found to be 530nm. 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.

[0269] Each of the segments were weighed to 0.1mg and then dissolved in 10ml 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 203-1200nm and later from only 500nm to 550nm at a 1nm scanning speed. The value recorded was the % transmission at the lowest wave length, which was most frequently 530nm.

[0270] 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

[0271] 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.

[0272] 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.

[0273] 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:

[0274] 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 6m 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**
Hydroxypropylmethyl 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

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

TABLE 7 (continued)

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

[0275] 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.

[0276] 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.

[0277] 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.

[0278] Composition T included a change in the solvent to 60/40 water ethanol. Composition T was stirred slowly for 45min. 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.

[0279] 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.

[0280] 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.

[0281] 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.

[0282] 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 3m 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

[0283] 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 10mg of drug 12.5 mg of the final dry product must be weighed.

[0284] 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.

[0285] 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.

[0286] 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.

[0287] The liquid was coated at 30 microns and dried in the oven in less than 5 min. The film was flexible and a 1" x .75" piece weighed 70 mg and contained 10 mg of Loratadine.

[0288] 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.

[0289] The products were sweet without any noticeable drug aftertaste.

[0290] 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. x 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:

[0291] 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.

[0292] 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.

[0293] 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.

[0294] 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:

[0295] 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

[0296] 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.

[0297] 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

[0298] 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

[0299] 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.

[0300] 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:

[0301] 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

[0302] 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.

[0303] 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.

[0304] 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.

[0305] 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:

[0306] 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.

[0307] 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 200g to about 1000g. 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.

[0308] 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:

[0309] 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

[0310] 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.

[0311] 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.

[0312] 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:

[0313] 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.

[0314] 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.

[0315] 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.

[0316] 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:

[0317] 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

[0318] 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.

[0319] 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.

[0320] 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.

[0321] 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:

[0322] 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	

[0323] 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
DB	100% HPC	well	well	2.01	Failed at crease	16, 17	Curl

[0324] The solution coating rating and solution leveling rating were both based upon panel observations made during casting of the film compositions.

[0325] 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.

[0326] 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).

[0327] For the curl test, samples of film (about 35mm by 35mm) 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.

[0328] 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:

[0329] 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

[0330] 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.

[0331] 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.

[0332] 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.

[0333] 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.

[0334] 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.

[0335] 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.

[0336] 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.

[0337] 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:

[0338] 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		

[0339] 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

[0340] 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.

[0341] 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).

[0342] 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.

[0343] 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:

[0344] 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

[0345] 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:

[0346] 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

[0347] 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		Amps
								P1	P2	
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

[0348] 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.

[0349] 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.

[0350] 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.

[0351] 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:

[0352] 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

[0353] 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	146.5mg/1.123
EF	126.5mg/0.969
EG	137mg/1.057
EH	146mg/1.119

[0354] 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:

[0355] 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.

[0356] 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.

[0357] 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:

[0358] 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

Component	Weight (in g, unless otherwise indicated)						
	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

Component	Weight (in g, unless otherwise indicated)						
	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				
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

[0359] 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.

[0360] 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.

CLAIMS:

1. 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.

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 bioeffecting agent.

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 the uniformity is determined by the presence of no more than a 10% by weight of drug variance throughout said matrix.

10. The drug delivery composition of claim 9, wherein said drug variance is less than 5% by weight.

11. The drug delivery composition of claim 9, wherein said drug variance is less than 2% by weight.

12. The drug delivery composition of claim 9, wherein said drug variance is less than 0.5% by weight.

13. 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. 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. 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. 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. 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. 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 and/or controlled-release agent, and

wherein the active component is uniformly distributed in the film composition.

19. The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. The drug delivery composition of claim 18, wherein the taste-masking and/or controlled-release agent is a thin film coating over the particulate active component.

21. The drug delivery composition of claim 18, wherein the taste-masking and/or controlled release agent is a water-soluble polymer.

22. The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. 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. 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. 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. 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. The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. 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. 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. 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. 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. The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. 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.

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

ABSTRACT

[0361] 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.

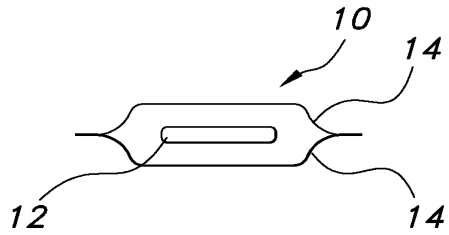


FIG. 1

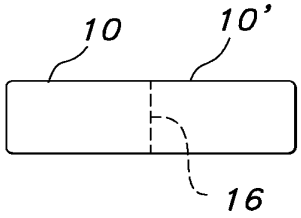


FIG. 2

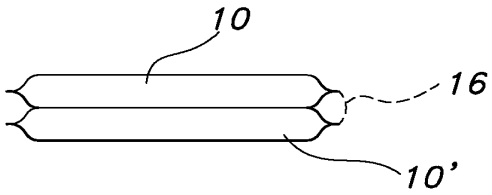


FIG. 3

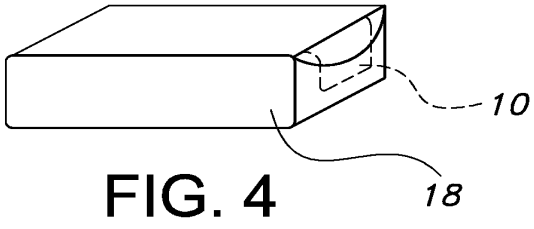


FIG. 4

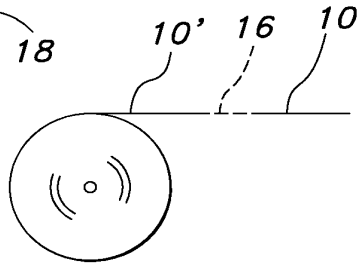


FIG. 5

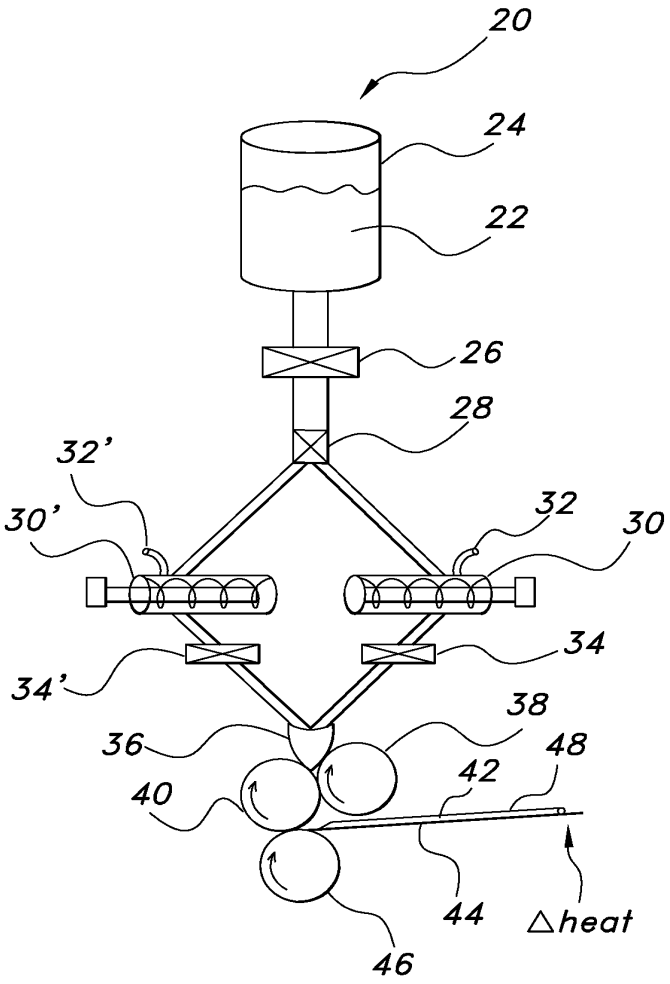


FIG. 6

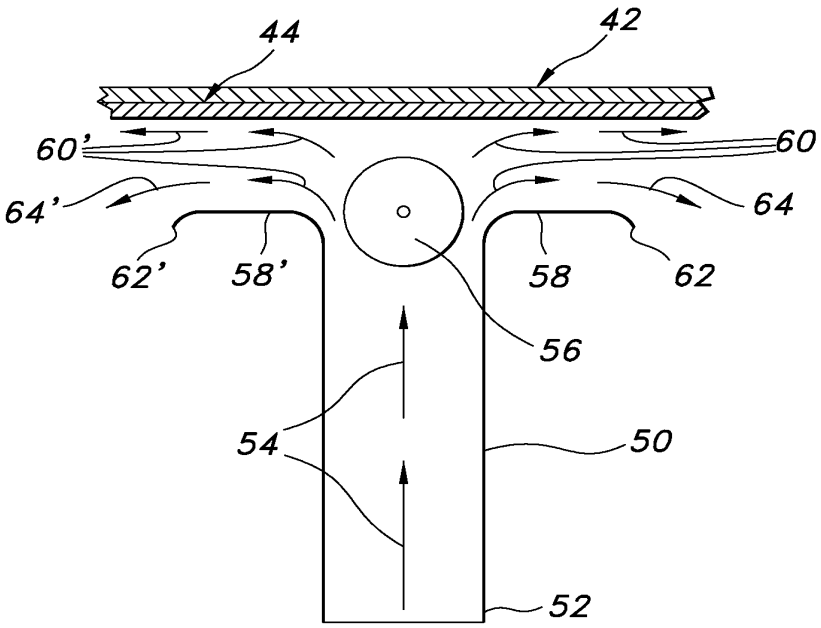


FIG. 7

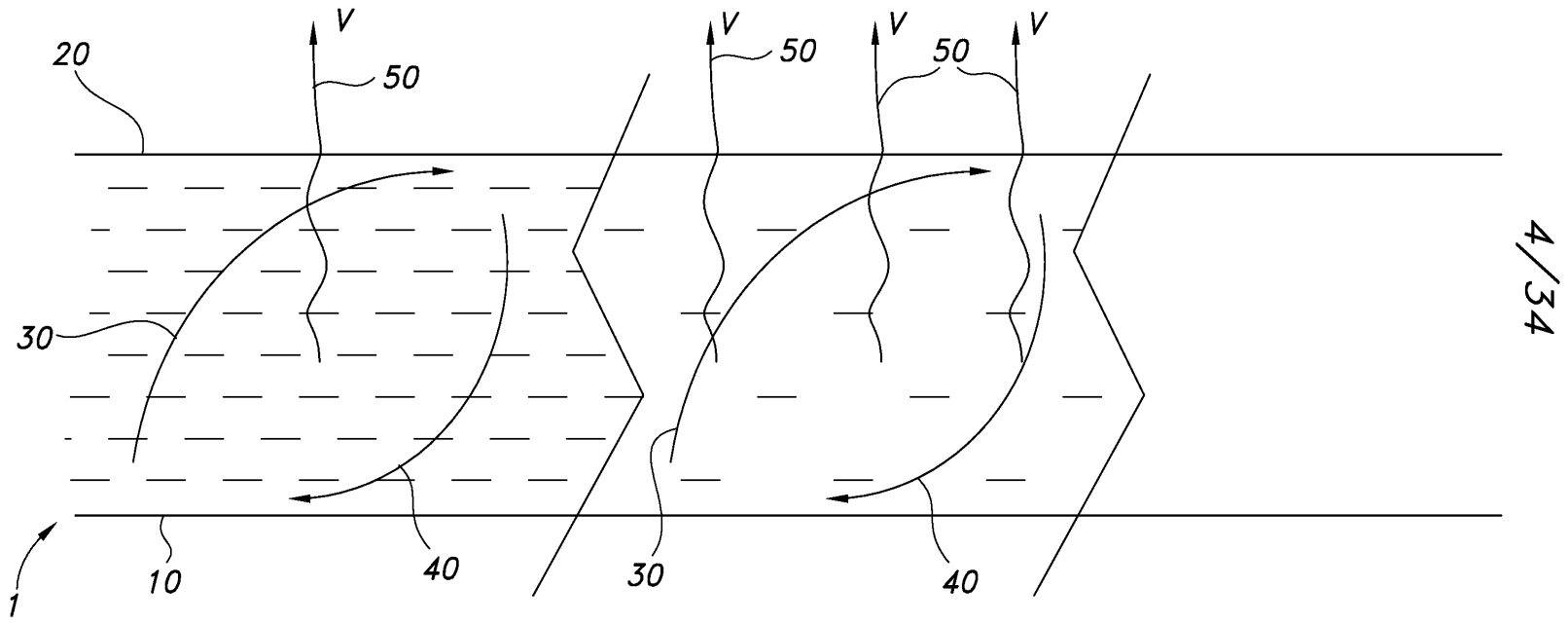


FIG. 8

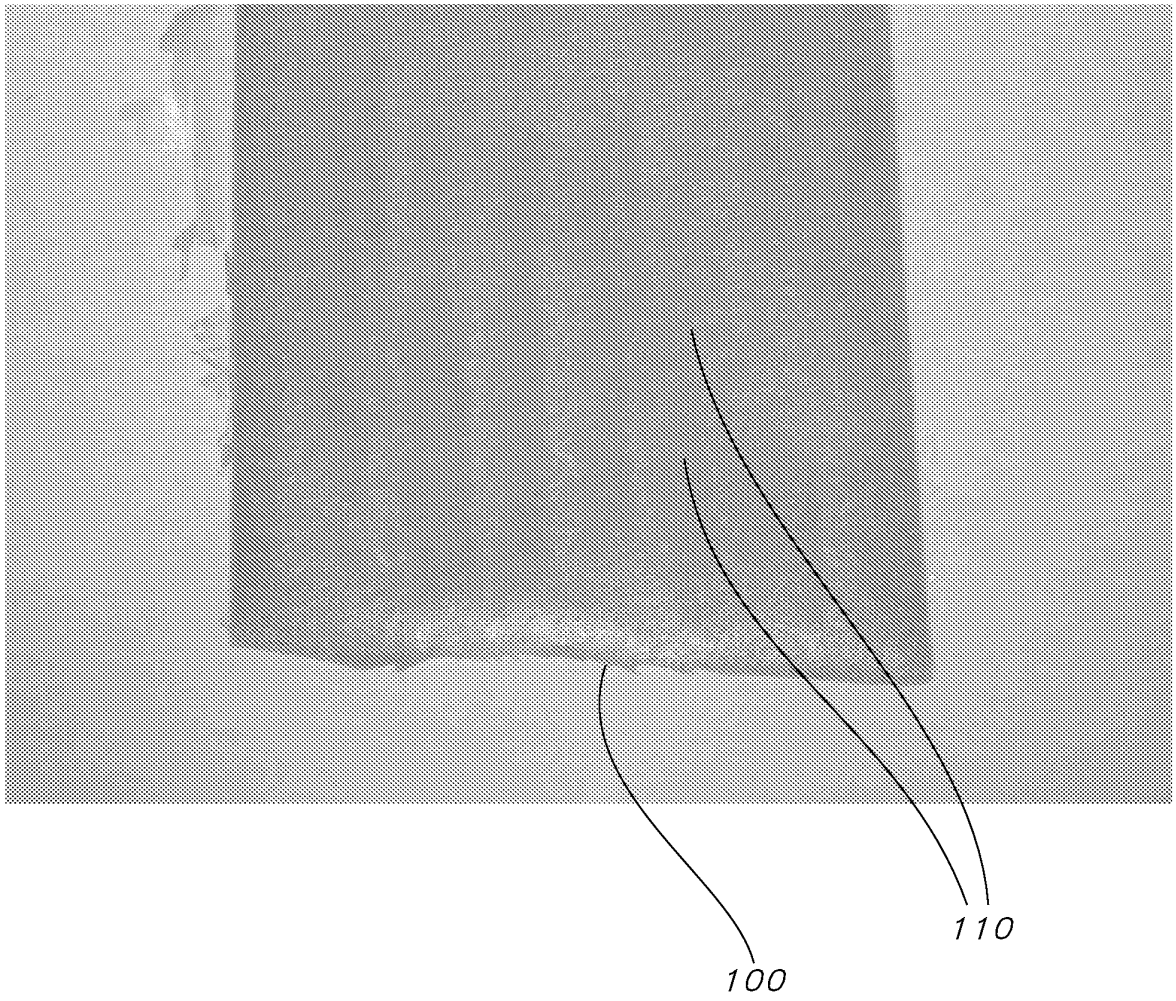


FIG. 9

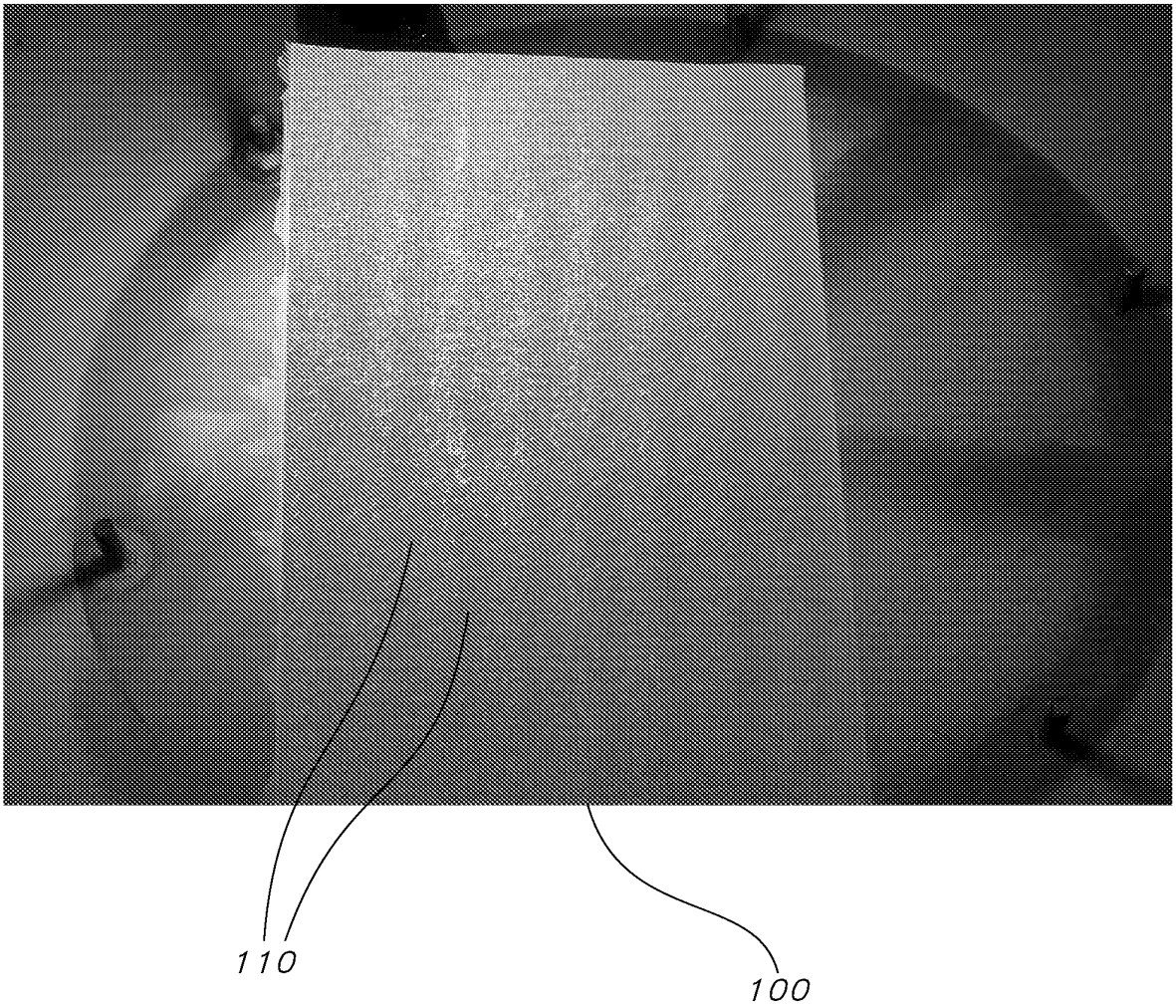


FIG. 10

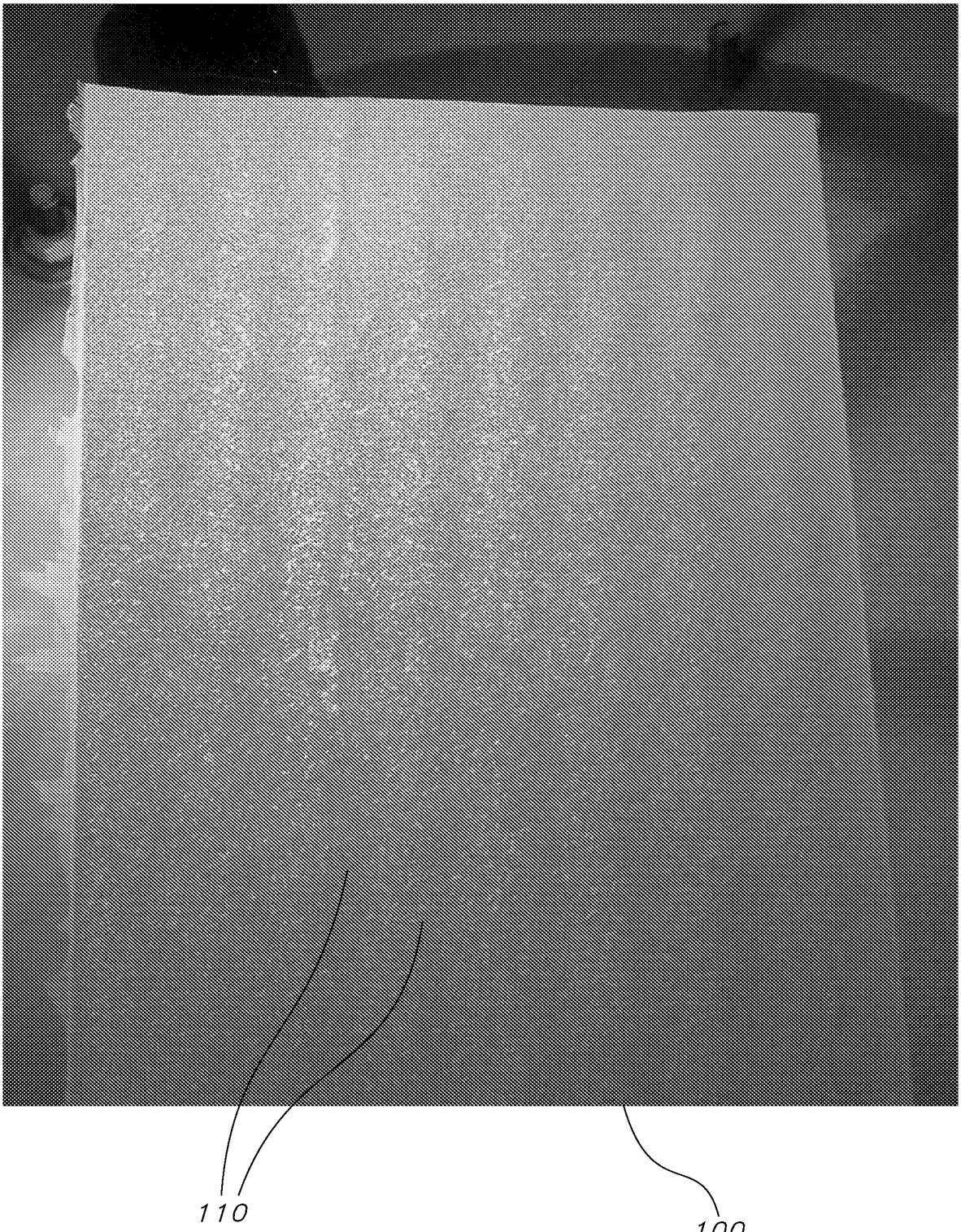


FIG. 11

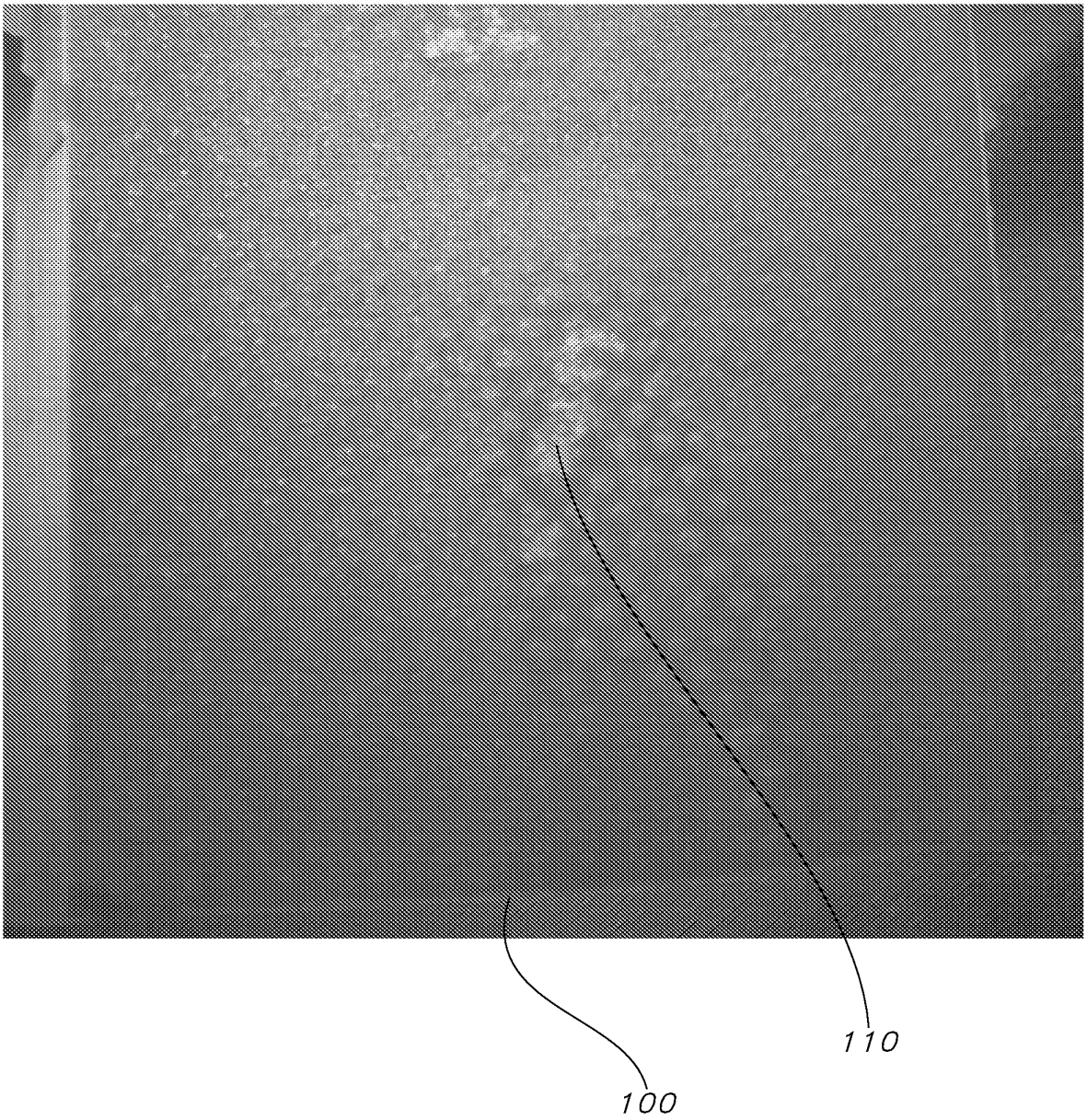


FIG. 12

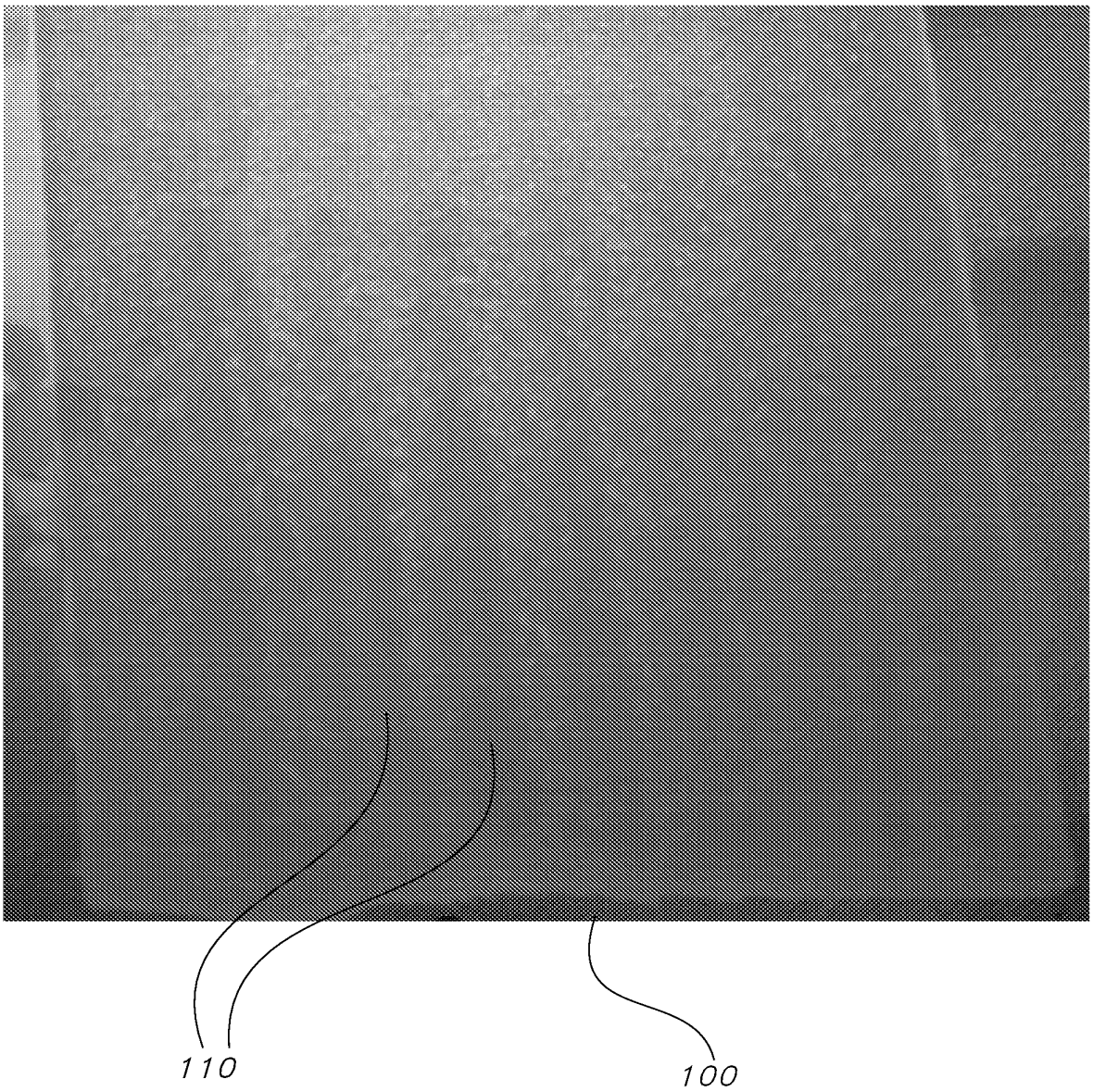


FIG. 13

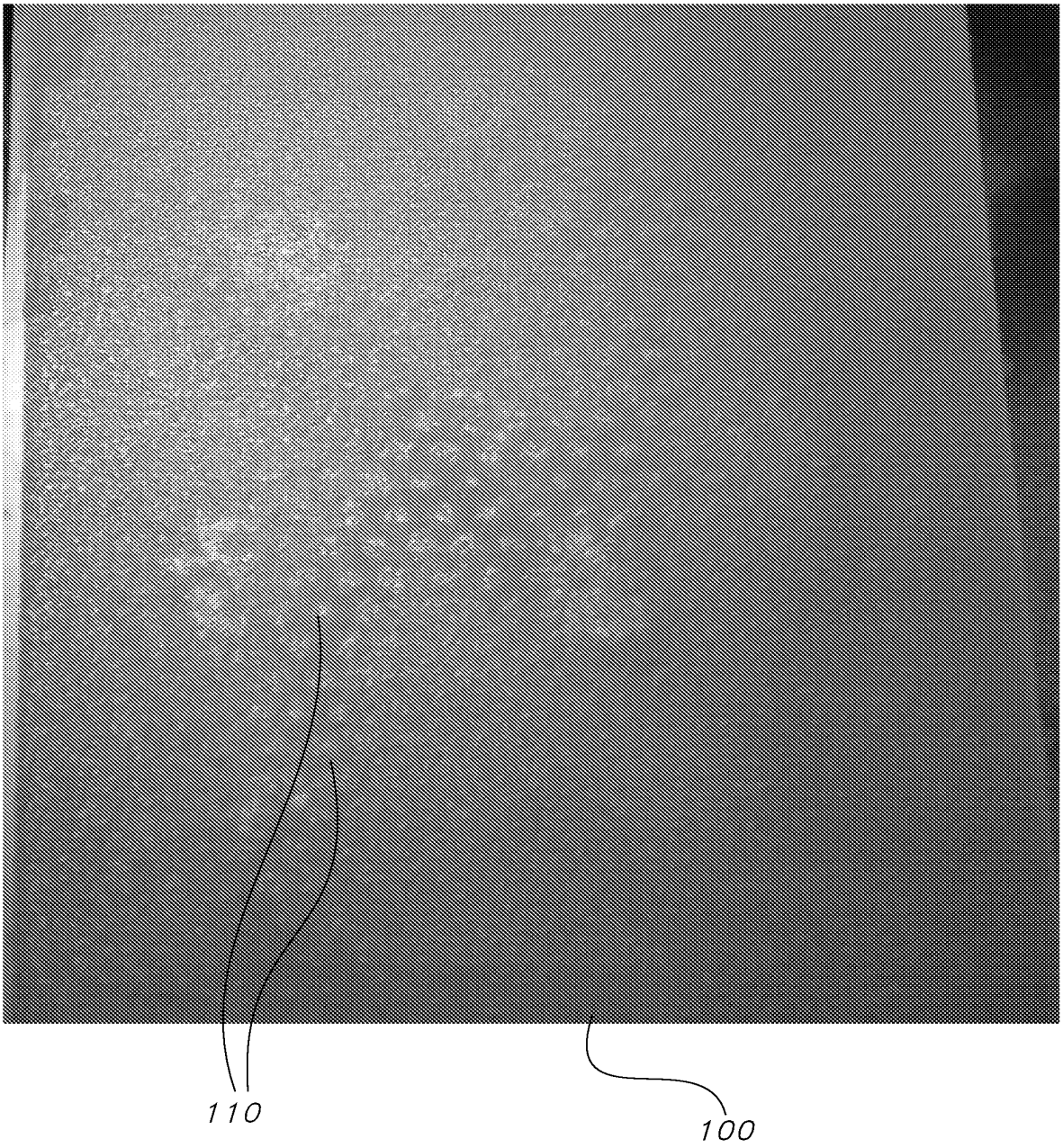


FIG. 14

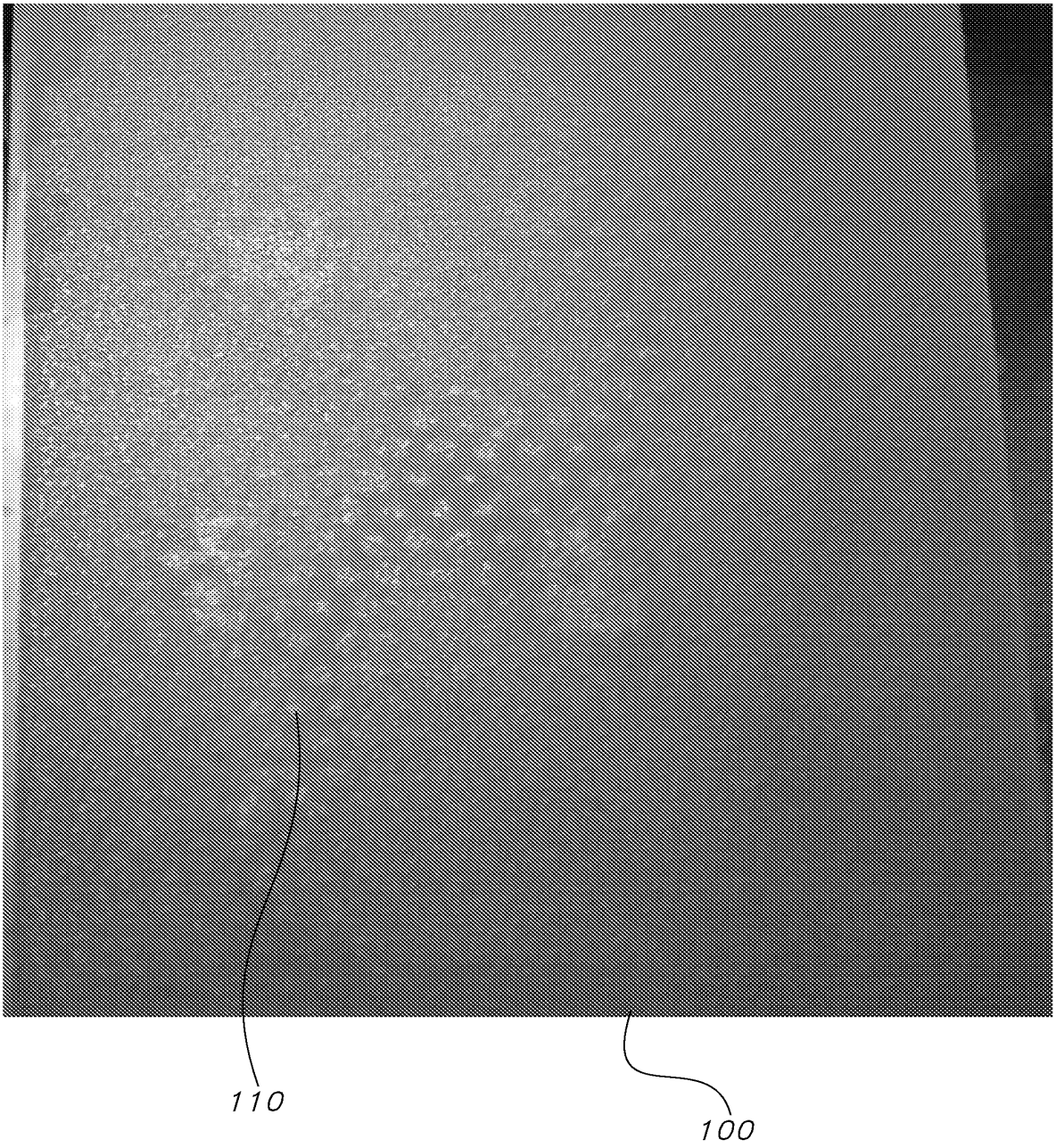


FIG. 15

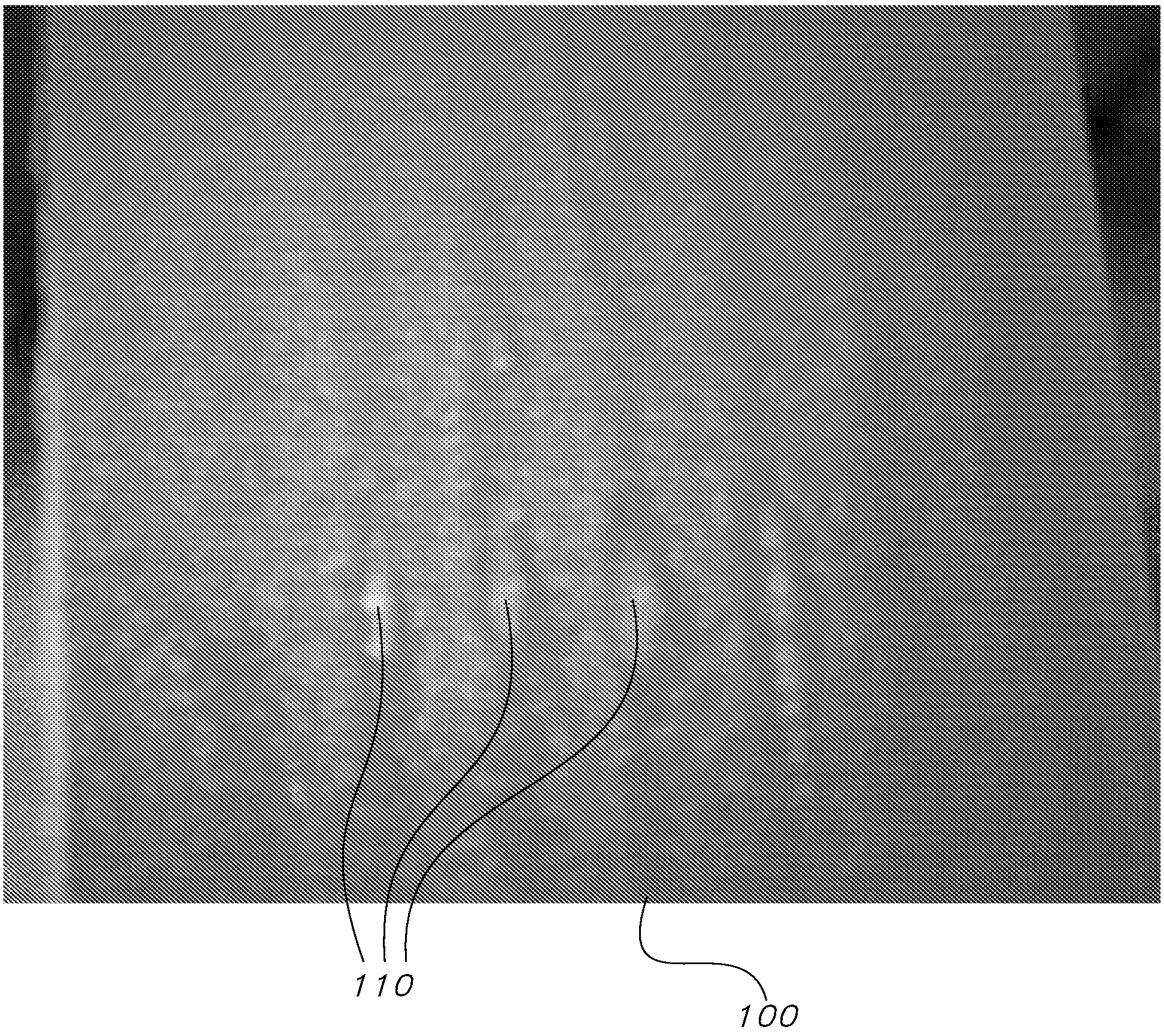


FIG. 16

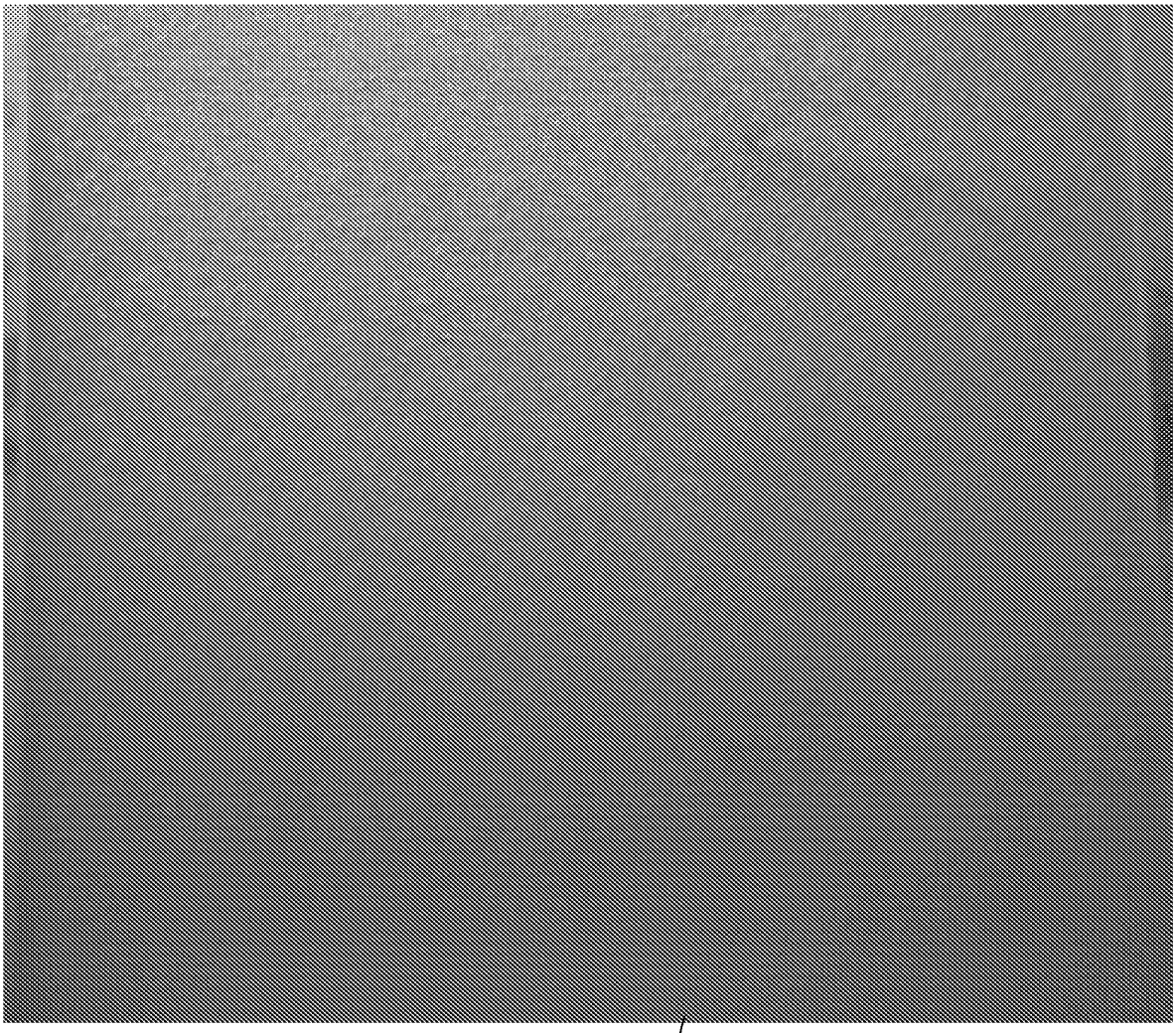


FIG. 17

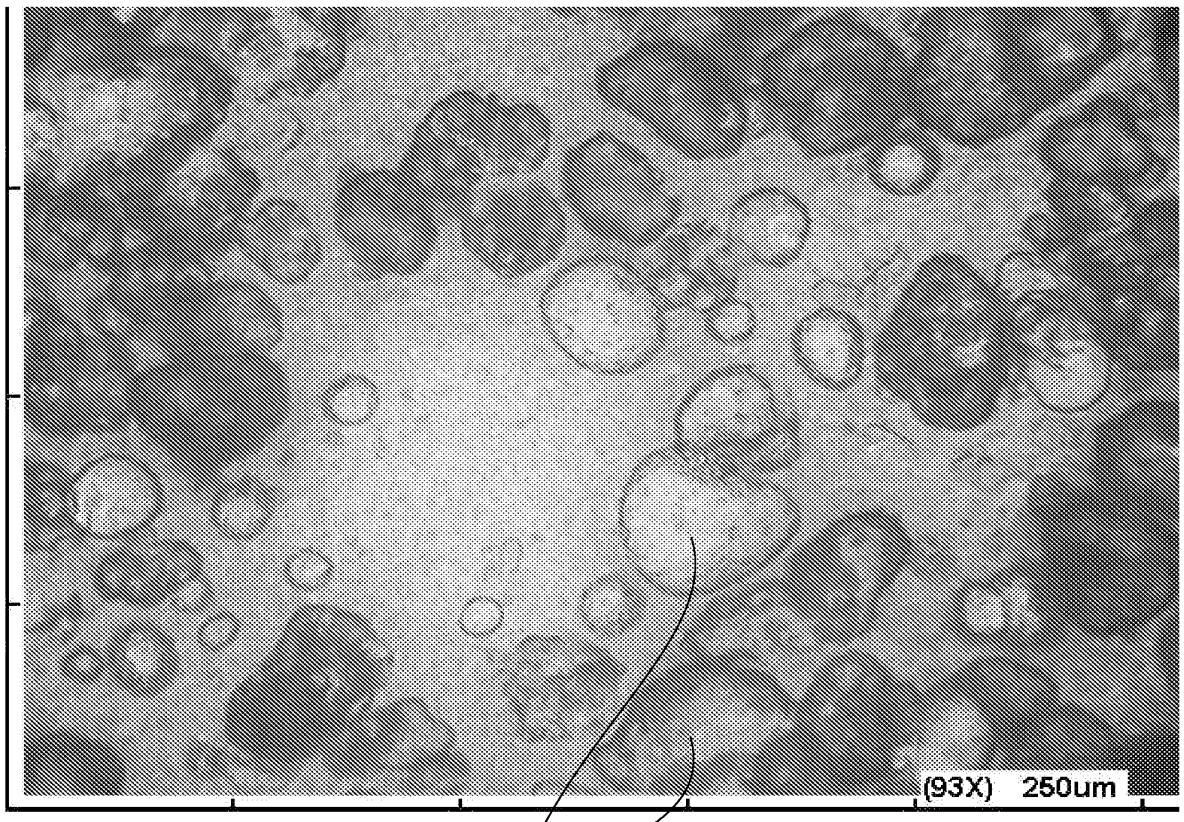


FIG. 18

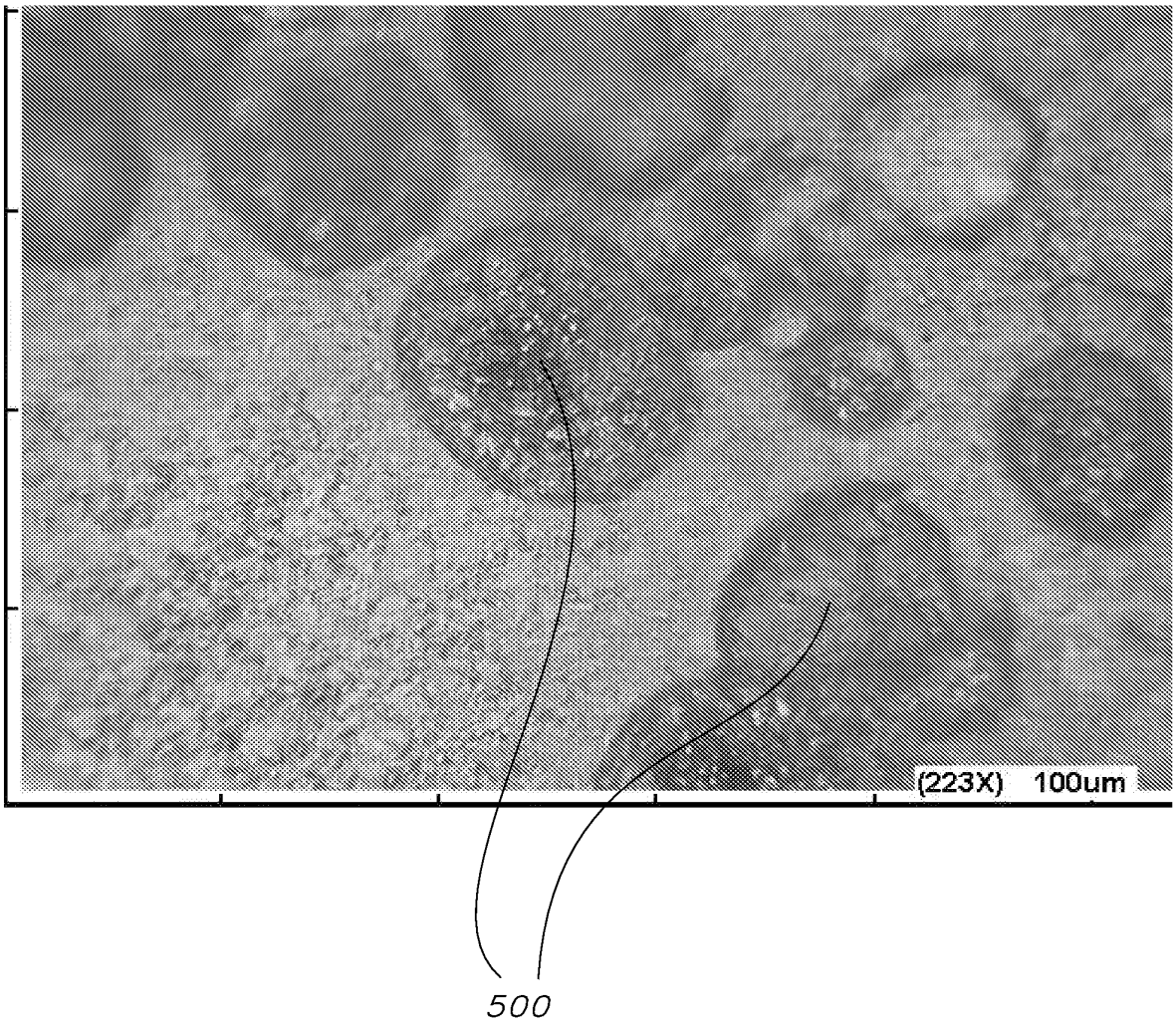


FIG. 19

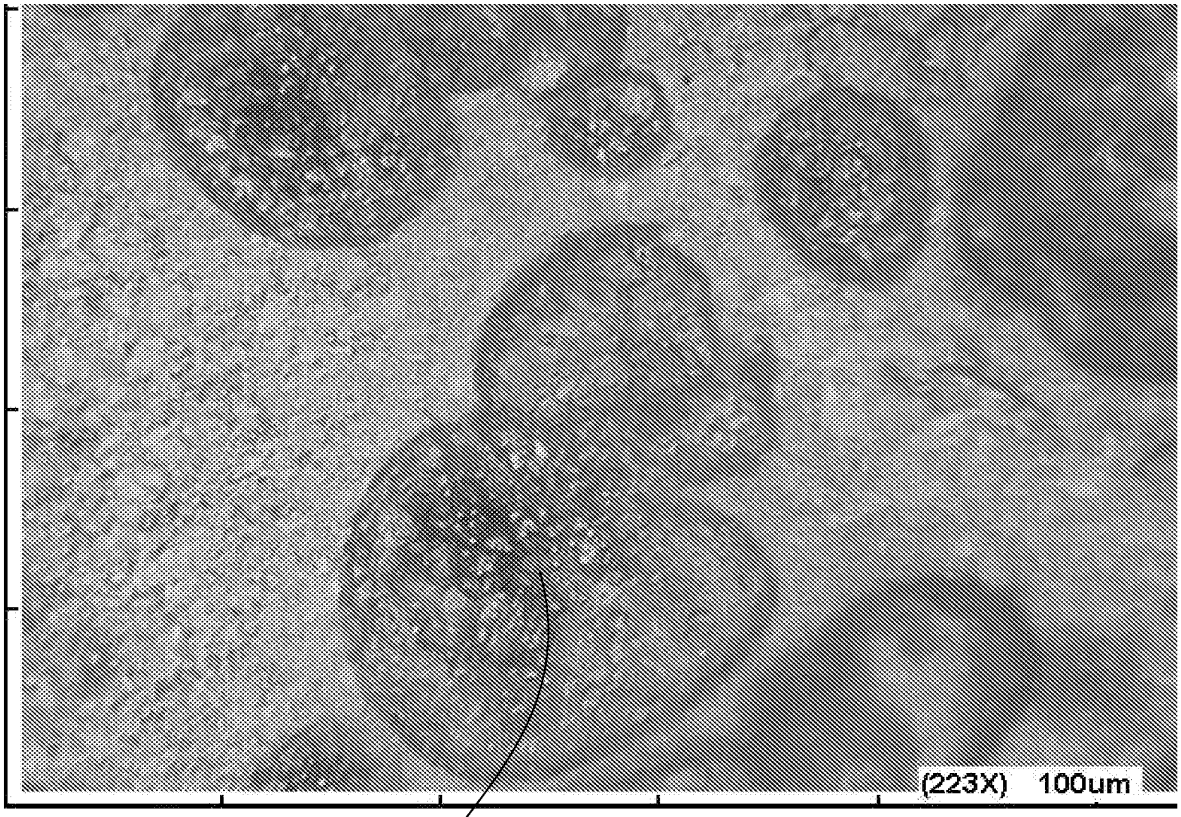


FIG. 20

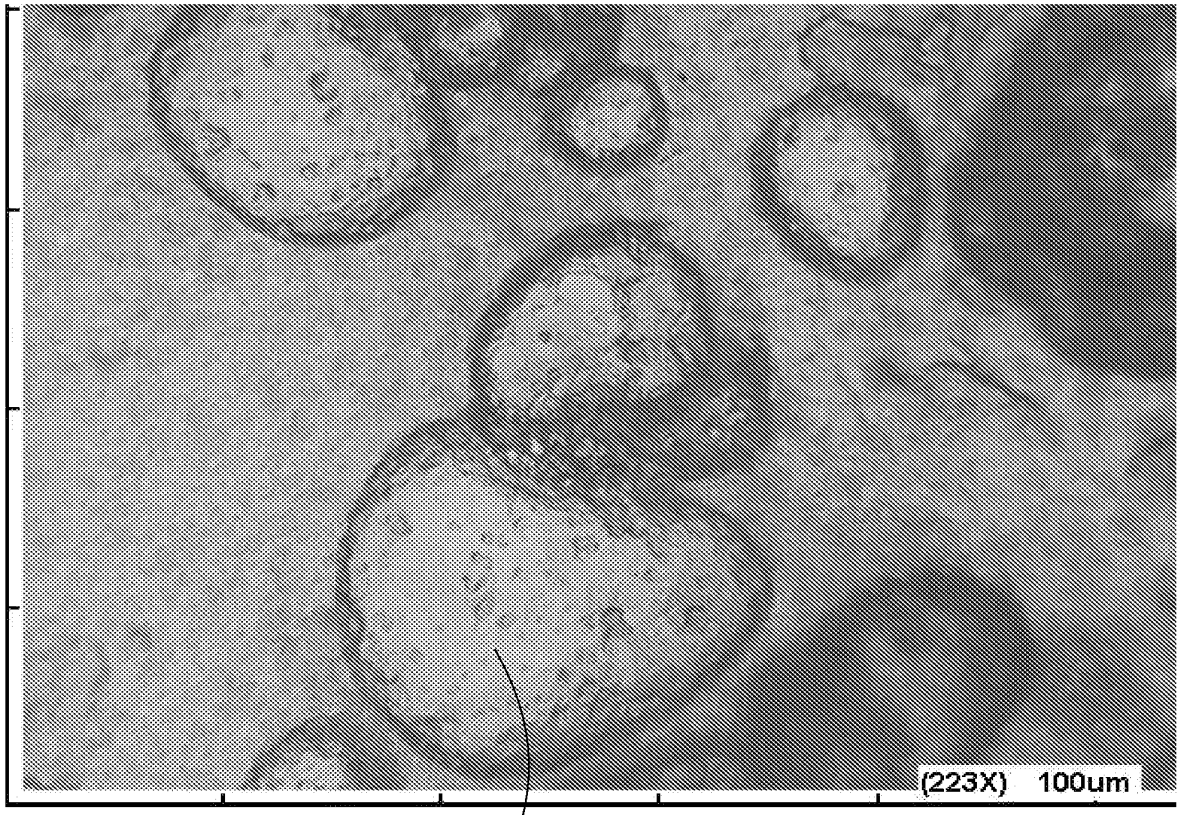


FIG. 21

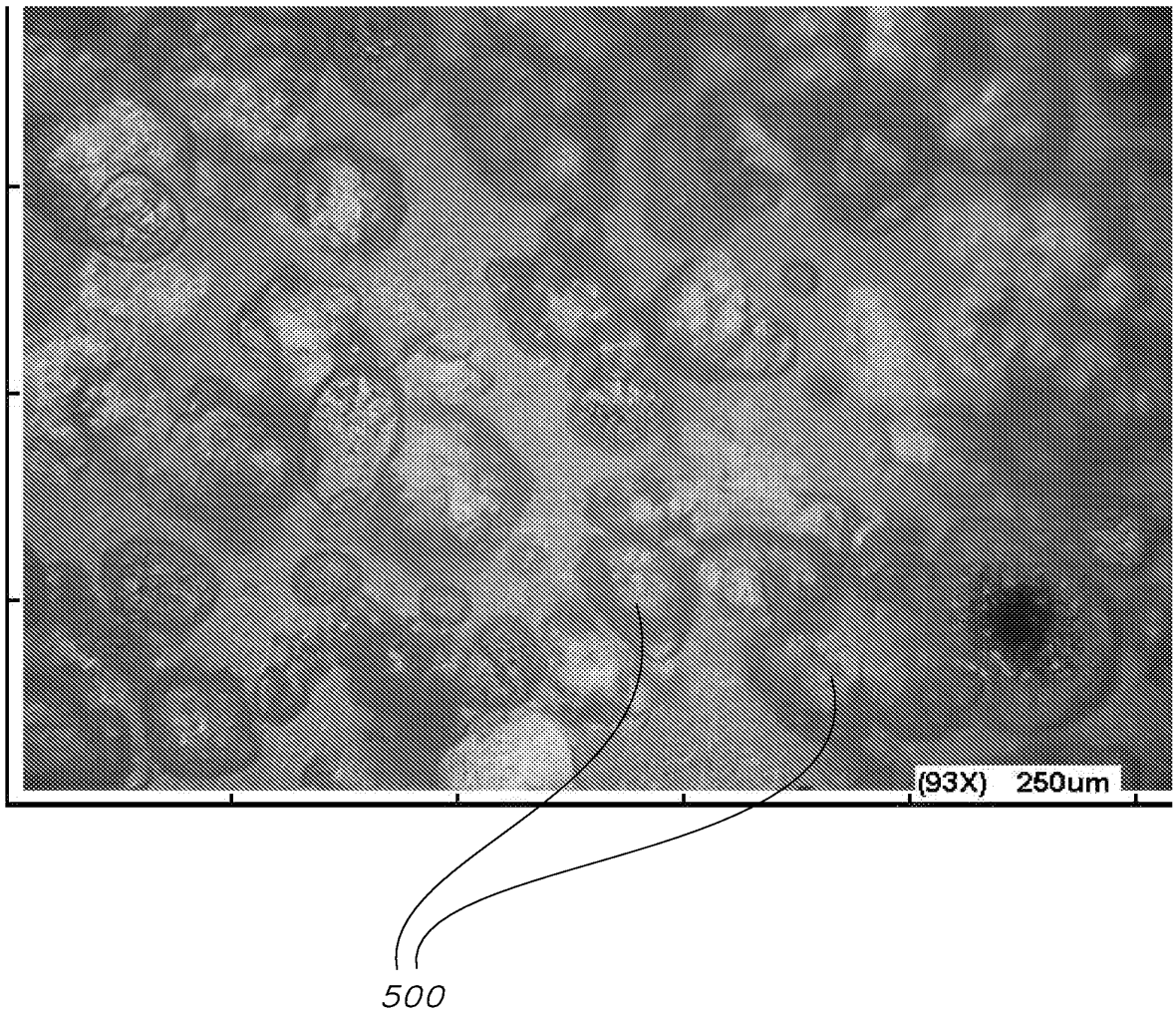


FIG. 22

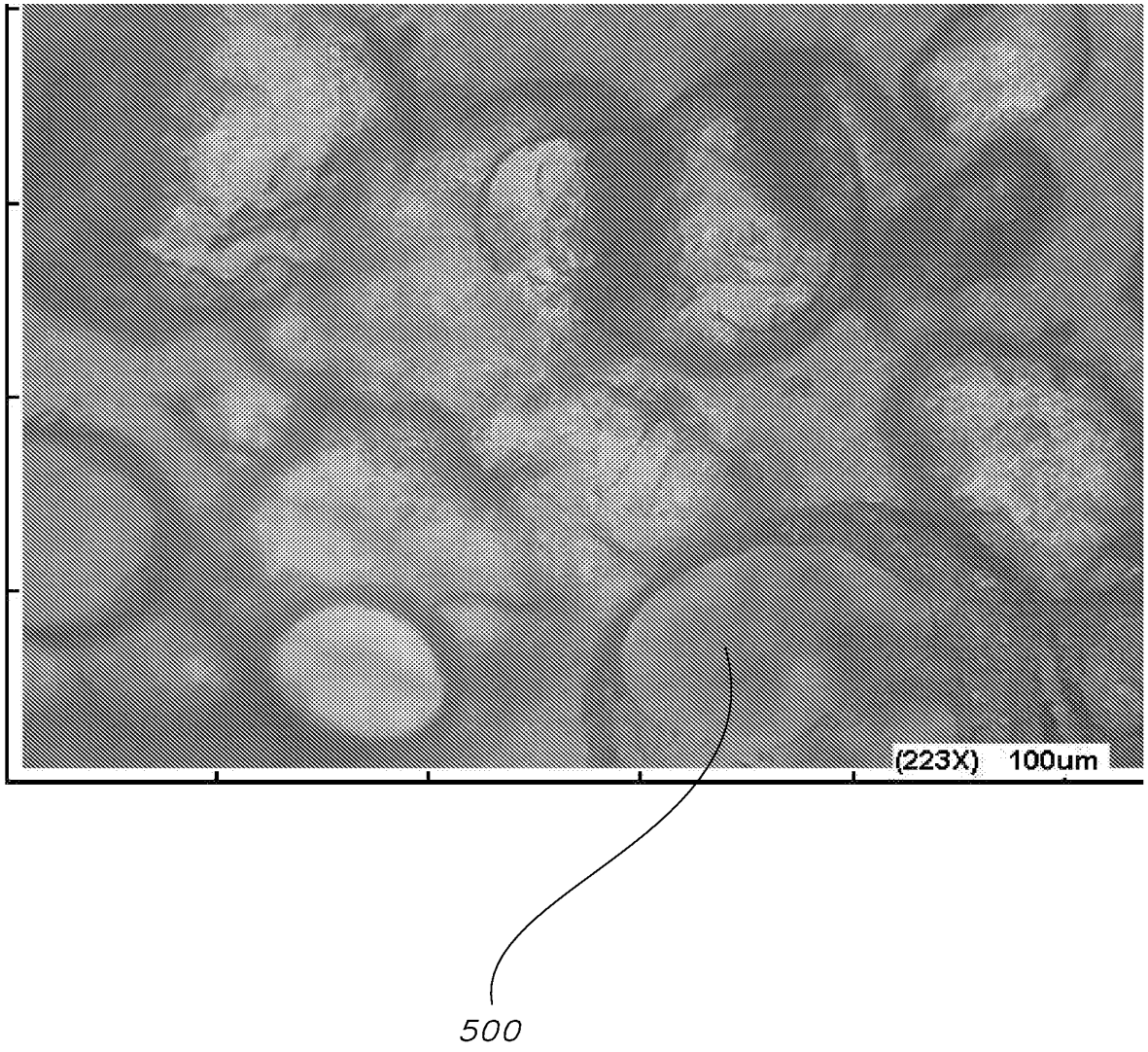


FIG. 23

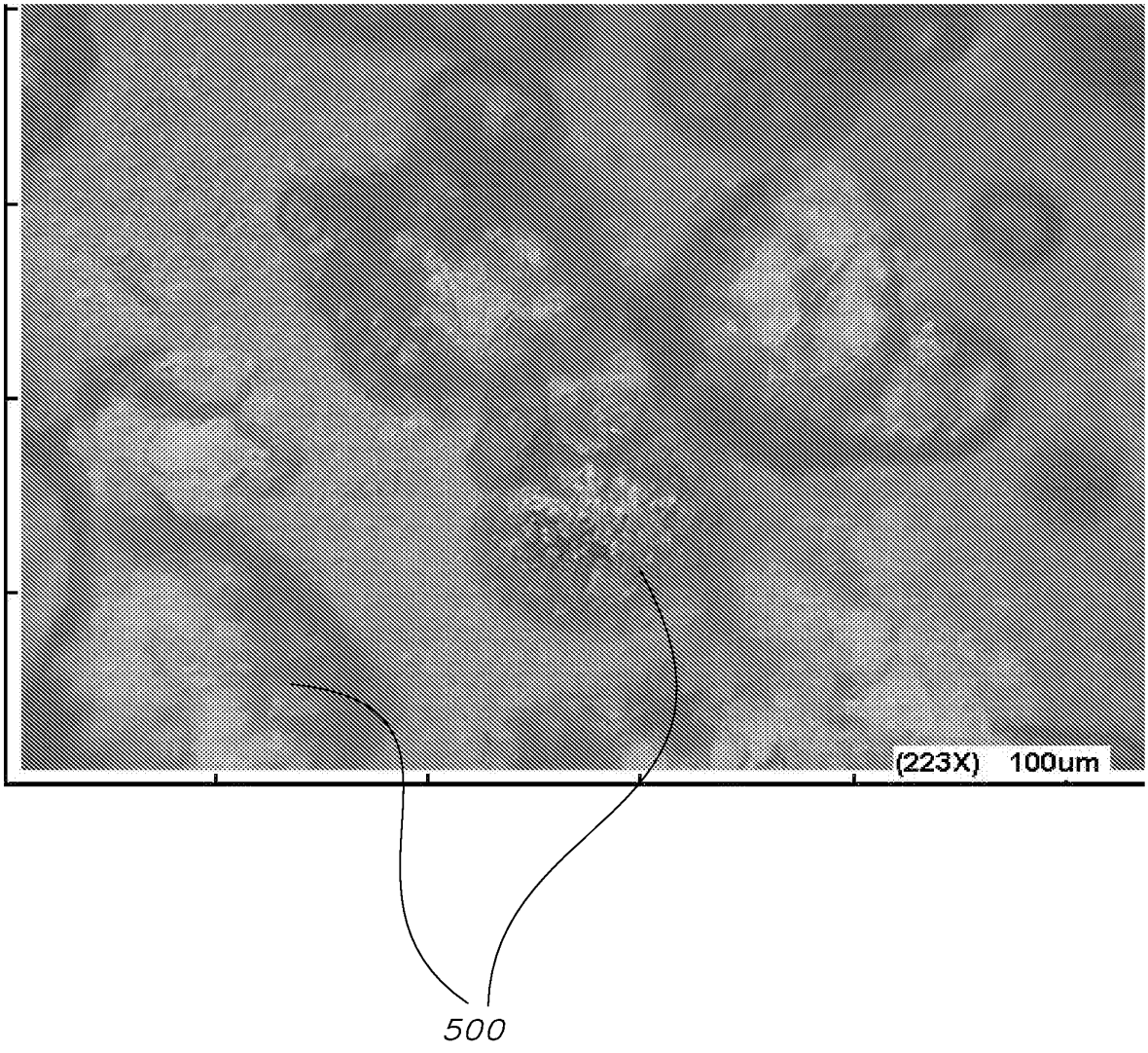


FIG. 24

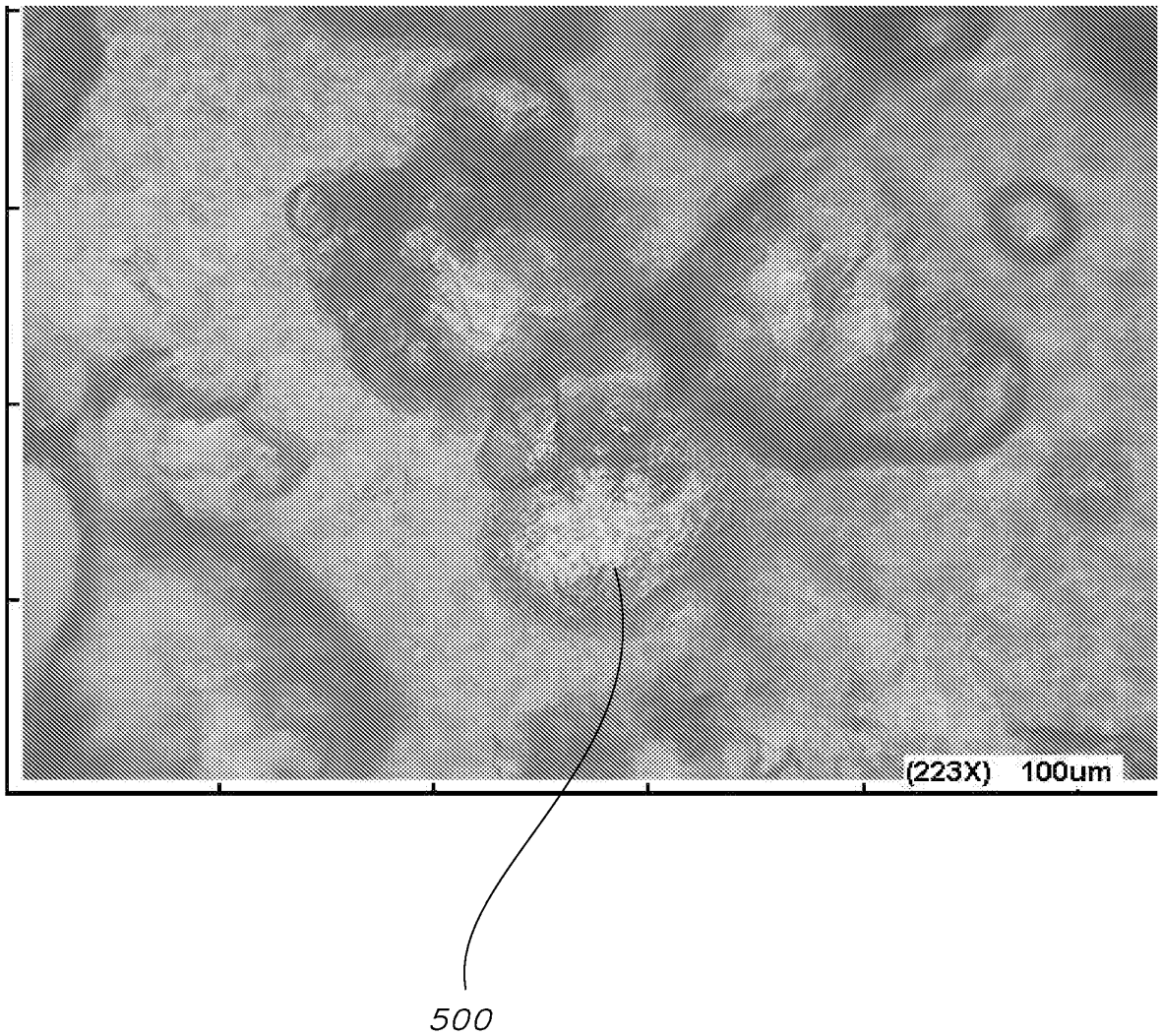


FIG. 25

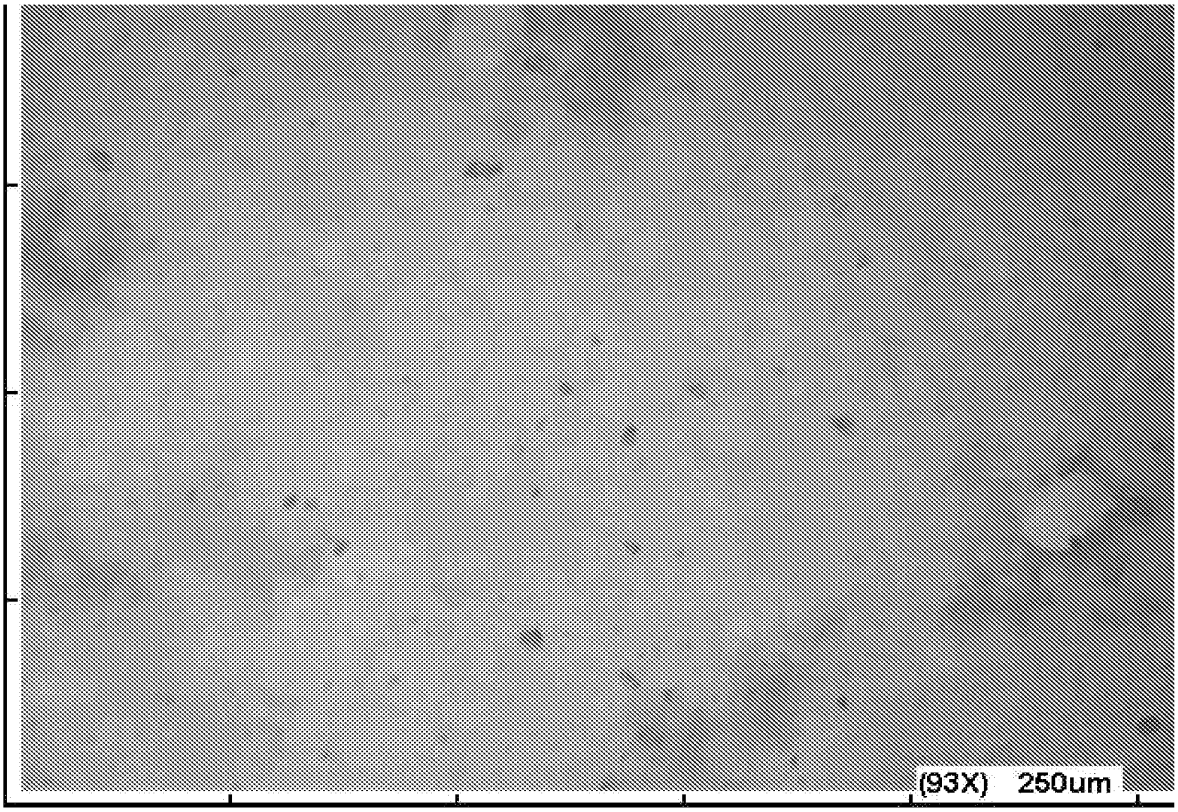


FIG. 26

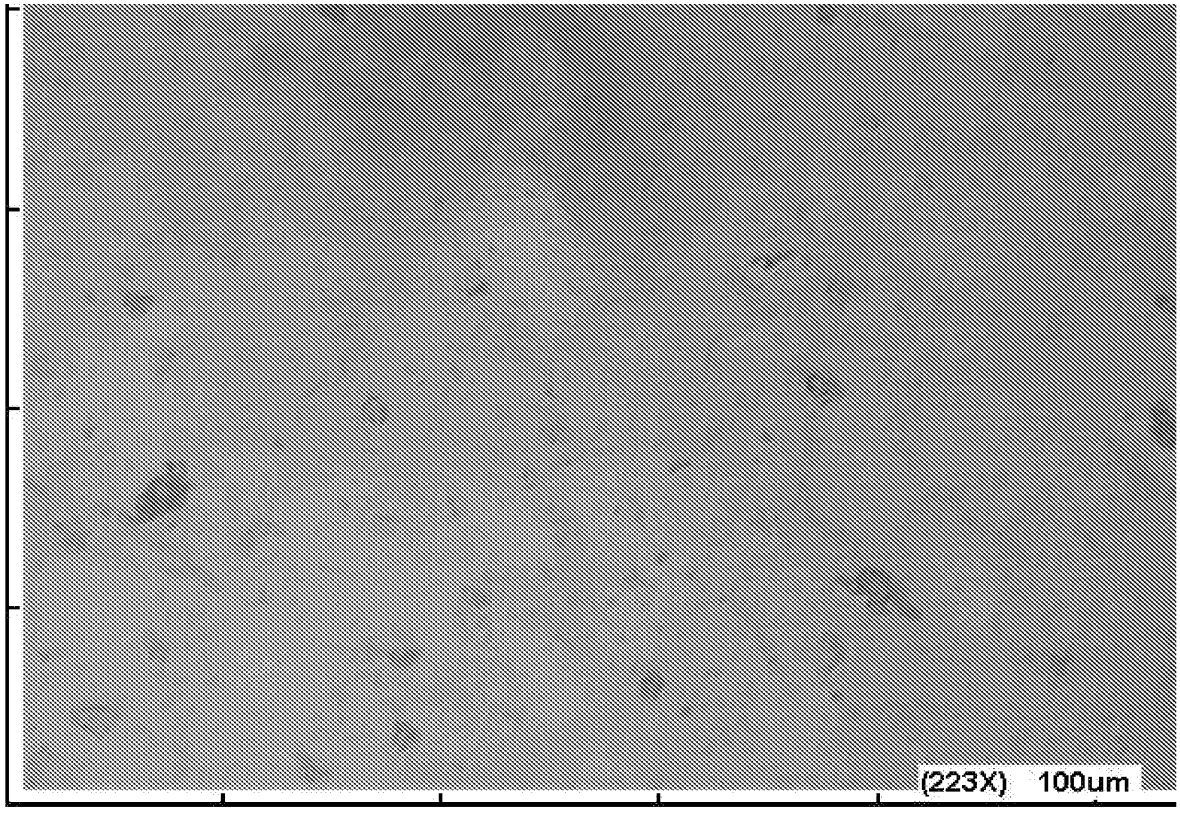


FIG. 27

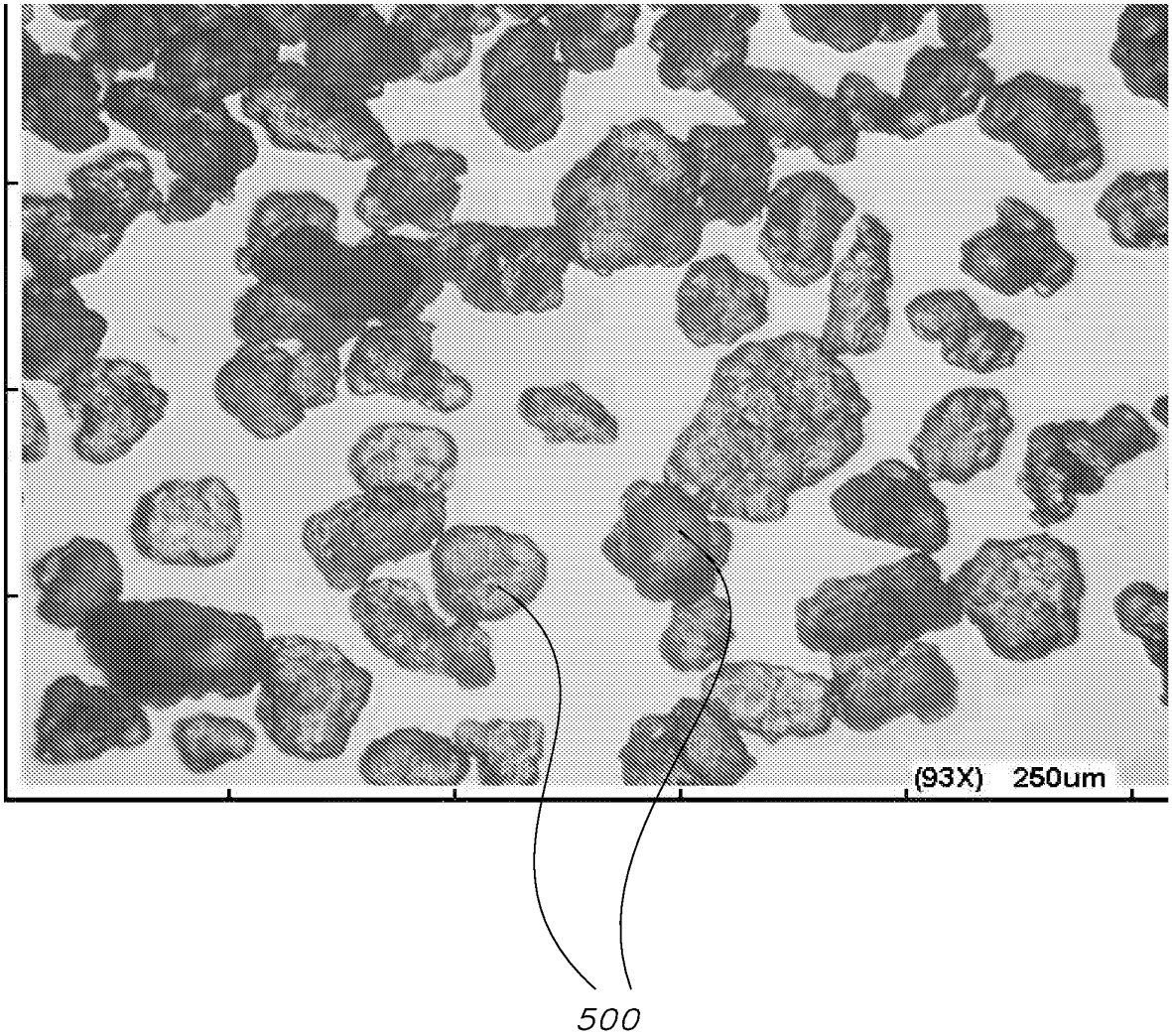


FIG. 28

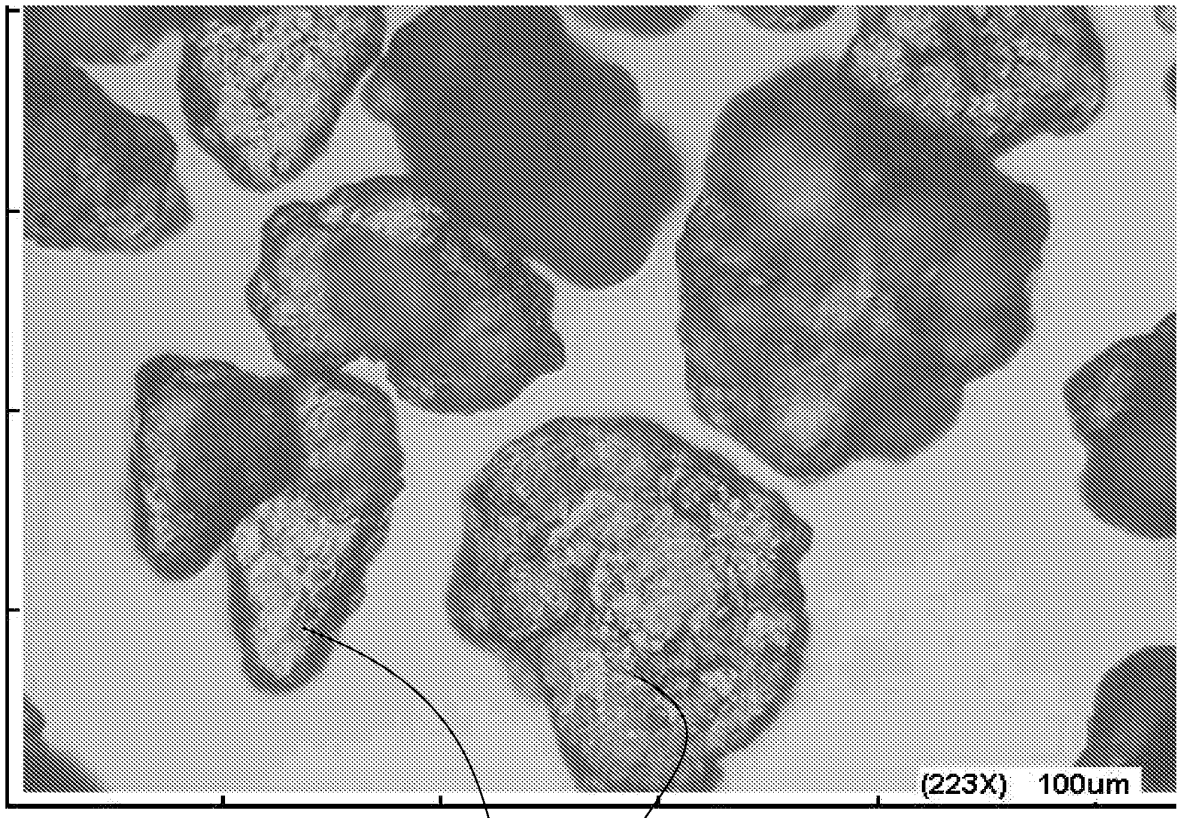


FIG. 29

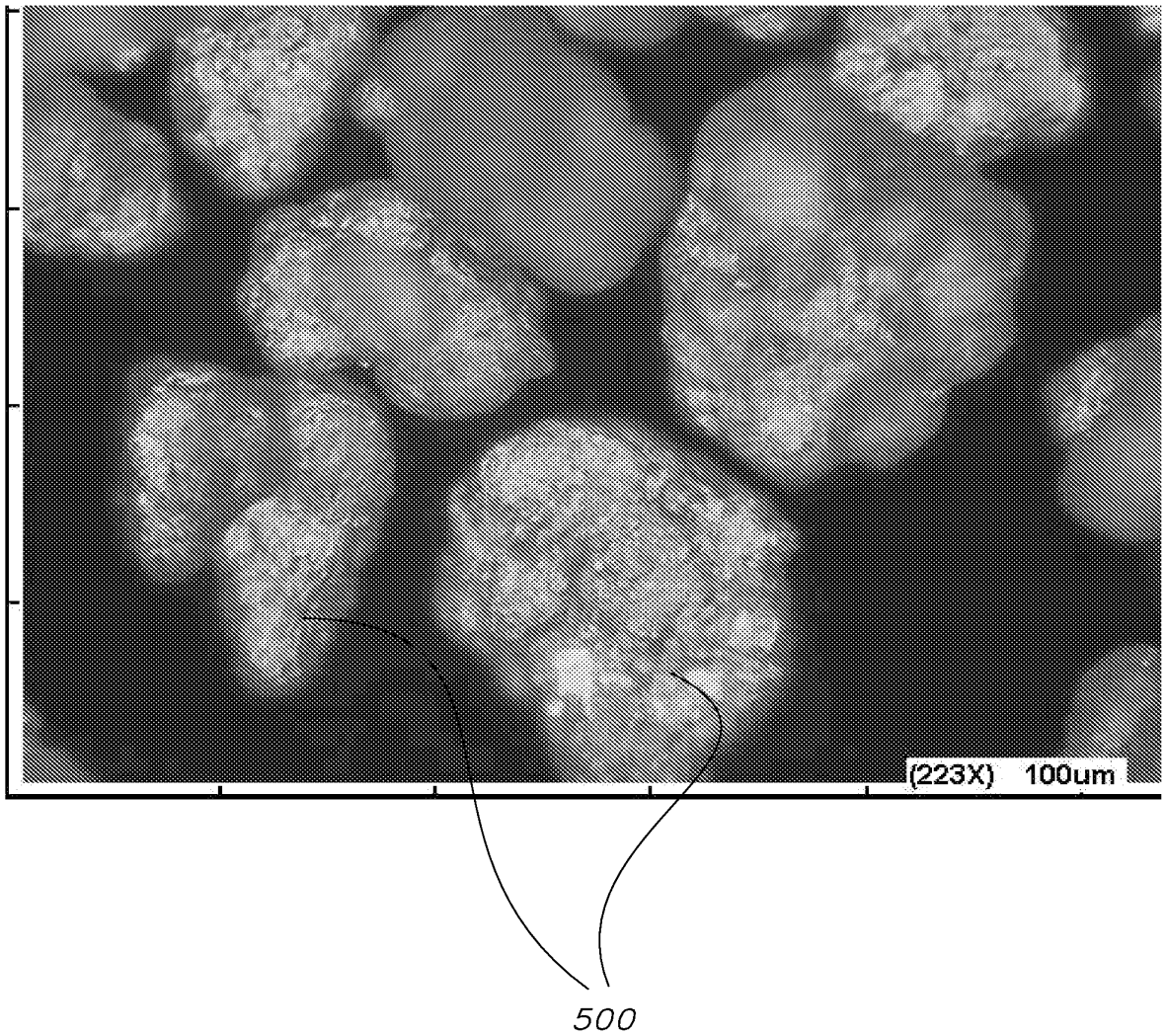


FIG. 30

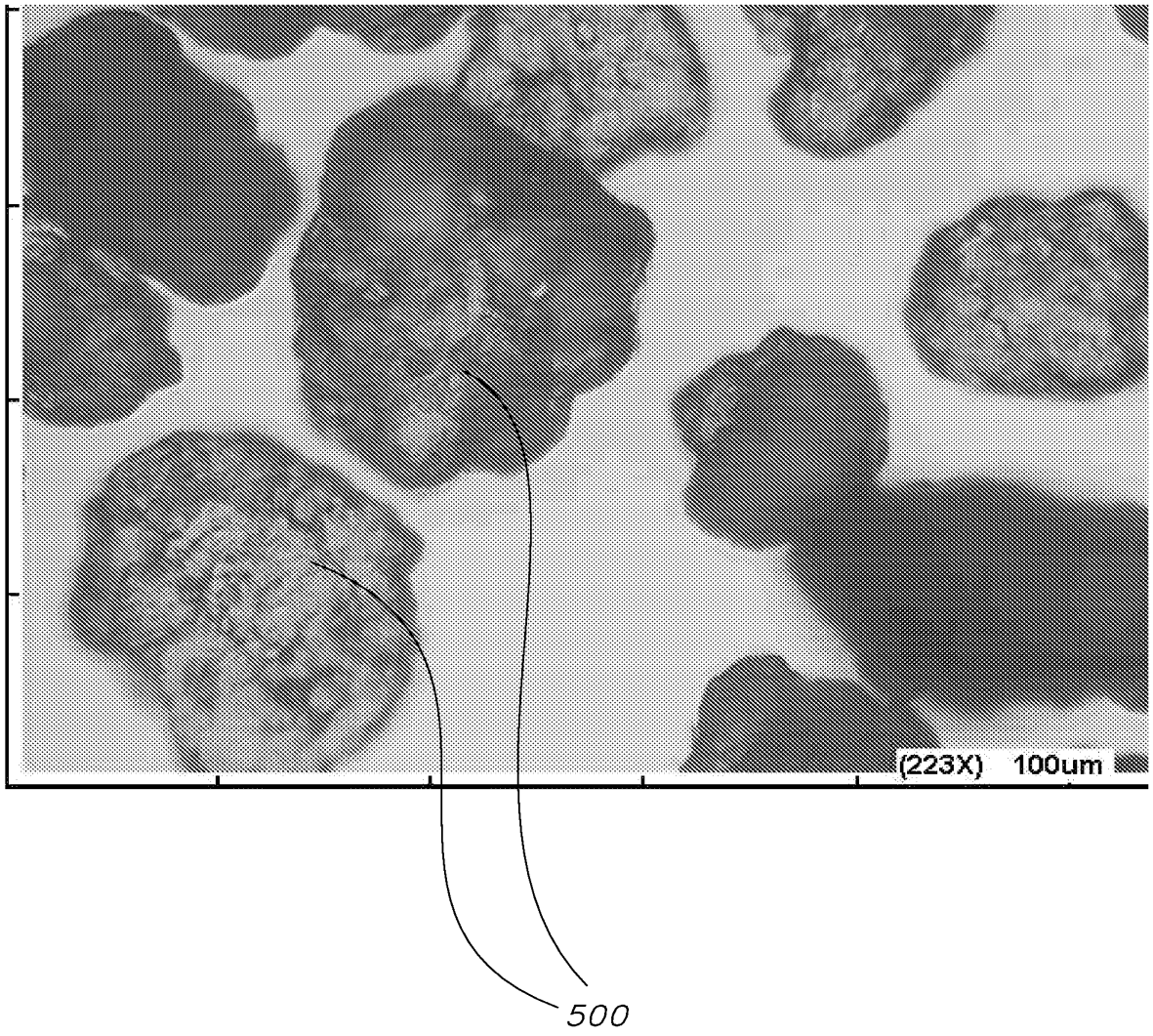
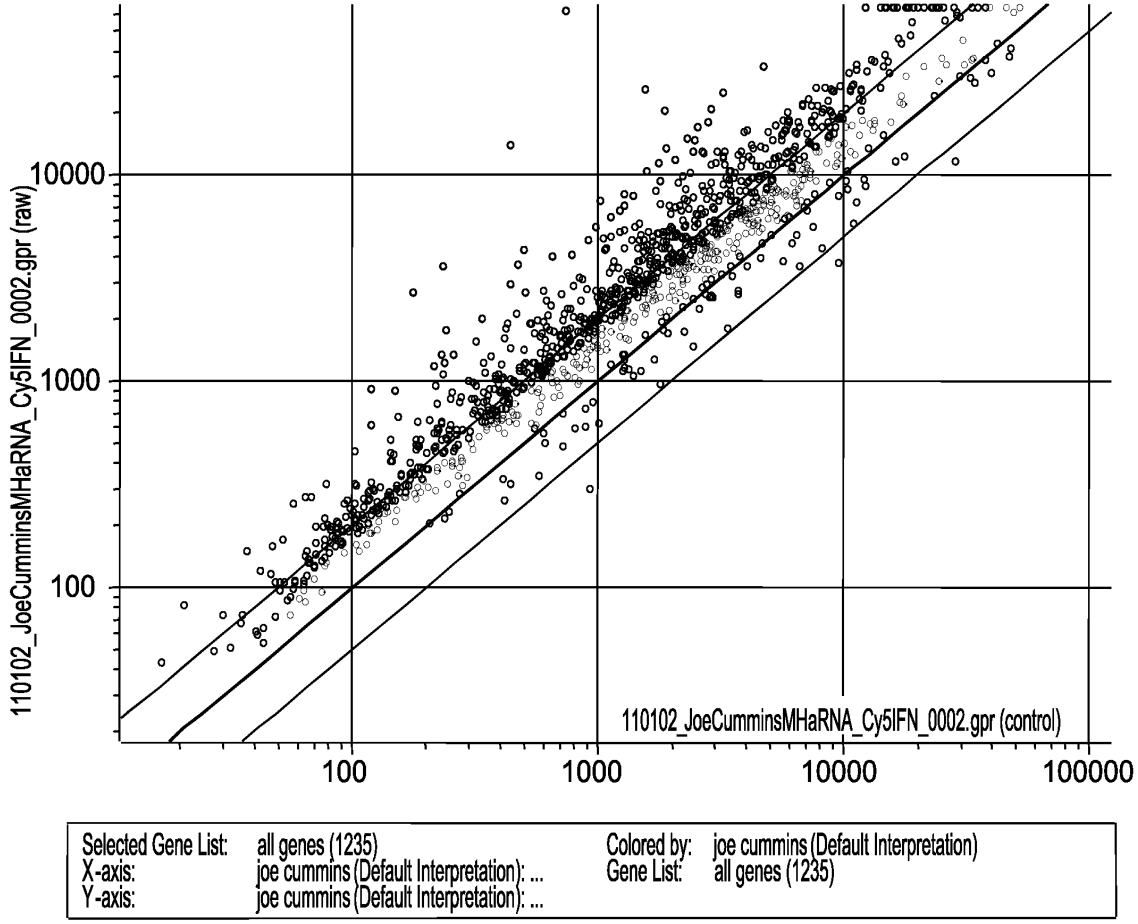


FIG. 31



Normalized to GAPDH, most of the ISGs are induced.

FIG. 32

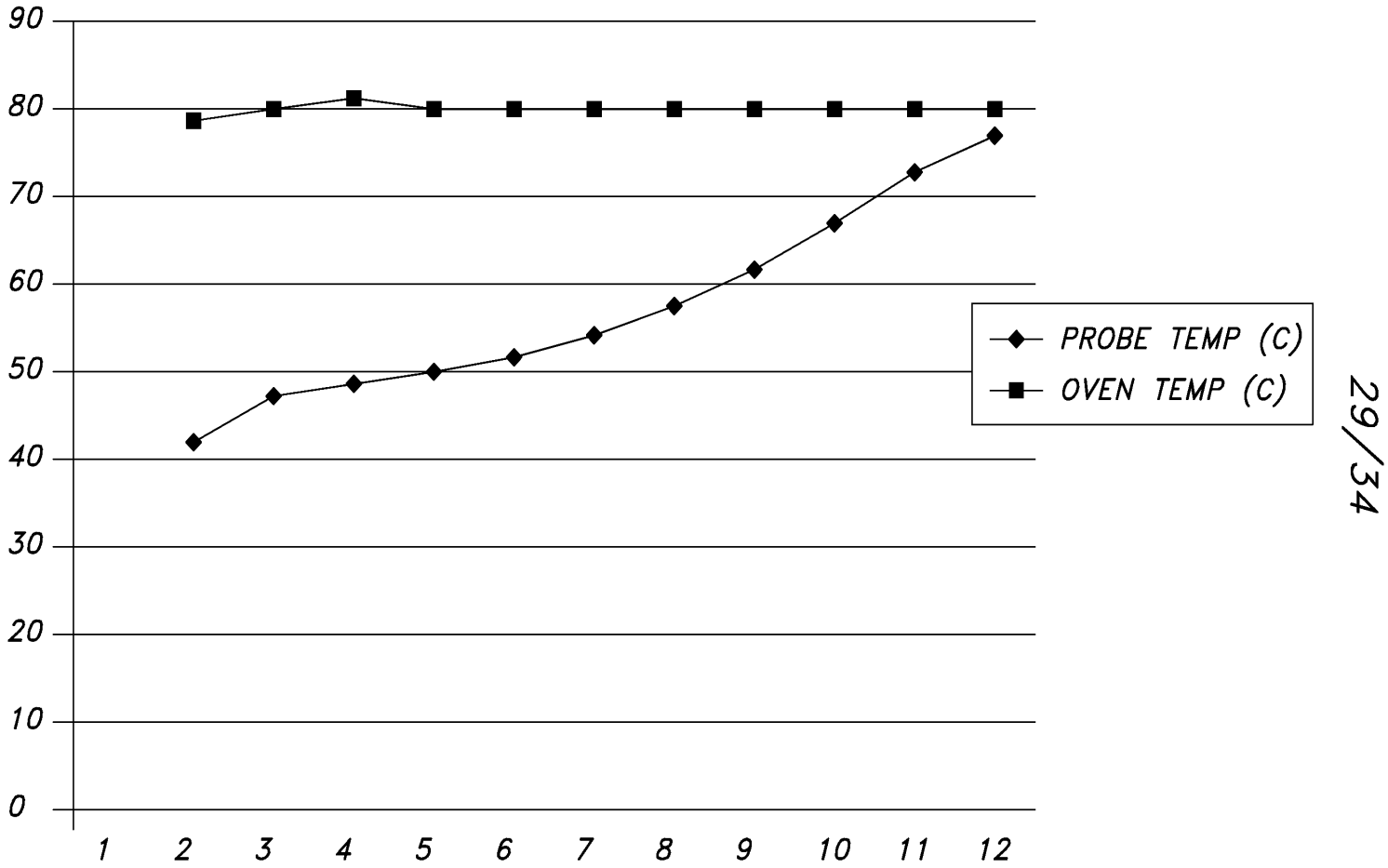

90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12
PROBE TEMP (C)
OVEN TEMP (C)

FIG. 33

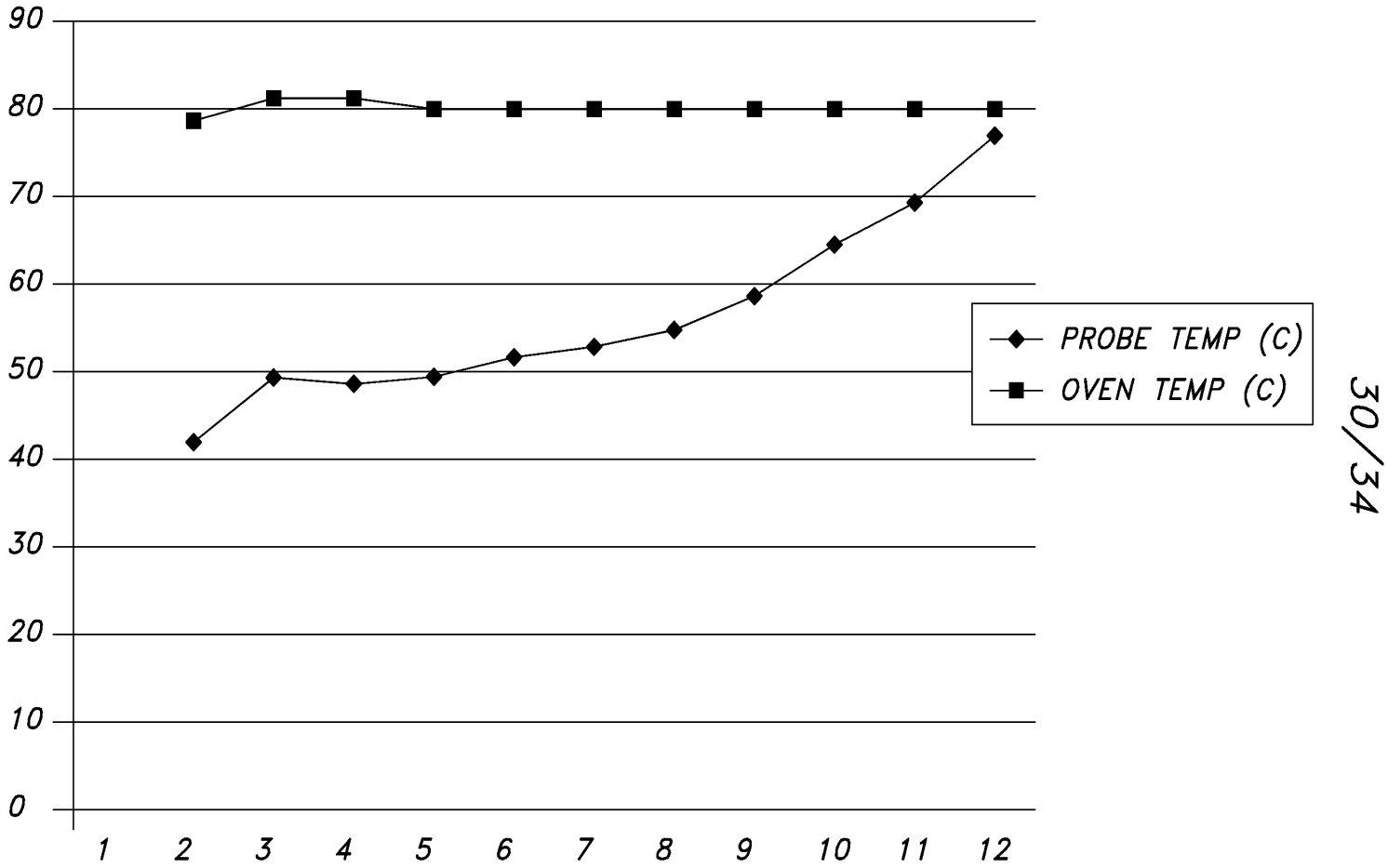


FIG. 34

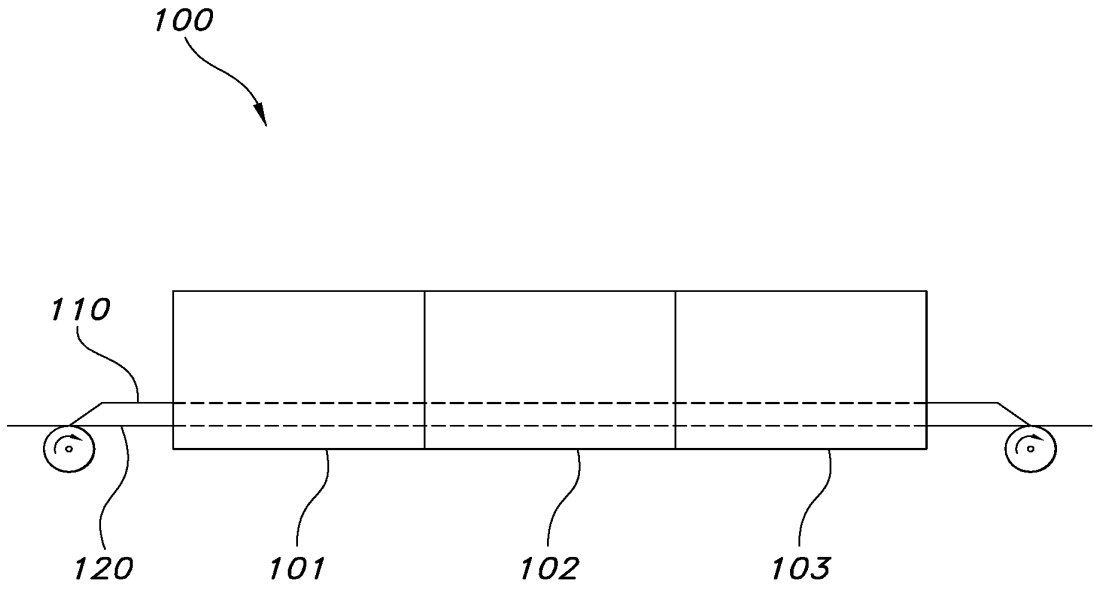


FIG. 35

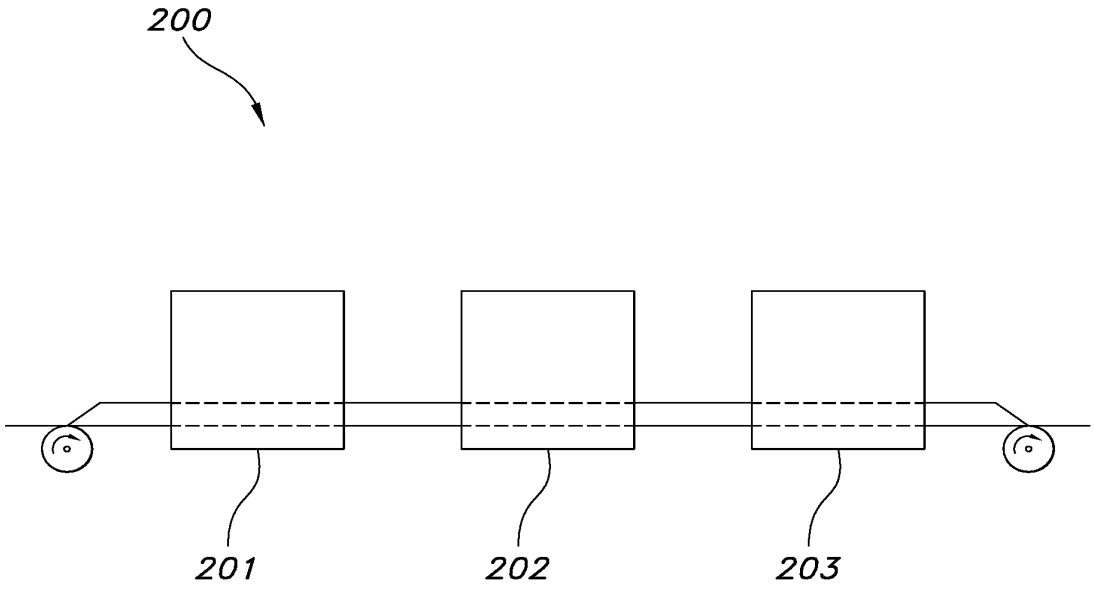


FIG. 36

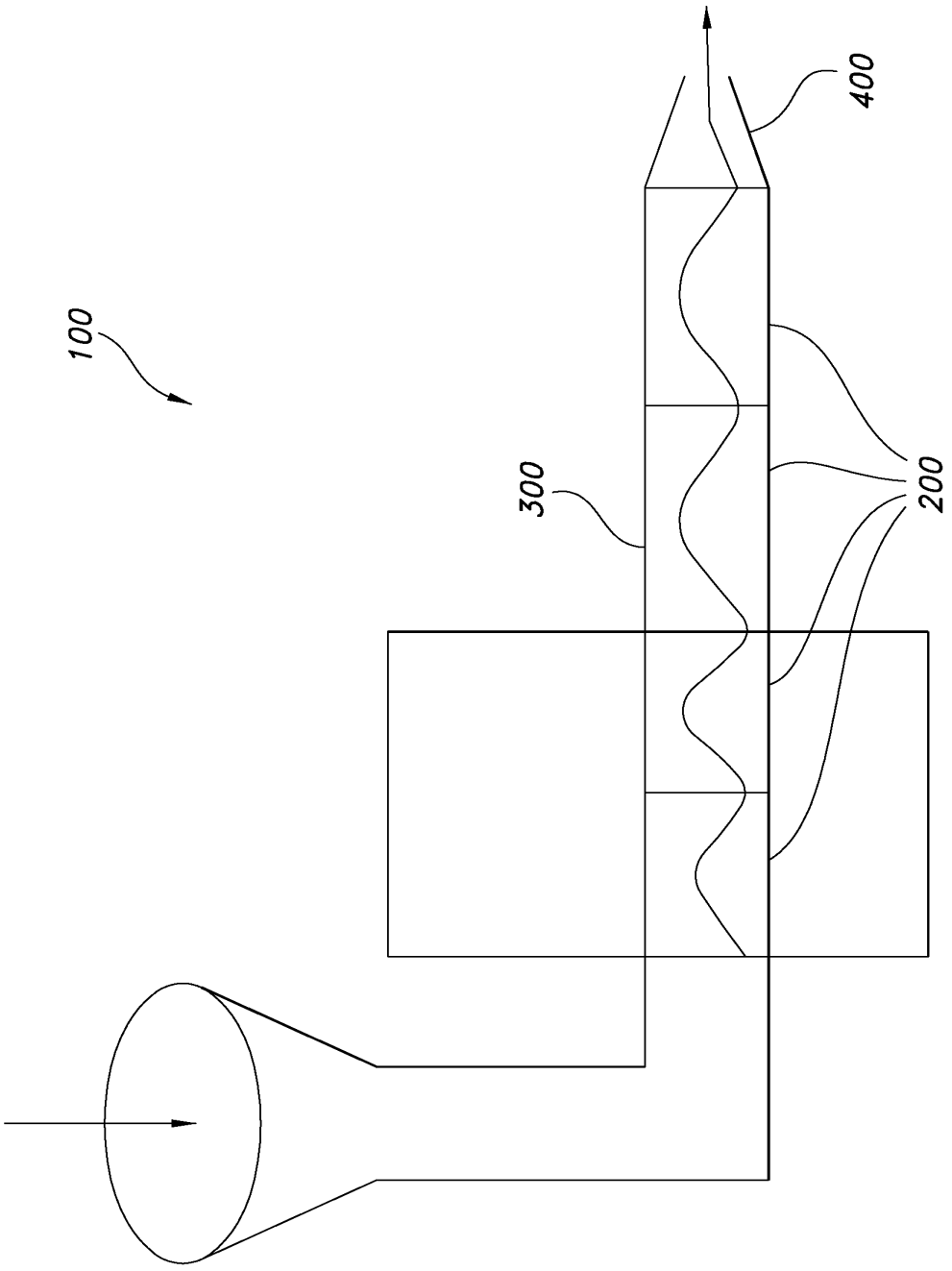


FIG. 37

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

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Jamie Mercer Larmann/Marcy Mancuso
Attorney Docket Number:	1199-4B CIP

Filed as Small Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	75	75
Utility Search Fee	2111	1	250	250
Utility Examination Fee	2311	1	100	100
Pages:				
Claims:				
Claims in excess of 20	2202	14	25	350
Independent claims in excess of 3	2201	3	100	300
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1075**

Electronic Acknowledgement Receipt

EFS ID:	1956185
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:	Jamie Mercer Larmann/Marcy Mancuso
Filer Authorized By:	Jamie Mercer Larmann
Attorney Docket Number:	1199-4B CIP
Receipt Date:	10-JUL-2007
Filing Date:	
Time Stamp:	15:05:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1075
RAM confirmation Number	303
Deposit Account	082461
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 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	sb0014_fill.pdf	16147681 f253d04332fa63ca5500e25f94108d6f3389c988	no	7
Warnings:					
Information:					
2		CIP_Application_as_filed.pdf	955866 ef6e36bec0c00f881d831864c7370b7d20f6002c	yes	112
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	105	
	Claims		106	111	
	Abstract		112	112	
Warnings:					
Information:					
3	Drawings	Formal_Drawings.pdf	6543635 3e784d018450597ece7c20083bebbbd047232f30	no	34
Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	8615 1e1e27e41a731061c33c061f0a8c3a52cdc2ef55	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	23655797		

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.

7/10/07

PTO/SB/06 (12-04)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

11/775,484

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY			OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))				75			
SEARCH FEE (37 CFR 1.16(k), (i), or (m))				250			
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))				100			
TOTAL CLAIMS (37 CFR 1.16(i))	34 minus 20 =	14	X 25=	350	OR	X 50=	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	6 minus 3 =	3	X 100=	300		X 200=	
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).			125			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			N/A			N/A	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1200		TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDI-TIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDI-TIONAL FEE ($)
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))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDI-TIONAL FEE ($)	OR	RATE ($)	ADDI-TIONAL FEE ($)
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))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T 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.

This collection of information is required by 37 CFR 1.16. 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 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. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Jamie Mercer Larmann/Marcy Mancuso
Attorney Docket Number:	1199-4B CIP

09/11/2007 MNGUYEN 00000019 082461 11775484
01 FC:2081 125.00 DA

Filed as Small Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	75	75
Utility Search Fee	2111	1	250	250
Utility Examination Fee	2311	1	100	100
Pages:				
Claims:				
Claims in excess of 20	2202	14	25	350
Independent claims in excess of 3	2201	3	100	300
Miscellaneous-Filing:				

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/775,484	07/10/2007	1615	1200	1199-4B CIP	34	6

CONFIRMATION NO. 5059

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY11791

FILING RECEIPT

Date Mailed: 09/13/2007

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Garry L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Assignment For Published Patent Application

MONOSOLRX LLC, Portage, IN

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CIP of 10/768,809 01/30/2004
which claims benefit of 60/443,741 01/30/2003
and is a CIP of PCT/US02/32575 10/11/2002
which claims benefit of 60/386,937 06/07/2002
and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32594 10/11/2002
which claims benefit of 60/414,276 09/27/2002
and claims benefit of 60/386,937 06/07/2002
and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32542 10/11/2002
which claims benefit of 60/386,937 06/07/2002
and claims benefit of 60/371,940 04/11/2002
This application 11/775,484
is a CIP of 10/856,176 05/28/2004
which claims benefit of 60/473,902 05/28/2003
and is a CIP of 10/768,809 01/30/2004

Foreign Applications

If Required, Foreign Filing License Granted: 09/12/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US11/775,484**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

** SMALL ENTITY **

Title

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

Preliminary Class

424

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP

CONFIRMATION NO. 5059

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

FORMALITIES LETTER

Date Mailed: 09/13/2007

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee, or oath or declaration) as set forth in 37 CFR 1.16(f) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$65** for a small entity

- **$65** Surcharge.

Replies should be mailed to: Mail Stop Missing Parts
Commissioner for Patents

P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199
PART 3 - OFFICE COPY

Electronic Patent Application Fee Transmittal

Application Number:	11775484
Filing Date:	10-Jul-2007
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Andrew Henry Berks/Barbara Thomas
Attorney Docket Number:	1199-4B CIP
Filed as Small Entity	

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	2051	1	65	65
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**65**

Electronic Acknowledgement Receipt

EFS ID:	2449436
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:	Andrew Henry Berks/Barbara Thomas
Filer Authorized By:	Andrew Henry Berks
Attorney Docket Number:	1199-4B CIP
Receipt Date:	09-NOV-2007
Filing Date:	10-JUL-2007
Time Stamp:	15:38:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$65
RAM confirmation Number	825
Deposit Account	082461
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 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	1199-4B_CIP_Response_to_Missing_Parts.pdf	61351 e16a8494268addfed3f43443e20be3087314fee0	no	2
Warnings:					
Information:					
2	Oath or Declaration filed	1199-4B_CIP_Declaration.pdf	246453 d5943a8f254b7a55f115db1c243b93d8395c55d7	no	7
Warnings:					
Information:					
3	Fee Worksheet (PTO-06)	fee-info.pdf	8216 487238241b54e530e0224a731c427d25b0429359	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	316020		

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Yang et al.	Examiner: Unassigned
Application No.: 11/775,484	Group Art Unit: 1615
Filed: July 10, 2007	Docket: 1199-4B CIP
For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS	Dated: November 9, 2007

Confirmation No. 5059

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION - FILING DATE GRANTED

Sir:

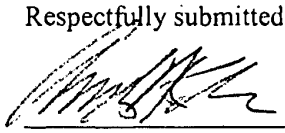
In response to the Notice to File Missing Parts of Nonprovisional Application - Filing Date Granted mailed September 13, 2007, a reply to which is due November 13, 2007, enclosed herewith are the following:

Combined Declaration and Power of Attorney executed by Inventors: Robert K. Yang, Richard C. Fuisz, Garry L. Myers and Joseph M. Fuisz.

A fee of $65.00 is believed to be due with this submission. The Commissioner is hereby authorized to charge payment of the fees associated with this communication 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.

In view of the documents submitted herewith, Applicant respectively urges that the application is in condition for examination. Please direct any questions regarding this submission to Applicant's undersigned agent.

Respectfully submitted,



Andrew H. Berks
Registration No. 36,089
Agent for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, NY 11791
(973) 331-1700

PATENT

Attorney's Docket No. **1199-4 B CIP**

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION OR CIP)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: *(check one)*

- ☐ Original
- ☐ Supplemental
- ☐ Design
- ☐ National Stage PCT
- ☐ Divisional
- ☐ Continuation
- ☒ Continuation-in-Part (CIP)

INVENTORSHIP IDENTIFICATION

NOTE: If the inventors are each not the inventors of all the claims an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

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

the specification of which: *(complete (a), (b) or (c))*

(a) ☐ is attached hereto.

(b) ☒ was filed on **July 10, 2007** as
☒ Serial No. **11/775,484** or
☐ Express Mail No. _____, as Serial No. not yet known and was amended on _____. *(If applicable)*

(c) ☐ was described and claimed in PCT International Application No. **PCT/**_____ filed on _____ and as amended under PCT Article 19 on _____. *(If any)*

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above, and that the filing of said specification, if heretofore filed, was authorized by me.

I acknowledge the duty to disclose information which is material to patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

CLAIM OF PRIORITY OF EARLIER FOREIGN APPLICATION(S) UNDER 35 U.S.C. §119(a)-(d)

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

(List prior foreign/PCT application(s) filed within 12 months (6 months for design) prior to this U.S. application.)

NOTE: Where item (c) is entered above and the International Application which designated the U.S. claimed priority check item (e), enter the details below and make the priority claim.

COUNTRY (orPCT)	APPLICATION NO.	DATE OF FILING *(Day/Month/Year)*	PRIORITY CLAIMED UNDER 35 USC §119
			☐ YES ☐ NO
			☐ YES ☐ NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

(List prior U.S. provisional applications.)

PROVISIONAL APPLICATION NO.	FILING DATE *(Day/Month/Year)*

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. 120

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(List prior U.S. applications or PCT international applications designating the U.S. for benefit under 35 U.S.C. §120.)

U.S. APPLICATIONS		STATUS *(Check One)*		
U.S. SERIAL NO.	U.S. FILING DATE *(Day/Month/Year)*	Patented	Pending	Abandoned
10/768,809	January 30, 2004	☐	☒	☐
10/856,176	May 28, 2004	☐	X	☐

PCT APPLICATIONS DESIGNATING THE U.S.			STATUS *(Check One)*		
PCT APPLN. NO.	PCT FILING DATE *(Day/Month/Year)*	U.S. SERIAL NOS ASSIGNED (If any)	Patented	Pending	Abandoned
PCT/US02/32575	10/11/2002		☐	☐	☐
PCT/US02/33594	10/11/2002		☐	☐	☐
PCT/US02/32542	10/11/2002				

35 USC 119 PRIORITY CLAIM, IF ANY, FOR ABOVE LISTED U.S./PCT APPLICATIONS

PRIORITY APPLICATION NO.	PRIORITY COUNTRY	FILING DATE *(Day/Month/Year)*	ISSUE DATE *(Day/Month/Year)*
60/443,741	US	01/30/2003	
60/386,937	US	06/07/2002	
60/414,276	US	09/27/2002	
60/371,940	US	04/11/2002	
60/473,902	US	05/28/2003	

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) at Customer Number **23869** to prosecute this application and transact all business in the Patent and Trademark Office in connection therewith.

PLEASE SEND CORRESPONDENCE TO:	PLEASE DIRECT TELEPHONE CALLS TO:
Daniel A. Scola, Jr. HOFFMANN & BARON, LLP 6900 Jericho Turnpike Syosset, NY 11791	Jamie M. Larmann (973) 331-1700

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Full Name of Sole or First Inventor:	Robert K. Yang
Country of Citizenship:	US
Residence Address:	138-10 Franklin Ave., Apt. 2C, Fushing, NY 11355
Post Office Address:	**Same as above**
Date: 9/22/2007	Inventor's signature Robert K. Yang
Full Name of Second Joint Inventor:	Richard C. Fulsz
Country of Citizenship:	US
Residence Address:	1127 Langley Lane, McLean, VA 22101
Post Office Address:	**Same as above**
Date:	Inventor's signature
Full Name of Third Joint Inventor:	Garry L. Myers
Country of Citizenship:	US
Residence Address:	908 Colfax Avenue, Kingsport, TN 37660
Post Office Address:	**Same as above**
Date:	Inventor's signature
Full Name of Fourth Joint Inventor:	Joseph M. Fulsz
Country of Citizenship:	US
Residence Address:	1200 23rd Street, Apt. 905, Washington, DC 20037
Post Office Address:	**Same as above**
Date:	Inventor's signature

NOTE: All above spaces identifying inventors must be completed or deleted before any inventor executes this application

PLEASE SEND CORRESPONDENCE TO:
Daniel A. Scola, Jr.
HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, NY 11791

PLEASE DIRECT TELEPHONE CALLS TO:
Jamie M. Larmann
(973) 331-1700

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Full Name of Sole or First Inventor:	Robert K. Yang
Country of Citizenship:	US
Residence Address:	138-10 Franklin Ave., Apt. 2C, Fushing, NY 11355
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____
Full Name of Second Joint Inventor:	Richard C. Fuisz
Country of Citizenship:	US
Residence Address:	1127 Langley Lane, McLean, VA 22101
Post Office Address:	**Same as above**
Date: 9/22/02	Inventor's signature
Full Name of Third Joint Inventor:	Garry L. Myers
Country of Citizenship:	US
Residence Address:	908 Colfax Avenue, Kingsport, TN 37660
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____
Full Name of Fourth Joint Inventor:	Joseph M. Fuisz
Country of Citizenship:	US
Residence Address:	1200 23rd Street, Apt. 905, Washington, DC 20037
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____

NOTE: All above spaces identifying inventors must be completed or deleted before any inventor executes this application

PLEASE SEND CORRESPONDENCE TO:	PLEASE DIRECT TELEPHONE CALLS TO:
Daniel A. Scola, Jr. HOFFMANN & BARON, LLP 6900 Jericho Turnpike Syosset, NY 11791	Jamie M. Larmann (973) 331-1700

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Full Name of Sole or First Inventor:	Robert K. Yang
Country of Citizenship:	US
Residence Address:	138-10 Franklin Ave., Apt. 2C, Fushing, NY 11355
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____
Full Name of Second Joint Inventor:	Richard C. Fuisz
Country of Citizenship:	US
Residence Address:	1127 Langley Lane, McLean, VA 22101
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____
Full Name of Third Joint Inventor:	Garry L. Myers
Country of Citizenship:	US
Residence Address:	908 Colfax Avenue, Kingsport, TN 37660
Post Office Address:	**Same as above**
Date: 11/5/02	Inventor's signature [signature]
Full Name of Fourth Joint Inventor:	Joseph M. Fuisz
Country of Citizenship:	US
Residence Address:	1200 23rd Street, Apt. 905, Washington, DC 20037
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____

NOTE: All above spaces identifying inventors must be completed or deleted before any inventor executes this application

PLEASE SEND CORRESPONDENCE TO:
Daniel A. Scola, Jr.
HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, NY 11791

PLEASE DIRECT TELEPHONE CALLS TO:
Jamie M. Larmann
(973) 331-1700

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Full Name of Sole or First Inventor:	Robert K. Yang
Country of Citizenship:	US
Residence Address:	138-10 Franklin Ave., Apt. 2C, Fushing, NY 11355
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____
Full Name of Second Joint Inventor:	Richard C. Fuisz
Country of Citizenship:	US
Residence Address:	1127 Langley Lane, McLean, VA 22101
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____
Full Name of Third Joint Inventor:	Garry L. Myers
Country of Citizenship:	US
Residence Address:	908 Colfax Avenue, Kingsport, TN 37660
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____
Full Name of Fourth Joint Inventor:	Joseph M. Fuisz
Country of Citizenship:	US
Residence Address:	1200 23rd Street, Apt. 905, Washington, DC 20037
Post Office Address:	**Same as above**
Date: 7 March 2007	Inventor's signature _____

NOTE: All above spaces identifying inventors must be completed or deleted before any inventor executes this application

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/775,484	07/10/2007	1615	1265	1199-4B CIP	34	6

CONFIRMATION NO. 5059

UPDATED FILING RECEIPT

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

OC00000026767125

Date Mailed: 11/16/2007

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Garry L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Assignment For Published Patent Application

MONOSOLRX LLC, Portage, IN

Power of Attorney: The patent practitioners associated with Customer Number 23869

Domestic Priority data as claimed by applicant

This application is a CIP of 10/768,809 01/30/2004
which claims benefit of 60/443,741 01/30/2003
and is a CIP of PCT/US02/32575 10/11/2002
which claims benefit of 60/386,937 06/07/2002
and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32594 10/11/2002
which claims benefit of 60/414,276 09/27/2002
and claims benefit of 60/386,937 06/07/2002
and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32542 10/11/2002
which claims benefit of 60/386,937 06/07/2002
and claims benefit of 60/371,940 04/11/2002
This application 11/775,484
is a CIP of 10/856,176 05/28/2004
which claims benefit of 60/473,902 05/28/2003

and is a CIP of 10/768,809 01/30/2004

Foreign Applications

If Required, Foreign Filing License Granted: 09/12/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/775,484**

Projected Publication Date: 02/21/2008

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

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

Preliminary Class

424

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative,

this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PTO/SB/08a (05-07)
Approved for use through 11/30/2007. 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	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

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	0307537		1884-11-04	Foulks	
	2	0688446		1901-12-10	Stempel	
	3	2142537		1939-01-03	Tisza	
	4	2277038		1942-03-24	Curtis	
	5	2352691		1944-07-04	Curtis	
	6	2501544		1950-03-21	Shrontz	
	7	2980554		1961-04-18	Gentile et al.	
	8	3249109		1966-05-03	Maeth et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

	9	3444858		1969-05-20	Russell	
	10	3536809		1970-10-27	Applezweig	
	11	3551556		1970-12-29	Kliment et al.	
	12	3598122		1971-08-10	Zaffaroni	
	13	3632740		1972-01-04	Robinson et al.	
	14	3640741		1972-02-08	Etes	
	15	3641237		1972-02-08	Gould et al.	
	16	3731683		1973-05-08	Zaffaroni	
	17	3753732		1973-08-21	Boroshok	
	18	3814095		1974-06-04	Lubens	
	19	3892905		1975-07-01	Albert	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

	20	3911099		1975-10-07	DeFoney et al.	
	21	3972995		1976-08-03	Tsuk et al.	
	22	3996934		1976-12-14	Zaffaroni	
	23	3998215		1976-12-21	Anderson et al.	
	24	4029757		1977-06-14	Mlodozeniec et al.	
	25	4029758		1977-06-14	Mlodozeniec et al.	
	26	4031200		1977-06-21	Reif	
	27	4123592		1978-10-31	Rainer et al.	
	28	4128445		1978-12-05	Sturzenegger et al.	
	29	4136145		1979-01-23	Fuchs et al.	
	30	4136162		1979-01-23	Fuchs et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

	31	4139627		1979-02-13	Lane et al.	
	32	4226848		1980-10-07	Nagai et al.	
	33	4251400		1981-02-17	Columbus	
	34	4292299		1981-09-28	Suzuki et al.	
	35	4294820		1981-10-13	Keith et al.	
	36	4302465		1981-11-24	Ekenstam et al.	
	37	4307075		1981-12-22	Martin	
	38	4325855		1982-04-20	Dickmann	
	39	4373036		1983-02-08	Chang et al.	
	40	4406708		1983-09-27	Hesselgren	
	41	4432975		1984-02-21	Libby	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

	42	4438258		1984-03-20	Graham	
	43	4460562		1984-07-17	Keith et al.	
	44	4466973		1984-08-21	Rennie	
	45	4503070		1985-03-05	Eby	
	46	4515162		1985-05-07	Katsuhiro	
	47	4517173		1985-05-14	Kizawa et al.	
	48	4529601		1985-07-16	Broberg et al.	
	49	4529748		1985-07-16	Wienecke	
	50	4562020		1985-12-31	Hijiya et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

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	2432925	DE		1976-01-22			☐
	2	2449865	DE		1976-04-29			☐
	3	3630603	DE		1988-03-10			☐
	4	0200508	EP		1991-10-02			☐
	5	0219762	EP		1990-12-27			☐
	6	0250187	EP		1993-09-29			☐
	7	0259749	EP		1991-08-14			☐
	8	0273069	EP		1992-10-14			☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

	9	0381194	EP		1994-08-31			☐
	10	0452446	EP		1993-12-29			☐
	11	0241178	EP		1987-10-14			☐
	12	0514691	EP		1992-11-25			☐
	13	1110546	EP		2001-06-27			☐
	14	200018365	WO		2000-04-06			☐
	15	200042992	WO		2000-07-27			☐
	16	200170194	WO		2001-09-27			☐
	17	200191721	WO		2001-12-06			☐
	18	199105540	WO		1991-05-02			☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

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		☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

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	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

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	/Andrew H. Berks, Reg. No. 36,089/	Date (YYYY-MM-DD)	2008-01-29
Name/Print	Andrew H. Berks	Registration Number	36089

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.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

(51) Int. Cl. 2: A 61 K 9-70

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

DT 24 32 925 A1

(11) Offenlegungsschrift 24 32 925

(21) Aktenzeichen: P 24 32 925.7

(22) Anmeldetag: 5. 7. 74

(43) Offenlegungstag: 22. 1. 76

(30) Unionspriorität:

(32) (33) (31) —

(54) Bezeichnung: Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff

(71) Anmelder: Schering AG, 1000 Berlin und 4619 Bergkamen

(72) Erfinder: Fuchs, Peter, Dr.; Hilmann, Jürgen; 1000 Berlin

DT 24 32 925 A1

© 1.76 509 884/988 12/80

SCHERING AG
Patentabteilung

2432925

4. Juli 1974

Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff

Die Erfindung betrifft Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff zur inneren und äußeren Anwendung.

Aus der belgischen Patentschrift sind Papierfolien bekannt, die mit Wirkstoff beschichtet zur oralen Anwendung geeignet sind. Die Folien bestehen aus in Wasser unlöslichen Cellulosefasern und einem wasserlöslichen Bindemittel. Als wasserlösliches Bindemittel wird vorzugsweise Carboxymethylcellulose-Natrium verwendet. Der Wirkstoff wird durch Auftropfen des gelösten Wirkstoffes, durch Aufstreuen des festen Wirkstoffes oder durch Durchziehen der Folie durch die Wirkstofflösung auf die Papierfolie gebracht. Das diskontinuierliche Verfahren der gesonderten Herstellung der Folie und Aufbringung des Wirkstoffes hat den Nachteil, daß die Dosierungsgenauigkeit nicht sehr gut ist, was bei den heute niedrig dosierten Wirkstoffen jedoch von großer Wichtigkeit ist. Ungenauigkeiten entstehen nicht nur bei dem Aufbringen des Wirkstoffes, sondern auch bei der Herstellung und Vorbehandlung des Trägers und durch Veränderungen bei der Lagerung des Trägermaterials. So hat es sich zum Beispiel gezeigt, daß

Vorstand: Hans-Jürgen Hamann · Karl Otto Mittelstenscheid
Dr. Gerhard Raspé · Dr. Horst Witzel
Stellv.: Dr. Christian Bruhn · Dr. Heinz Hannse
Vorsitzender des Aufsichtsrats: Dr. Eduard v. Schwartzkoppen
Sitz der Gesellschaft: Berlin und Bergkamen
Handelsregister: AG Charlottenburg 93 HRB 283 u. AG Kamen HRB 0061

Postanschrift: SCHERING AG · D-1 Berlin 65 · Postfach 65 03 11
Postscheck-Konto: Berlin-West 11 75-101, Bankleitzahl 100 100 10
Berliner Commerzbank AG, Berlin, Konto-Nr. 108 7006 00, Bankleitzahl 100 400 00
Berliner Disconto-Bank AG, Berlin, Konto-Nr. 241/5008, Bankleitzahl 100 705 00
Berliner Handels-Gesellschaft – Frankfurter Bank –, Berlin,
Konto-Nr. 14-362, Bankleitzahl 100 202 00

nach der Rezeptur der belgischen Patentschrift bei Verwendung von Folienziehmaschinen keine gleichmäßige Folienschicht entsteht und daß die Folie bei der Trocknung

schrumpft. Es ist jedoch leicht einzusehen, daß bei nicht einheitlichem Material auch die Wirkstoffaufnahme nicht gleichmäßig sein wird. Ein nur oberflächlich gebundener Wirkstoff kann außerdem bei der Handhabung der Folien, wie zum Beispiel bei der Verpackung, teilweise wieder abgelöst werden. Die als Bindemittel verwendete Natrium-Carboxymethylcellulose wird im Magen angelöst und setzt dabei die Carboxymethylcellulose frei, die den Wirkstoff teilweise einschließt und nur verzögert oder überhaupt nicht freigibt.

Es wurde nun gefunden, daß man Folien mit gleichbleibender Dicke und gleichmäßiger Wirkstoffverteilung erhält, wenn man Folien mit inkorporiertem Wirkstoff herstellt und Folienbildner verwendet, die in Wasser oder in organischen Lösungsmitteln löslich sind. Bevorzugt geeignet sind Folienbildner, die sich sowohl in Wasser als auch in organischen Lösungsmitteln lösen.

Als Folienbildner kommen zum Beispiel Poly-N-Vinylpyrrolidon, Vinylpyrrolidon-Vinylacetat, Methyl- und Äthylcellulose, vorzugsweise jedoch nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose, wie Hydroxypropylcellulose, Hydroxyäthylcellulose und Methylhydroxypropylcellulose, in Betracht.

- 3 -

Dem Folienbildner können Füllstoffe und Wirkstoffe und zweckmäßigerweise eine geringe Menge eines Trennmittels zugesetzt werden.

Geeignete Trennmittel sind u.a. Polyoxyäthylenpolyoxypropylenpolymeres (PLURONIC F 68 (R)), Polyoxylstearate, Alkyl- bzw. Acylsubstiutierte Polyadditionsprodukte des Äthylenoxids zum Beispiel CREMOPHOR EL (R), Silikone und Silkontrennemulsionen, Glycerin, Propylenglykol und Metallseifen.

Als Füllstoffe sind zum Beispiel Cellulose, Zucker, wie zum Beispiel Lactose, Dextrose, Rohrzucker usw., Stärken, mehrwertige Alkohole, wie zum Beispiel Mannit, Calciumcarbonat, Calciumphosphat, Talkum und Farbstoffe in löslicher Form oder als Pigmente geeignet. Die Füllstoffe können teilweise oder vollständig durch Wirkstoffe ersetzt werden. Werden lösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine transparente, glatte Folie, werden unlösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine weiße oder farbige, papierartige Folie.

Erfindungsgemäß können alle in der Human- und Veterinärmedizin verwendeten Wirkstoffe eingesetzt werden. Für die innere Anwendung kommt insbesondere die orale Verabreichung infrage. Unter der äußeren Anwendung sollen insbesondere die topikale Verabreichung auf der Haut und in Körperhöhlungen wie Nase, Ohr, Vagina usw. verstanden werden. Als Wirkstoffe seien

beispielsweise genannt: Gestagene, Östrogene, Gemische aus Gestagenen und Östrogenen, Tranquilizer, Antidiabetika, Sulfonamide, Antibiotika, Trichomonadenmittel, Entzündungshemmer, wie zum Beispiel Corticoide, usw.
Der Azneimittelwirkstoff kann im Trägermaterial gelöst oder gleichmäßig suspendiert vorliegen. Der Wirkstoffanteil in der Folie kann etwa 0-60 % betragen. Als Einzeldosis (Einheit) werden Flächen geschnitten bwz. perforiert, die Wirkstoffmengen enthalten wie sie üblicherweise auch in Tabletten, Dragees, Salben, Zäpfchen usw. enthalten sind. So kann die Wirkstoffmenge pro Einzeldosis je nach Anwendungsart beliebig hoch sein und zwischen etwa 1µg und 0,5 g betragen, wobei die untere und obere Dosis leicht unter- oder überschritten werden können. Selbstverständlich können auch wirkstofffreie Träger (Placebos) hergestellt werden.

Zur Herstellung des erfindungsgemäßen Arzneimittels in Folienform werden der Wirkstoff und/oder das Trennmittel gelöst bzw. suspendiert, der Folienbildner und gegebenenfalls der Füllstoff eingetragen, gegebenenfalls homogenisiert und die Lösung bzw. Suspension auf einer Folienziehmaschine zu einem Ausstrich ausgezogen. Die durch Trocknung des Ausstrichs erhaltene Folie wird in beliebige Abschnitte (Einheiten) aufgeteilt.

In der Lösung bzw. Suspension wird der Folienbildner in Gewichtsmengen von etwa 6-20 %, der Füllstoff in Gewichtsmengen von etwa

0-30 % und das Trennmittel vorzugsweise in Gewichtsmengen von 0,01-2 % eingesetzt.

Das Lösungs- bzw. Suspensionsmittel ist zu etwa 48-84 % (W/W) enthalten und besteht aus Wasser und/oder einem oder mehreren organischen Lösungsmitteln. Als organische Lösungsmittel kommen physiologisch verträgliche Lösungsmittel oder solche Lösungsmittel in Betracht, die bei der Trocknung bis auf einen physiologisch unbedenklichen Rest entfernt werden können. Solche Lösungmittel sind zum Beispiel Äthylalkohol, Isopropanol, Methylenchlorid usw. und ihre Mischungen. Wasser und Äthylalkohol bzw. Gemische aus Wasser und Äthylalkohol werden bevorzugt angewandt.

Die Schichtdicke des nassen Ausstrichs beträgt etwa 0,1 bis 2 mm und die der trockenen Folie etwa 0,05 bis 1 mm, vorzugsweise 0,07 bis 0,3 mm.

Das Verfahren zur Herstellung des Arzneimittels in Folienform in einem Arbeitsgang (kontinuierliches Verfahren) bietet den Vorteil, daß der Wirkstoff homogen und gleichmäßig verteilt in dem Wirkstoffträger vorliegt. Durch die Konzentration des Wirkstoffs im Träger, die Dicke der Folie und die Fläche der Folie kann man die Einzeldosis sehr einfach variieren.

Die Erfindung betrifft auch die Verwendung von in Wasser und/oder organischen Lösungsmitteln löslichen Filmbildern für die Herstellung von Arzneimittelwirkstoffträgern, insbesondere die Verwendung von nichtionogenen, wasserlöslichen Hydroxyalkyläthern der Cellulose, wie Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose.

2432925

Beispiel 1

Herstellung für 1000 Einheiten

0,25	g	D-Norgestrel
0,05	g	Äthinylöstradiol
		und
0,84	g	Polyoxyäthylenpolyoxypropylenpolymeres
		werden in
95,00	g	Äthylalkohol unter Rühren gelöst, in diese
		Lösung wird eine Pulvermischung aus
16,93	g	Hydroxypropylcellulose und
16,93	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrichmit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,25 mg	D-Norgestrel
0,05 mg	Äthinylöstradiol
0,84 mg	Polyoxyäthylenpolyoxypropylenpolymeres
16,93 mg	Hydroxypropylcellulose
16,93 mg	Cellulose
35,00 mg	

509884/0988

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 2

Herstellung für 1000 Einheiten

1,10	g	Cremophor EL (R) werden in
152,00	g	Wasser gelöst. In dieser Lösung werden
0,25	g	mikronisiertes D-Norgestrel und
0,05	g	mikronisiertes Äthinylöstradiol suspendiert und evtl homogenisiert. In die Suspension werden
22,10	g	Hydroxypropylcellulose und
16,50	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,25	mg	D-Norgestrel
0,05	mg	Äthinylöstradiol
1,10	mg	Cremophor EL (R)
22,10	mg	Hydroxypropylcellulose
16,50	mg	Cellulose
40,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

B e i s p i e l 3

Herstellung für 1000 Einheiten

0,03	g	D-Norgestrel und
0,84	g	Polyoxyl-40-stearat werden in
95,00	g	Äthylalkohol unter Rühren gelöst.
		In diese Lösung wird eine Pulvermischung aus
16,93	g	Hydroxypropylcellulose und
17,20	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,03	mg	D-Norgestrel
0,84	mg	Polyoxyl-40-stearat
16,93	mg	Hydroxypropylcellulose
17,20	mg	Cellulose
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

B e i s p i e l 4

Herstellung für 1000 Einheiten

1,10	g	Polyoxyäthylenpolyoxypropylenpolymeres werden in
152,00	g	demineralisiertem Wasser gelöst.
		In dieser Lösung werden
0,03	g	mikronisiertes D-Norgestrel suspendiert und evtl. homogenisiert.
		In die Suspension werden
22,10	g	Hydroxypropylcellulose und
16,77	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich miteiner Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,03	mg	D-Norgestrel
1,10	mg	Polyoxyäthylenpolyoxypropylenpolymeres
22,10	mg	Hydroxypropylcellulose
16,77	mg	Cellulose
40,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 5

Herstellung für 1000 Einheiten

0,025	g	Fluocortolontrimethylacetat und
0,183	g	Glycerin werden in
30,000	g	Äthylalkohol gelöst.
		In diese Lösung werden
7,292	g	Hydroxypropylcellulose eingetragen.

Die erhaltene Lösung wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,025	mg	Fluocortolontrimethylacetat
0,183	mg	Glycerin
7,292	mg	Hydroxypropylcellulose
7,500	mg	

Eine Einheit entspricht einer Fläche von ca. 1 cm^2.

Aussehen der Folie: transparent.

Die trockene Folie hat eine Dicke von ca. 70 µm.

B e i s p i e l 6

Herstellung für 1000 Einheiten

10,00 g 7-Chlor-2-methylamino-5-phenyl-3H-1,4-benzodiazepin-4-oxid und

0,84 g Polyoxyäthylenpolyoxypropylenpolymeres werden in

95,00 g Äthylalkohol gelöst.

In diese Lösung wird ein Pulvergemisch aus

16,93 g Hydroxypropylcellulose und

7,23 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

10,00	mg	7-Chlor-2-methylamino-5-phenyl-3H-1,4-benzodiazepin-4-oxid
0,84	mg	Polyoxyäthylenpolyoxypropylenpolymeres
16,93	mg	Hydroxypropylcellulose
7,23	mg	Cellulose
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: gelb, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 7

Herstellung für 1000 Einheiten

1,00	g	Norethisteronacetat
0,03	g	Äthinylöstradiol und
0,84	g	Polyoxyäthylenpolyoxypropylenpolymeres werden in
95,00	g	Äthylalkohol gelöst.
		In diese Lösung wird ein Pulvergemisch aus
16,93	g	Hydroxypropylcellulose und
16,20	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrichmit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00	mg	Norethisteronacetat
0,03	mg	Äthinylöstradiol
0,84	mg	Polyoxyäthylenpolyoxypropylenpolymeres
16,93	mg	Hydroxypropylcellulose
16,20	mg	Cellulose
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 8

Herstellung für 1000 Tabletten:

1,00	g	Norethisteronacetat
0,03	g	Äthinylöstradiol und
0,84	g	Propylenglykol werden in einem Gemisch aus
101,60	g	Methylenchlorid und
26,40	g	Äthylalkohol gelöst.
		In diese Lösung wird ein Pulvergemisch aus
8,47	g	Hydroxypropylcellulose
8,47	g	Hydroxyäthylcellulose und
16,19	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich miteiner Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00	mg	Norethisteronacetat
0,03	mg	Äthinylöstradiol
0,84	mg	Propylenglykol
8,47	mg	Hydroxypropylcellulose
8,47	mg	Hydroxyäthylcellulose
16,19	mg	Cellulose
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 9

Herstellung für 1000 Einheiten:

1,00	g	Norethisteronacetat
0,03	g	Äthinylöstradiol und
0,84	g	Polyoxyäthylpolyoxypropylenpolymeres werden in einem Gemisch aus
101,60	g	Methylenchlorid und
25,40	g	Äthylalkohol gelöst.
		In diese Lösung wird ein Pulvergemisch aus .
16,93	g	Hydroxyäthylcellulose und
16,20	g	Stärke eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich miteiner Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00	mg	Norethisteronacetat
0,03	mg	Äthinylöstradiol
0,84	mg	Polyoxyäthylenpolyoxypropylenpolymeres
16,93	mg	Hydroxyäthylcellulose und
16,20	mg	Stärke
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

B e i s p i e l 10

Herstellung für 1000 Einheiten:

1,00	g	Norethisteronacetat
0,03	g	Äthinylöstradiol und
0,84	g	Polyoxyl-40-stearat werden in
95,00	g	Äthylalkohol gelöst.
		In diese Lösung wird ein Pulvergemisch aus
16,93	g	Hydroxypropylcellulose
8,10	g	Lactose und
8,10	g	Maisstärke eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

1,00	mg	Norethisteronacetat
0,03	mg	Äthinylöstradiol
0,84	mg	Polyoxyl-40-stearat
16,93	mg	Hydroxypropylcellulose
8,10	mg	Lactose
8,10	mg	Maisstärke
35,00	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

B e i s p i e l 11

Herstellung für 1000 Einheiten:

25,0	g	5-Morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl)-methylamino-2-oxazolidinon · HCl werden in
2,1	g	Cremophor EL (R) gelöst in
152,0	g	Alkohol und Wasser 1 x 1 suspendiert. In diese Suspension werden
42,3	g	Methylhydroxypropylcellulose und
18,1	g	Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und getrocknet.

Zusammensetzung für eine Einheit:

25,0	mg	5-Morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl) methylamino-2-oxazolidinon · HCl
2,1	mg	Cremophor EL (R)
42,3	mg	Methylhydroxypropylcellulose
18,1	mg	Cellulose
87,5	mg	

Eine Einheit entspricht einer Fläche von ca. 8 cm^2.

Aussehen der Folie: hellgelb, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

B e i s p i e l 12

Herstellung für 1000 Einheiten:

4,0	g	Glisoxepid in mikronisierter Form werden in
0,9	g	Polyoxyl-40-stearat gelöst in
152,0	g	Wasser suspendiert und eventuell homogenisiert.
		In die Suspension werden
15,0	g	Hydroxyäthylcellulose und
15,1	g	Calciumcarbonat eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziegerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und getrocknet.

Zusammensetzung für eine Einheit:

4,00 mg	Glisoxepid
0,90 mg	Polyoxyl-40-stearat
15,00 mg	Hydroxyäthylcellulose
15,10 mg	Calciumcarbonat
35,00 mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

2432925

Beispiel 13

Herstellung für 1000 Einheiten:

0,030	g	D-Norgestrel werden in
40,000	g	Methylenchlorid und
55,000	g	Äthanol gelöst.
		In diese Lösung werden
0,840	g	Silikonöl
6,930	g	Methylcellulose und
10,000	g	Poly-N-vinylpyrrolidon und
17,200	g	Stärke eingetragen, eventuell homogenisiert.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und getrocknet.

Zusammensetzung für eine Einheit:

0,030	mg	D-Norgestrel
0,840	mg	Silikonöl
6,930	mg	Methylcellulose
10,000	mg	Poly-N-vinylprrolidon
17,200	mg	Stärke
35,000	mg	

Eine Einheit entspricht einer Fläche von ca. 3 cm^2.

Aussehen der Folie: weiß, papierartig.

Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 14

Herstellung für 1000 Einheiten

0,84 g Polyoxyäthylenpolyoxypropylenpolymeres
werden in
95,00 g Äthylalkohol unter Rühren gelöst, in diese
Lösung wird eine Pulvermischung aus
17,08 g Hydroxypropylcellulose und
17,08 g Cellulose eingetragen.

Die erhaltene Suspension wird auf einem geeigneten Folienziehgerät zu einem Ausstrich mit einer Schichtdicke von 500 µm ausgezogen und anschließend getrocknet.

Zusammensetzung für eine Einheit:

0,84 mg Polyoxyäthylenpolyoxypropylenpolymeres
17,08 mg Hydroxypropylcellulose
17,08 mg Cellulose
35,00 mg

Patentansprüche

1.) Arzneimittelstoffträger in Folienform mit inkorporiertem Wirkstoff, dadurch gekennzeichnet, daß er in Wasser oder organischen Lösungsmitteln lösliche Folienbildner enthält.

2.) Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß die Folienbildner in Wasser und in organischen Lösungsmitteln löslich sind.

3.) Arzneimittel nach Anspruch 1 und 2, dadurch gekennzeichnet, daß nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose als Folienbildner verwendet werden.

4.) Arzneimittel nach Anspruch 1 bis 3, dadurch gekennzeichnet, daß Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose als Folienbildner verwendet werden.

5.) Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoffanteil in der Folie etwa 0-60 % beträgt.

6.) Arzneimittel nach Anspruch 1 und 5, dadurch gekennzeichnet, daß der Arzneimittelwirkstoff im Trägermaterial gelöst oder gleichmäßig suspendiert ist.

509884/0988

2432925

7.) Verfahren zur Herstellung eines Arzneimittels in Folienform, dadurch gekennzeichnet, daß man den Wirkstoff und/oder das Trennmittel löst bzw. suspendiert, einen Folienbildner und gegebenenfalls einen Füllstoff einträgt, gegebenenfalls homogenisiert, die Lösung bzw. Suspension auf einer Folienziehmaschine zu einem Ausstrich auszieht und die durch Trocknung des Ausstrichs erhaltene Folie in beliebige Abschnitte (Einheit) aufteilt.

8.) Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß man den Folienbildner in Mengen von etwa 6-20 %, den Füllstoff in Mengen von etwa 0-30 % und das Trennmittel vorzugsweise in Mengen von 0,01-2 % einsetzt.

9.) Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß man als Lösungs- bzw. Suspensionsmittel Wasser und/oder ein organisches Lösungsmittel verwendet.

10.) Verfahren nach Anspruch 7 und 9, dadurch gekennzeichnet, daß das Lösungs- bzw. Suspensionsmittel zu etwa 48-84 % enthalten ist.

11.) Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß die Schichtdicke des Ausstrichs etwa 0,1-2 mm beträgt und die der trockenen Folie etwa 0,05-1 mm beträgt.

509884/0988

12.) Verwendung von in Wasser und/oder organischen Lösungsmitteln löslichen Filmbildnern für die Herstellung von Arzneimittelwirkstoffträgern.

13.) Verwendung nach Anspruch 12 von nichtionogenen, wasserlöslichen Hydroxyalkyläthern der Cellulose.

14.) Verwendung nach Anspruch 12 von Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose.

(51) Int. Cl. 2: A 61 K 9/70

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

DT 24 49 865 A1

(11) Offenlegungsschrift 24 49 865

(21) Aktenzeichen: P 24 49 865.5

(22) Anmeldetag: 17. 10. 74

(43) Offenlegungstag: 29. 4. 76

(30) Unionspriorität:

(32) (33) (31) –

(54) Bezeichnung: Arzneimittel in Folienform mit inkorporiertem Wirkstoff

(61) Zusatz zu: P 24 32 925.7

(71) Anmelder: Schering AG, 1000 Berlin und 4619 Bergkamen

(72) Erfinder: Fuchs, Peter, Dr.; Hilmann, Jürgen; 1000 Berlin

DT 24 49 865 A1

4. 76 609 818/897 10/80

SCHERING AG
Gewerblicher Rechtsschutz

2449865

Berlin, den 16. Oktober 1974

Arzneimittel in Folienform mit
inkorporiertem Wirkstoff

Das Hauptpatent ..... (Patentanmeldung P 24 32 925.7) betrifft Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff zu inneren und äußeren Anwendung.

Es wurde gefunden, daß man Folien mit inkorporiertem Wirkstoff bei gleichbleibender Dicke und gleichmäßiger Wirkstoffverteilung erhält, wenn man Folienbildner verwendet, die in Wasser und/oder organischen Lösungsmitteln löslich sind.

Zur Herstellung des erfindungsgemäßen Arzneimittels in Folienform werden der Wirkstoff und/oder das Trennmittel gelöst bzw. suspendiert, der Folienbildner und gegebenenfalls der Füllstoff eingetragen, gegebenenfalls homogenisiert und die Lösung bzw. Suspension auf einer Folienziehmaschine zu einem Ausstrich ausgezogen. Die durch Trocknung des Ausstrichs erhaltene Folie wird in beliebige Abschnitte (Dosierungseinheiten) aufgeteilt.

In Weiterentwicklung der Erfindung des Hauptpatents wurde nun gefunden, daß man mit einem Ausstrich Folien herstellen kann, in denen nebeneinander unterschiedliche Wirkstoffe und/oder

609818/0897

verschiedene Wirkstoffkonzentrationen inkorporiert sind. Mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, können unterschiedliche Lösungen bzw. Suspensionen ohne Vermischen zu einem zusammenhängenden Ausstrich ausgezogen werden. Die Breite und die Dicke des Ausstrichs ist für jede Kammer separat einstellbar. Gewünschtenfalls können Zonen (Streifen) mit unterschiedlichen Wirkstoffen bzw. verschiedenen Konzentrationen durch unterschiedliche Farbstoffe sichtbar gemacht werden. Durch Trocknung des nassen Ausstrichs wird eine Folie erhalten, die bei entsprechender Teilung, zum Beispiel durch Perforation, Einheiten mit verschiedenen Wirkstoffen und/oder Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff liefert. Folien mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen werden zur Herstellung von Mehrphasenpräparaten benötigt, beispielsweise zur Herstellung von Präparaten zur Konzeptionsverhütung.

Durch die Möglichkeit der räumlichen Trennung von miteinander inkompatibler Wirkstoffe in einer Folieneinheit wird die Stabilität der einzelnen Wirkstoffe verbessert.

Die Erfindung betrifft demnach Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff gemäß Hauptpatent ..... (Patentanmeldung P 24 32 925.7), dadurch

- 3 -

gekennzeichnet, daß in einer Folie für mehrere Dosierungseinheiten nebeneinander unterschiedliche Wirkstoffe und/oder verschiedene Wirkstoffkonzentrationen inkorporiert sind.

Erfindungsgemäß werden Folienbildner verwendet, die in Wasser oder in organischen Lösungsmitteln löslich sind. Bevorzugt geeignet sind Folienbildner, die sich sowohl in Wasser als auch in organischen Lösungsmitteln lösen.

Als Folienbildner kommen zum Beispiel in Betracht: Poly-N-Vinylpyrrolidon, Vinylpyrrolidon-Vinylacetat, Methyl- und Äthylcellulose, vorzugsweise jedoch nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose, wie Hydroxypropylcellulose, Hydroxyäthylcellulose und Methylhydroxypropylcellulose.

Dem Folienbildner können Füllstoffe und Wirkstoffe und zweckmäßigerweise eine geringe Menge eines Trennmittels zugesetzt werden.

Geeignete Trennmittel sind u.a. Polyoxyäthylenpolyoxypropylenpolymeres (PLURONIC F 68 (R)), Polyoxylstearate, Alkyl- bzw. Acylsubstituierte Polyadditionsprodukte des Äthylenoxids, zum Beispiel CREMOPHOR EL (R), Silikone und Silkontrennemulsionen, Glycerin, Propylenglykol und Metallseifen.

- 4 -

Vorstand: Dr. Christian Bruhn · Hans-Jürgen Hamann · Dr. Heinz Hannse · Karl Otto Mittelstenscheid · Dr. Gerhard Raspé · Dr. Horst Witzel
Stellv.: Dr. Herbert Asmis
Vorsitzender des Aufsichtsrats: Dr. Eduard v. Schwartzkoppen
Sitz der Gesellschaft: Berlin und Bergkamen
Handelsregister: AG Charlottenburg 93 HRB 283 u. AG Kamen HRB 0061

Postanschrift: SCHERING AG · D-1 Berlin 65 · Postfach 65 03 11
Postscheck-Konto: Berlin-West 11 75-101, Bankleitzahl 100 100 10
Berliner Commerzbank AG, Berlin, Konto-Nr. 108 7006 00, Bankleitzahl 100 400 00
Berliner Disconto-Bank AG, Berlin, Konto-Nr. 241/5008, Bankleitzahl 100 700 00
Berliner Handels-Gesellschaft – Frankfurter Bank –, Berlin,
Konto-Nr. 14-362, Bankleitzahl 100 202 00

Als Füllstoffe sind zum Beispiel Cellulose, Zucker, wie zum Beispiel Lactose, Dextrose, Rohrzucker usw., Stärken, mehrwertige Alkohole, wie zum Beispiel Mannit, Calciumcarbonat, Calciumphosphat, Talkum, Geschmacks- und Farbstoffe geeignet. Farbstoffe werden in löslicher Form oder als Pigmente eingesetzt. Die Füllstoffe können teilweise oder vollständig durch Wirkstoffe ersetzt werden. Werden lösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine transparente, glatte Folie, werden unlösliche Füll- bzw. Wirkstoffe verwendet, entsteht eine weiße oder farbige, papierartige Folie.

Erfindungsgemäß können alle in der Human- und Veterinärmedizin verwendeten Wirkstoffe eingesetzt werden. Für die innere Anwendung kommt insbesondere die orale Verabreichung infrage. Unter der äußeren Anwendung sollen insbesondere die topikale Verabreichung auf der Haut und in Körperhöhlungen wie Nase, Ohr, Vagina usw. verstanden werden. Als Wirkstoffe seien beispielsweise genannt: Gestagene, Östrogene, Gemische aus Gestagenen und Östrogenen, Tranquilizer, Antidiabetika, Sulfonamide, Antibiotika, Trichomonadenmittel, Entzündungshemmer, wie zum Beispiel Corticoide, usw.

Der Arzneimittelwirkstoff kann im Trägermaterial gelöst oder gleichmäßig suspendiert vorliegen. Der Wirkstoffanteil in der

Folie kann etwa 0-60 % betragen. Als Einzeldosis (Einheit) werden Flächen geschnitten bzw. perforiert, die Wirkstoffmengen enthalten wie sie üblicherweise auch in Tabletten, Dragees, Salben, Zäpfchen usw. enthalten sind. So kann die Wirkstoffmenge pro Einzeldosis je nach Anwendungsart beliebig hoch sein und zwischen etwa 1 µg und 0,5 g betragen, wobei die untere und obere Dosis leicht unter- oder überschritten werden können. Selbstverständlich können auch wirkstofffreie Träger (Placebos) hergestellt werden.

Zur Herstellung der Folien mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen werden zwei oder mehrere unterschiedliche Lösungen bzw. Suspensionen aus Wirkstoff und/oder Trennmittel, Folienbildner und gegebenenfalls Füllstoff hergestellt, die unterschiedlichen Lösungen bzw. Suspensionen mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, auf einer Folienziehmaschine zu einem Ausstrich ausgezogen und die durch Trocknung des Ausstrichs erhaltene Folie in Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentration bzw. Einheiten ohne Wirkstoff geteilt.

Pro Lösung bzw. Suspension wird der Folienbildner in Gewichtsmengen von etwa 6-20 %, der Füllstoff in Gewichtsmengen von etwa 0-30 % und das Trennmittel vorzugsweise in Gewichtsmengen von 0,01-2 % eingesetzt.

- 6 -

Das Lösungs- bzw. Suspensionsmittel ist zu etwa 48-84 % (W/W) enthalten und besteht aus Wasser und/oder einem oder mehreren organischen Lösungsmitteln. Als organische Lösungsmittel kommen physiologisch verträgliche Lösungsmittel oder solche Lösungsmittel in Betracht, die bei der Trocknung bis auf einen physiologisch unbedenklichen Rest entfernt werden können. Solche Lösungsmittel sind zum Beispiel Äthylalkohol, Isopropanol, Methylenchlorid usw. und ihre Mischungen. Wasser und Äthylalkohol bzw. Gemische aus Wasser und Äthylalkohol werden bevorzugt angewandt.

Die Schichtdicke des nassen Ausstrichs beträgt etwa 0,1 bis 2 mm und die der trockenen Folie etwa 0,05 bis 1 mm, vorzugsweise 0,07 bis 0,3 mm.

Die Erfindung betrifft auch die Verwendung von in Wasser und/oder organischen Lösungsmitteln löslichen Folienbildnern für die Herstellung von Arzneimittelwirkstoffträgern in Folienform mit inkorporiertem Wirkstoff, wobei in einer Folie für mehrere Dosierungseinheiten unterschiedliche Wirkstoffe und/oder ver-

schiedene Wirkstoffkonzentrationen inkorporiert sind, insbesondere die Verwendung von nichtionogenen, wasserlöslichen Hydroxyäthern der Cellulose, wie Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose.

Das Verfahren zur Herstellung des Arzneimittels in Folienform in einem Arbeitsgang (kontinuierliches Verfahren) bietet den Vorteil, daß der Wirkstoff homogen verteilt in dem Wirkstoffträger vorliegt. Durch die Konzentration des Wirkstoffs im Träger, die Dicke der Folie und die Fläche der Folie kann man die Einzeldosis sehr einfach variieren.

Aus der belgischen Patentschrift Nr. 637 363 ist ein diskontinuierliches Verfahren der gesonderten Herstellung einer Folie und der nachträglichen Aufbringung des Wirkstoffes bekannt: Das bekannte Verfahren hat den Nachteil, daß die Dosierungsgenauigkeit nicht sehr gut ist und daß der nur oberflächlich gebundene Wirkstoff leicht abgelöst wird. Außerdem enthält die dort beschriebene Folie Carboxymethylcellulose, die den Wirkstoff teilweise einschließt und nur verzögert oder überhaupt nicht freigibt.

Die beispielsmäßig beschriebenen Folien sind vorwiegend für die orale Applikation geeignet.

- 8 -

Beispiel 1

Zweiphasenpräparat

Teil 1 : 21 Einheiten mit Wirkstoff

Teil 2 : 7 Einheiten ohne Wirkstoff

Herstellung für 3000 Einheiten Teil 1

0,75 g D-Norgestrel,
0,15 g Äthinylöstradiol und
0,54 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
237,00 g Äthylalkohol und
12,00 g Wasser gelöst. In diese Lösung werden
44,28 g Hydroxypropylcellulose und
44,28 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2

0,18 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
79,00 g Äthylalkohol und
4,00 g Wasser gelöst. In diese Lösung werden
14,91 g Hydroxypropylcellulose und
14,91 g Cellulose eingetragen und gegebenenfalls homogenisie

Vorstand: Dr. Christian Bruhn · Hans-Jürgen Hamann · Dr. Heinz Hannse
Karl Otto Mittelstenscheid · Dr. Gerhard Raspé · Dr. Horst Witzel
Stellv.: Dr. Herbert Asmis
Vorsitzender des Aufsichtsrats: Dr. Eduard v. Schwartzkoppen
Sitz der Gesellschaft: Berlin und Bergkamen
Handelsregister: AG Charlottenburg 93 HRB 203 u. AG Kamen HRB 0061

Postanschrift: SCHERING AG · D-1 Berlin 65 · Postfach 65 03 11
Postscheck-Konto: Berlin-West 11 75-101, Bankleitzahl 100 100 10
Berliner Commerzbank AG, Berlin, Konto-Nr. 108 7006 00, Bankleitzahl 100 400 00
Berliner Disconto-Bank AG, Berlin, Konto-Nr. 241/5009, Bankleitzahl 100 700 00
Berliner Handels-Gesellschaft – Frankfurter Bank –, Berlin,
Konto-Nr. 14 3?2, Bankleitzahl 100 2?2 00

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Zweikammer-Spezialrakel (Breite der Kammern: 1 = 54 mm; 2 = 18 mm) zu einem Ausstrich von 0,5 mm ausgezogen und anschließend getrocknet. Bei entsprechender Teilung in Einheiten zu 18 x 18 mm, zum Beispiel durch Perforation, können über die Breite der Folie drei Einheiten mit Wirkstoff und eine wirkstofffreie Einheit abgeteilt werden. Aus dem Folienband lassen sich nun beliebig viele Abschnitte im Verhältnis von drei Einheiten mit Wirkstoff und einer Einheit ohne Wirkstoff herstellen.

Zusammensetzung für je eine Einheit:

Teil 1 (wirkstoffhaltig)		Teil 2 (wirkstofffrei)
0,25 mg	D-Norgestrel	-
0,05 mg	Äthinylöstradiol	-
14,76 mg	Hydroxypropylcellulose	14,91 mg
14,76 mg	Cellulose	14,91 mg
0,18 mg	Polyoxyäthylenpolyoxypropylenpolymeres	0,18 mg
30,00 mg	Gewicht pro Einheit	30,00 mg

Fläche pro Einheit: ca. 3 cm^2.

Aussehen: weiß.

Beispiel 2

Dreiphasenpräparat (Zweiwirkstoffstufenpräparat)

Teil 1 : 11 Einheiten mit 0,05 mg D-Norgestrel
0,05 mg Äthinylöstradiol

Teil 2 : 10 Einheiten mit 0,125 mg D-Norgestrel
0,050 mg Äthinylöstradiol

Teil 3 : 7 Einheiten ohne Wirkstoff

Herstellung für 1100 Einheiten Teil 1:

0,055 g D-Norgestrel,
0,055 g Äthinylöstradiol und
0,198 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
86,900 g Äthylalkohol und
4,400 g Wasser gelöst. In diese Lösung werden
16,346 g Hydroxypropylcellulose und
16,346 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2:

0,125 g D-Norgestrel,
0,050 g Äthinylöstradiol und
0,180 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus

79,000 g Äthylalkohol und
4,000 g Wasser gelöst. In diese Lösung werden
14,823 g Hydroxypropylcellulose und
14,822 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 700 Einheiten Teil 3:

0,189 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
82,950 g Äthylalkohol und
4,200 g Wasser gelöst. In diese Lösung werden
15,656 g Hydroxypropylcellulose und
15,655 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Dreikammer-Spezialrakel (Breite pro Kammer 18 mm) zu einem Ausstrich ausgezogen und getrocknet. Bei entsprechender Teilung, zum Beispiel durch Perforation, zu Einheiten von 18 x 18 mm für Teil 1, 18 x 19,8 mm für Teil 2 und 18 x 28 mm für Teil 3 können über die Breite der Folie drei Einheiten mit unterschiedlichem Wirkstoffgehalt abgeteilt werden. Aus dem Folienband lassen sich Präparate mit 11 Einheiten Teil 1, 10 Einheiten Teil 2 und 7 Einheiten Teil 3 abtrennen.

Zusammensetzung pro Einheit:

Teil 1	Teil 2	Teil 3	Inhaltsstoffe
0,050 mg	0,125 mg	-	D-Norgestrel
0,050 mg	0,050 mg	-	Äthinylöstradiol
0,180 mg	0,180 mg	0,270 mg	Polyoxyäthylenpolyoxypropylenpolymeres
14,860 mg	14,823 mg	22,366 mg	Hydroxypropylcellulose
14,860 mg	14,822 mg	22,364 mg	Cellulose
30,000 mg	30,000 mg	45,000 mg	Gewicht pro Einheit
ca. 3 cm^2	ca. 3,5 cm^2	ca. 5 cm^2	Fläche pro Einheit
weiß	weiß	weiß	Aussehen

B e i s p i e l 3

Dreiphasenpräparat

Teil 1 : 11 Einheiten mit 0,05 mg D-Norgestrel
0,05 mg Äthinylöstradiol

Teil 2 : 10 Einheiten mit 0,125 mg D-Norgestrel
0,050 mg Äthinylöstradiol

Teil 3 : 7 Einheiten mit 50,00 mg Eisen(II)fumarat

Herstellung für 1100 Einheiten Teil 1:

0,066 g Lebensmittelgelb Nr. 2 (Tartrazin; E 102) werden in
4,400 g Wasser gelöst und anschließend in
86,900 g Äthylalkohol eingetragen. In dieser Lösung werden
0,055 g D-Norgestrel,
0,055 g Äthinylöstradiol und
0,198 g Polyoxyäthylenpolyoxypropylenpolymeres gelöst.
In diese Lösung werden
16,313 g Hydroxypropylcellulose und
16,313 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 1000 Einheiten Teil 2:

0,065 g Lebensmittelorange Nr. 2 (Sunset Yellow; E 110) werden in
4,000 g Wasser gelöst und anschließend in
79,000 g Äthylalkohol eingetragen. In dieser Lösung werden
0,125 g D-Norgestrel,
0,050 g Äthinylöstradiol und
0,180 g Polyoxyäthylenpolyoxypropylenpolymeres gelöst.
In diese Lösung werden
14,790 g Hydroxypropylcellulose und
14,790 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 700 Einheiten Teil 3:

0,042 g Saccharin,

0,042 g Sahne-Essenz und

0,406 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus

55,300 g Äthylalkohol und

2,800 g Wasser gelöst. In diese Lösung werden

35,000 g Eisen(II)fumarat,

17,500 g Hydroxypropylcellulose,

5,950 g Kakao und

4,060 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Die so erhaltenen Suspensionen werden auf einem geeigneten Folienziehgerät mit einem Dreikammer-Spezialrakel (Breite pro Kammer 18 mm) zu einem Ausstrich ausgezogen und anschließend getrocknet. Bei entsprechender Teilung, zum Beispiel durch Perforation, zu Einheiten von 18 x 18 mm für Teil 1, 18 x 19,8 mm für Teil 2 und 18 x 28 mm für Teil 3 können über die Breite der Folie drei Einheiten mit unterschiedlichem Wirkstoffgehalt abgeteilt werden. Aus dem Folienband lassen sich Präparate mit 11 Einheiten Teil 1, 10 Einheiten Teil 2 und 7 Einheiten Teil 3 abtrennen.

Zusammensetzung pro Einheit:

Teil 1	Teil 2	Teil 3	Inhaltsstoffe
0,050 mg	0,125 mg	-	D-Norgestrel
0,050 mg	0,050 mg	-	Äthinylöstradiol
-	-	50,000 mg	Eisen(II)fumarat
0,180 mg	0,180 mg	0,580 mg	Polyoxyäthylenpolyoxypropylen-polymeres
0,060 mg	-	-	Lebensmittelgelb Nr. 2
-	0,065 mg	-	Lebensmittelorange Nr. 2
14,830 mg	14,790 mg	25,000 mg	Hydroxypropylcellulose
14,830 mg	14,790 mg	5,800 mg	Cellulose
-	-	8,500 mg	Kakao
-	-	0,060 mg	Saccharin
-	-	0,060 mg	Sahne-Essenz
30,000 mg	30,000 mg	90,000 mg	Gewicht pro Einheit
ca.3 cm^2	ca.3,5 cm^2	ca.5 cm^2	Fläche pro Einheit
gelb	orange	braun	Aussehen

- 16 -

Patentansprüche

1.) Arzneimittelwirkstoffträger in Folienform mit inkorporiertem Wirkstoff gemäß Hauptpatent.....(Patentanmeldung P 24 32 925.7), dadurch gekennzeichnet, daß in einer Folie für mehrere Dosierungseinheiten nebeneinander unterschiedliche Wirkstoffe und/oder verschiedene Wirkstoffkonzentrationen inkorporiert sind.

2.) Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß sie in Wasser oder organischen Lösungsmitteln lösliche Folienbildner enthalten.

3.) Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß die Folienbildner in Wasser und in organischen Lösungsmitteln löslich sind.

4.) Arzneimittel nach Anspruch 1 bis 3, dadurch gekennzeichnet, daß nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose als Folienbildner verwendet werden.

5.) Arzneimittel nach Anspruch 1 bis 4, dadurch gekennzeichnet, daß Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose als Folienbildner verwendet werden.

- 17 -

6.) Arzneimitel nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoffanteil in der Folie etwa 0-60 % beträgt.

7.) Arzneimittel nach Anspruch 1 und 6, dadurch gekennzeichnet, daß der Arzneimittelwirkstoff im Trägermaterial gelöst oder gleichmäßig suspendiert ist.

8.) Verfahren zur Herstellung von Folien mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen, dadurch gekennzeichnet, daß man zwei oder mehrere unterschiedliche Lösungen bzw. Suspensionen aus Wirkstoff und/oder Trennmittel, Folienbildner und gegebenenfalls Füllstoff gemäß Hauptpatent.....(Patentanmeldung P 24 32 925.7) herstellt, die unterschiedlichen Lösungen bzw. Suspensionen mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, auf einer Folienziehmaschine zu einem Ausstrich auszieht und die durch Trocknung des Ausstrichs erhaltene Folie in Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff teilt.

9.) Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß man den Folienbildner in Mengen von etwa 6-20 %, den Füllstoff in Mengen von etwa 0-30 % und das Trennmittel vorzugsweise in Mengen von 0,01-2 % einsetzt.

10.) Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß man als Lösungs- bzw. Suspensionsmittel Wasser und/oder ein organisches Lösungsmittel verwendet.

11.) Verfahren nach Anspruch 8 und 10, dadurch gekennzeichnet, daß das Lösungs- bzw. Suspensionsmittel zu etwa 48-84 % enthalten ist.

12.) Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß die Schichtdicke des Ausstrichs etwa 0,1-2 mm beträgt und die der trockenen Folie etwa 0,05-1 mm beträgt.

13.) Verwendung von in Wasser und/oder organischen Lösungsmitteln löslichen Folienbildnern für die Herstellung von Arzneimittelwirkstoffträgern nach Anspruch 1.

14.) Verwendung nach Anspruch 13 von nichtionogenen, wasserlöslichen Hydroxyalkyläthern der Cellulose.

15.) Verwendung nach Anspruch 13 von Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose.

Vorstand: Dr. Christian Bruhn · Hans-Jürgen Hamann · Dr. Heinz Hannse
Karl Otto Mittelstenscheid · Dr. Gerhard Raspé · Dr. Horst Witzel
Stellv.: Dr. Herbert Asmis
Vorsitzender des Aufsichtsrats: Dr. Eduard v. Schwartzkoppen
Sitz der Gesellschaft: Berlin und Bergkamen
Handelsregister: AG Charlottenburg 93 HRB 283 u. AG Kamen HRB 0061

Postanschrift: SCHERING AG · D-1 Berlin 65 · Postfach 65 03 11
Postscheck-Konto: Berlin-West 11 75-101, Bankleitzahl 100 100 10
Berliner Commerzbank AG, Berlin, Konto-Nr. 108 7006 00, Bankleitzahl 100 400 00
Berliner Disconto-Bank AG, Berlin, Konto-Nr. 241/5008, Bankleitzahl 100 700 00
Berliner Handels-Gesellschaft – Frankfurter Bank –, Berlin,
Konto-Nr. 14-362, Bankleitzahl 100 202 00

83 DE IV 26520

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

(12) **Offenlegungsschrift**

(11) **DE 3630603 A1**

(51) Int. Cl. 4:
A 61 K 9/70
A 61 K 9/00
A 61 J 3/00
D 21 H 5/00
// C08J 5/18,7/04

(21) Aktenzeichen: P 36 30 603.7
(22) Anmeldetag: 9. 9. 86
(43) Offenlegungstag: 10. 3. 88

DE 3630603 A1

(71) Anmelder:
Desitin Arzneimittel GmbH, 2000 Hamburg, DE

(74) Vertreter:
Frhr. von Uexküll, J., Dipl.-Chem. Dr.rer.nat.; Graf zu Stolberg-Wernigerode, U., Dipl.-Chem. Dr.rer.nat.; Suchantke, J., Dipl.-Ing.; Huber, A., Dipl.-Ing.; von Kameke, A., Dipl.-Chem. Dr.rer.nat.; Voelker, I., Dipl.-Biol., Pat.-Anwälte, 2000 Hamburg

(72) Erfinder:
Schmidt, Wolfgang, Dr., 2000 Hamburg, DE

Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder dergleichen sowie Verfahren zu deren Herstellung

Eine neue Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder andere Wirkstoffe besteht aus einem Trägermaterial in Form eines Releasepapiers, eines Releasefilms oder einer Releasefolie, die einseitig mit einer wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist. Die abgezogenen wirkstoffhaltigen Abschnitte eignen sich insbesondere als orale Arzneimittel.

DE 3630603 A1

BUNDESDRUCKEREI 01 88 708 870/445 8/70

Patentansprüche

1. Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder dergleichen in Form eines folienförmigen Trägermaterials mit einer wirkstoffhaltigen Beschichtung, **dadurch gekennzeichnet,** daß das Trägermaterial ein Releasepapier, ein Releasefilm oder eine Releasefolie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

2. Darreichungsform nach Anspruch 1, dadurch gekennzeichnet, daß das Trägermaterial ein silicon- oder wachsbeschichtetes Releasepapier ist.

3. Darreichungsform nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die wirkstoffhaltige Beschichtung durch Stanzung in Dosiseinheiten vorzerteilt ist.

4. Darreichungsform nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die Beschichtung einen oder mehrere Arzneimittelwirkstoffe enthält.

5. Darreichungsform nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Beschichtung wasserlösliche Quellstoffe als polymere Filmbildner und gegebenenfalls Weichmacher enthält.

6. Darreichungsform nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß sie zur Viskositätseinstellung polymere Quellstoffe enthält, welche gleichzeitig als Haftvermittler dienen können.

7. Darreichungsform nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufgebracht ist.

8. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß miteinander inkompatible Wirkstoffe in getrennten Schichten nacheinander auf das Trägermaterial aufgebracht sind.

9. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten angeordnet ist, welche die Wirkstoff-Resorption im Magen/Darmtrakt in an sich bekannter Weise steuern.

10. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß über der Wirkstoffschicht eine weitere Schicht aufgebracht ist, die den Wirkstoff gegen Berührung mit der Atmosphäre und/oder gegen Licht schützt.

11. Darreichungsform nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß die Rückseite des Trägermaterials mit die Wirkstoffzusammensetzung und/oder deren Einnahme betreffenden Informationen bedruckbar ist.

12. Verfahren zur Herstellung der Arzneimitteldarreichungsform der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß man eine wirkstoffhaltige Zusammensetzug mit Hilfe von Walzen auf die nichthaftend ausgerüstete Seite eines Releasepapiers, eines Releasefilms oder einer Releasefolie aufbringt.

Beschreibung

Arzneimittel können in Form von Pulvern, Tropflösungen oder Säften oral verabreicht werden. Da bei diesen Abgabeformen eine genaue Dosierung jedoch schwierig ist, werden vom Hersteller dosierte Applikationsformen wie Tabletten, Dragees oder Kapseln generell bevorzugt. Auch Reagentien und andere Wirkstoffe, z.B. Süßstoffe, werden für eine genaue dosierte Anwendung häufig tablettiert. Die Herstellungstechnik für Tabletten, Dragees, Kapseln und dergleichen ist zwar weitgehend ausgereift, doch sind eine Reihe von systembedingten Nachteilen nicht zu übersehen.

Für niedrig dosierte Wirkstoffe muß ein großer Anteil an Hilfsstoffen zugesetzt werden, um zu einer handhabbaren Größe der Einzeldosis zu gelangen. Weiterhin ist eine genaue Kennzeichnung einzelner Tabletten oder Dragees praktisch nicht möglich. Es haben sich deshalb Durchdrückpackungen durchgesetzt, welche eine Mehrzahl von Tabletten, Dragees oder auch Kapseln enthalten und welche mit den notwendigen Informationen, insbesondere dem Namen des Präparates bedruckt sind. Die Herstellung solcher Verpackungen erfordert naturgemäß einen zusätzlichen Arbeitsgang und es werden Umverpackungen in Form von Faltschachteln benötigt, welche ein beträchtliches Leervolumen aufweisen und dadurch zusätzlich Lagerraum beanspruchen. Ein besonders gravierender Nachteil von Dragees und Kapseln besteht darin, daß eine Zerteilung praktisch unmöglich ist, die kleinste Dosis somit vorgegeben ist. Auch bei Tabletten ist eine genaue Zerteilung schwierig, lediglich größere Tabletten mit einer Kerbe als Sollbruchstelle lassen sich allenfalls teilen, wobei häufig ungleichgroße Bruchstücke entstehen.

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekanntgeworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-PS 6 37 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Aus den DE-OS 24 32 925 und 24 49 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Auch die so erhaltenen wirkstoffhaltigen Folien lassen sich zur Dosierung durch Perforation in einzelne Abschnitte aufteilen. Diese Vorschläge haben keinen Eingang in die Praxis gefunden und in dem neuesten Lehrbuch der "Arzneiformenlehre" von P.H. List, 4. Auflage, Stuttgart, 1985, finden sie keine Erwähnung. Dies beruht ersichtlich darauf, daß die bislang bekanntgewordenen Vorschläge es nicht ermöglichen, die geforderte Gewichtskonstanz und gleichmäßige Wirkstoffverteilung zu erreichen, welche heute gefordert werden. Die Ph. Eur. setzt zum Beispiel Maßstäbe für die Gleichförmigkeit des Gewichtes einzeldosierter Arzneiformen, wobei diese dem jeweiligen Durchschnittsgewicht entsprechend nach höchstzulässigen Abweichungen in % gestaffelt sind. Die Forderung liegt im allgemeinen bei +/− 5 bis max. 10%. Entsprechende Werte für feste Arzneiformen bestehen auch hinsichtlich anderer Parameter wie Zerfallzeit und Lösungsgeschwindigkeit.

Die oben erwähnten Vorschläge des Standes der Technik führen zu Produkten ungenügender Akzeptanz durch die Patienten (Papierabschnitte lassen sich nur schlecht einnehmen) und erlauben keine exakte Dosierung pro Flächeneinheit, wie sie unbedingt gefordert werden muß. Bei Inkorporieren des Wirkstoffes in eine Folie bereitet nicht nur die genaue Dosierung Schwierigkeiten, sondern ein wesentlicher weiterer Nachteil besteht darin, daß für jeden Wirkstoff eine entsprechen

de Folie gesondert hergestellt werden muß, so daß die Wirtschaftlichkeit des Herstellungsverfahrens nicht gegeben ist.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine "zweidimensionale" Darreichungs- und Dosierungsform zu schaffen, welche die genannten Nachteile nicht aufweist, sich leicht herstellen läßt und mit großer Flexibilität an die Anforderungen des Marktes und verschiedener Wirkstoffe angepaßt werden kann.

Gegenstand der Erfindung ist eine Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder dergleichen in Form eines folienförmigen Trägermaterials mit einer wirkstoffhaltigen Beschichtung, wobei diese Darreichungsform dadurch gekennzeichnet ist, daß das Trägermaterial ein Release-Papier, ein Release-Film oder eine Release-Folie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

Die erfindungsgemäße Darreichungsform weist mehrere wesentliche Vorteile auf:

- Da der Träger im Gegensatz zu den vorbekannten Ausführungsformen keinen Teil der Darreichungsform bildet, kann er die erforderliche Festigkeit aufweisen, ohne die Akzeptanz des Arzneimittels durch Patienten zu beeinträchtigen,
- die wirkstoffhaltige Schicht kann bei hochwirksamen Arzneimitteln sehr dünn sein, da das Trägermaterial die mechanische Festigkeit gewährleistet,
- mit Hilfe moderner Auftragverfahren läßt sich die wirkstoffhaltige Beschichtung mit konstanter Schichtdicke aufbringen, so daß die erforderlichen Toleranzen eingehalten werden können,
- falls eine Sterilisierung erforderlich ist, kann diese wegen der geringen Schichtdicke problemlos mittels Strahlenbehandlung erreicht werden,
- der Träger läßt sich auf der Vorder- und insbesondere der Rückseite mit verschiedenen Informationen bedrucken,
- aufgrund der relativ großen Fläche von beispielsweise 4 bis 10 cm^2 lassen sich ausführliche Informationen für den Benutzer auf das unbeschichtete Trägermaterial oder auch nachträglich aufdrucken,
- die Dosiseinheiten lassen sich durch entsprechende Vorzerteilung flexibel gestalten, so daß für verschiedenen Dosierungen (z.B. für Erwachsene und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

Mit den vorbekannten Darreichungsformen in Folienform hat die erfindungsgemäße Darreichungsform darüber hinaus den Vorteil des äußerst geringen Platzbedarfes gemeinsam. Statt Faltschachteln können daher beispielsweise Taschen oder Beutel aus Kunststoffolie oder kunststoffbeschichtetem Papier verwendet werden, in welche das Produkt eingesiegelt wird, ähnlich wie feuchte Erfrischungstücher.

Als Trägermaterialien eignen sich die verschiedensten Materialien, beispielsweise Papiere mit einem Gewicht von etwa 80 bis 120, vorzugsweise 100 g/m^2, Kunststoffilme bzw. -folien auf Basis von Polyethylen, Polyvinylchlorid, Polyvinylidenchlorid, Polyester und anderen indifferenten Polymeren oder dünne Metallfolien, beispielsweise solche aus Aluminium. Bevorzugt werden siliconisierte Papiere, welche in unterschiedlichen Qualitäten im Handel erhältlich sind, und welche insbesondere zur Abdeckung von selbstklebenden Produkten wie Pflastern, Klebebändern oder Haftetiketten Verwendung finden. Die an sich auch geeigneten mit Wachs oder Paraffin beschichten Release-Papiere sind dagegen in der Praxis weitgehend durch die mit inerten Siliconen beschichteten Papiere ersetzt worden. Bei einem Auftrag der wirkstoffhaltigen Beschichtung auf nur eine Seite der Trägerfolie reicht es aus, wenn nur diese mit einer nicht haftenden Beschichtung versehen ist. Die Rückseite sollte dagegen vorzugsweise so beschaffen sein, daß sie mit Informationen unterschiedlicher Art gut und dauerhaft bedruckbar ist.

Die Möglichkeit der vorder- und rückseitigen Bedruckung ist ein besonderer Vorteil der erfindungsgemäßen Darreichungsform. Beispielsweise können die Kennzeichnung, Angaben über die Inhaltsstoffe sowie Dosierungsangaben aufgedruckt werden. Gegebenenfalls läßt sich sogar der ganze Inhalt eines Beipackzettels rückseitig aufdrucken mit der Folge, daß ein separater Beipackzettel, der auch häufig verlorengeht, überflüssig wird. Bei Arzneimitteln, welche regelmäßig genommen werden müssen, beispielsweise bei hormonalen Contrazeptiva, kann der gesamte Verabreichungsplan so angebracht werden, daß eine einfache Einnahmekontrolle gewährleistet ist. Da die einzelnen Dosiseinheiten von dem Träger abgezogen werden, bleibt dieser bis zum vollständigen Aufbrauch des Arzneimittels erhalten und es gehen keine der aufgedruckten Informationen verloren.

Für die wirkstoffhaltige Beschichtung findet vorzugsweise eine wäßrige Beschichtungsmasse Verwendung, die physiologisch inert ist und deren Einzelkomponenten für Arzneimittel bzw. Lebensmittel geeignet sind. Dabei handelt es sich zum einen um wasserlösliche Quellstoffe in der Art polymerer Filmbildner, vorzugsweise Gelatine, Zellulosen oder Hemizellulosen, quellende oder lösliche Stärken. Vorzugsweise werden ferner Weichmacher zugesetzt, insbesondere mehrwertige Alkohole wie Glycerin oder Sorbitol. Zur Einstellung der erwünschten Viskosität der Beschichtungsmasse, welche etwa die Konsistenz eines Schleimes aufweist, finden polymere Quellstoffe Verwendung, vorzugsweise Alginate, Pectine, Chitine, Lecithine oder Polyethylenglykole. Diese letzteren Stoffe können gleichzeitig als Haftvermittler dienen. Andererseits können auch wasserlösliche Gumme oder Gummi arabicum zugesetzt werden, um die Haftung der Beschichtung auf dem Trägermaterial zu verbessern. Schließlich können noch Konservierungsmittel wie z.B. p-Hydroxybenzoesäureester, Farbstoffe (Lebensmittelfarbstoffe), Pigmente wie Titandioxid oder Aroma- und Süßstoffe zugesetzt werden.

Coatingmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10000 cPs haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

Folgende Rahmenrezeptur hat sich bewährt:

Gelatine	8 bis 10 g
Stärke	3 bis 8 g

Glycerin	1 bis 2 g
Wasser	30 bis 50 g

In dieser Grundmasse wird der Wirkstoff gelöst bzw. dispergiert. Im Fall der Verwendung einer Dispersion muß der Wirkstoff für eine gleichmäßige Verteilung äußerst feinteilig sein. Vorzugsweise liegt die mittlere Teilchengröße im Bereich von etwa 1 bis 20 µm.

Die gewünschte Dosis des Wirkstoffes und die angestrebte Fläche der Dosiseinheiten bestimmen letztlich die Dicke der Schicht, wobei der Feuchtigkeitsgehalt der Beschichtungsmasse und der fertigen Beschichtung zu berücksichtigen sind.

Im Rahmen der Erfindung ist es auch möglich, die Beschichtungsmasse zu einer wirkstoffhaltigen Folie zu verarbeiten und diese anschließend, gegebenenfalls unter Verwendung eines physiologisch einsetzbaren inerten Klebstoffes, auf das Trägermaterial aufzukaschieren. Diese Ausführungsform kommt insbesondere dann in Betracht, wenn die wirkstoffhaltige Beschichtung eine größere Dicke aufweisen soll, so daß die Verarbeitung zu einer Folie möglich und sinnvoll ist.

Die erfindungsgemäße Darreichungsform ist besonders geeignet für Arzneimittel, welche niedrig dosiert verabreicht werden, d.h. bei welchen die Einzeldosis für die orale Applikation zwischen 0 mg (Placebo) und etwa 20 mg liegt. Geeignete Arzneimittelwirkstoffe finden sich in allen Bereichen der oralen Therapie; hervorzuheben sind u.a. Analeptika, Antibiotika, Antidiabetika, Antiemetika, Antiepileptika, Antihypertonika, Cortikoide, Geriatrika, Hypnotika, Cardiaka, Hytostatika und Biowirkstoffe.

Die Beschichtung kann einen oder mehrere Arzneimittelwirkstoffe enthalten. Falls bei Verwendung mehrerer Wirkstoffe diese nicht ohne weiteres miteinander verträglich sind, ist es bei der erfindungsgemäßen Darreichungsform möglich, die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufzubringen und die Wirkstoffe dadurch voneinander zu trennen, wobei erforderlichenfalls eine wirkstofffreie Zwischenschicht vorgesehen werden kann. Weiterhin ist es möglich, über der wirkstoffhaltigen Schicht noch eine weitere Schutzschicht vorzusehen, welche den/die Wirkstoff(e) gegen eine Berührung mit der Atmosphäre und/oder gegen Licht schützt. In diesen Fällen muß die Schutzschicht demgemäß luft- und feuchtigkeitsundurchlässig und/oder durch Zusatz entsprechender Farbstoffe bzw. Pigmente lichtundurchlässig sein.

Weiterhin kann durch entsprechenden Aufbau der Beschichtung die Wirkstoffabgabe nach Verabreichung des Arzneimittels gesteuert werden. Beispielsweise ist es möglich, eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten anzuordnen, welche die Wirkstoffresorption im Magen/Darmtrakt in an sich bekannter Weise steuern. Dabei kann die Wirkstoffschicht z.B. zwischen zwei säureunlöslichen Schichten angeordnet werden, so daß bei Verabreichung der Magen passiert wird und die Resorption erst im Darmtrakt erfolgt. In ähnlicher Weise können unterschiedliche Wirkstoffe in verschiedenen Schichten übereinander auf die Trägerfolie aufgebracht werden, damit die Resorption nacheinander und/oder verzögert erfolgt. Ähnliche pharmakokinetische Effekte lassen sich durch das Einarbeiten (z.B. Suspendieren) von unterschiedlich vorbehandelten mikroverkapselten Wirkstoffen erzielen.

Die Aufbringung der wirkstoffhaltigen Beschichtungen auf den Träger, z.B. ein Release-Papier oder eine Release-Kunststoffolie, erfolgt vorzugsweise mit Hilfe eines Glattwalzen-Beschichtungsverfahrens. Die vorzugsweise auf ca. 60 bis 80°C erwärmte Beschichtungsmasse wird dabei au einem geschlossenen Auftragssystem auf eine beheizte Walze in dünner Schicht übertragen. Mit verzögertem Gleichlauf in bestimmten wählbaren Verhältnissen wird die Masse auf eine parallel angeordnete Walze übertragen, wobei eine Reduzierung der Schichtdicke im Verhältnis 1:2 bis 1:10 erfolgen kann, wodurch gleichzeitig die Toleranzen bei der Auftragung um diese Faktoren verringert werden. Im Gleichlauf erfolgt dann über ein weiteres Walzensystem die Beschichtung des Trägermaterials. Bei einer Anpassung der Wirkstoffbeschichtungsmasse an den Release-Wert des Trägermaterials kann auf den Zusatz eines Klebemittels völlig verzichtet werden. Gegebenenfalls können jedoch auch geeignete Haftvermittler zugesetzt werden.

Bei Aufbringung mehrerer Schichten, wie dies oben bereits beschrieben wurde, werden diese nacheinander aufgebracht, wobei ggf. jede Beschichtung zuvor eine Trocknungsstation durchläuft. Diese kann beispielsweise aus einem temperierten Walzenpaar und einem in Sektionen steuerbaren Trockentunnel bestehen. Nach dem letzten Beschichtungsvorgang wird das beschichtete Material auf Rollen aufgewickelt.

Die wirkstoffhaltige Beschichtung wird anschließend in Dosiseinheiten vorzerteilt, welche ähnlich wie Haftetiketten vom Trägermaterial abziehbar sind. Normalerweise wird diese Vorzerteilung beim Arzneimittelhersteller erfolgen, es ist jedoch auch denkbar, das beschichtete Material beispielsweise an Krankenhäuser oder Apotheken auszuliefern, wo dann die Vorzerteilung dosisabhängig oder auch individuell nach ärztlicher Vorgabe durchgeführt werden kann.

Die Vorzerteilung erfolgt in besonders einfacher Weise durch Stanzung, wobei es möglich ist, diesen Schritt mit der Bedruckung des Trägermaterials zu kombinieren. In vielen Fällen wird es allerdings günstiger sein, die Bedruckung des Trägermaterials vor der Beschichtung vorzunehmen.

Vor oder besser nach Vorzerteilung der wirkstoffhaltigen Beschichtung in Dosiseinheiten wird das beschichtete Trägermaterial zu gebrauchsfertigen Abschnitten zerschnitten, welche eine bestimmte Anzahl von Dosiseinheiten enthalten. Es ist auch denkbar, das Material auf Rollen zu schmalen Bändern zu zerschneiden. Von einer solchen Einzelrolle können dann die einzelnen Dosiseinheiten ähnlich wie einzelne Haftetiketten abgezogen werden.

Vorstehend wurde die Erfindung im wesentlichen im Zusammenhang mit Arzneimitteln beschrieben, worauf sie jedoch keineswegs beschränkt ist. Beispielsweise lassen sich in derselben Weise auch Dosierungsformen für chemische Reagentien, Aromastoffe und dergleichen herstellen.

Zur näheren Erläuterung der Erfindung sollen die nachfolgenden Ausführungsbeispiele dienen.

Beispiel 1

Herstellung eines Cardiakum

Zum Naßauftrag auf ein Releasepapier (Silikonpapier mit einem Flächengewicht von 100 g/m²) wurde eine Beschichtungsmasse gemäß folgender Rezeptur hergestellt:

Gelatine	10,0 Gew.-Teile =	22,22%
Kartoffelstärke	3,0 Gew.-Teile =	6,67%
Glycerin	1,5 Gew.-Teile =	3,33%
Titandioxid	0,3 Gew.-Teile =	0,67%
α-Actyldigoxin	0,2 Gew.-Teile =	4,44%
Wasser	30,0 Gew.-Teile =	66,67%

Diese Beschichtungsmasse wurde in einer Schichtdikke von 90 g/m² mittels Walzen auf das Releasepapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Das Beschichtungsgewicht lag bei 34 g/m², was einem Arzneimittelanteil von 0,4 g/m² entspricht. Ein Abschnitt von 2 × 2,5 cm = 5 cm² (entsprechend den Abmessungen einer üblichen Briefmarke) enthält 0,2 mg α-Acetyldigoxin, was mit dem Gehalt der handelsüblichen Tabletten übereinstimmt.

Beispiel 2

Herstellung eines Contrazeptivum

Zum Naßauftrag auf ein Releasepapier (einseitig siliconisiertes Papier von 110 g/m²) wurde eine Beschichtungsmasse von schleimartiger Konsistenz nach folgender Rezeptur hergestellt:

Gelatine	10,00 Gew.-Teile =	22,222%
Maisstärke	3,17 Gew.-Teile =	7,044%
Glycerin	1,50 Gew.-Teile =	3,333%
Titandioxid	0,30 Gew.-Teile =	0,667%
Levonorgestrel	0,03 Gew.-Teile =	0,067%
Wasser	30,00 Gew.-Teile =	66,663%

Die Beschichtungsmasse wurde mittels eines Walzenübertragungsverfahrens mit einem Beschichtungsgewicht von 45 g/m² auf das Releasepapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Bei einem Beschichtungsgewicht von 17 g/m² betrug der Arzneimittelanteil 0,03 g/m².

Ein Abschnitt von 2,5 × 4 cm bzw. zwei Abschnitte von 2,5 × 2 cm = 10 cm² enthalten somit 0,03 mg Levonorgestrel, was dem Gehalt der handelsüblichen Dragees entspricht.

– Leerseite –

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 200 508 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **02.10.91** (51) Int. Cl.5: **A61K 9/70**, A61L 15/16

(21) Application number: **86303170.4**

(22) Date of filing: **25.04.86**

(54) Adhesive oral bandages and oral pharmaceutical preparations.

(30) Priority: **27.04.85 JP 91580/85**
27.04.85 JP 91581/85

(43) Date of publication of application:
10.12.86 Bulletin 86/45

(45) Publication of the grant of the patent:
02.10.91 Bulletin 91/40

(84) Designated Contracting States:
CH DE FR GB LI NL SE

(56) References cited:
EP-A- 0 081 987
EP-A- 0 122 344
DE-A- 2 133 709
FR-A- 2 497 098
GB-A- 2 086 224

PATENT ABSTRACTS OF JAPAN, vol. 9, no. 45 (C-268)[1768] 26th February 1985; & JP-A-59 186 913 (TEIKOKU SEIYAKU K.K.) 23-10-1984

(73) Proprietor: **NITTO DENKO CORPORATION**
1-2, Shimohozumi 1-chome Ibaraki-shi Osaka(JP)

Proprietor: **SUNSTAR INC.**
3-1 Asahi-cho
Takatsuki-shi Osaka(JP)

(72) Inventor: **Inoue, Yuichi**
Nitto Elec. Ind. Co. Ltd. 1-2 Shinohozumi 1-chome
Ibaraki-shi Osaka(JP)
Inventor: **Horiuchi, Tetuo**
Nitto Elec. Ind. Co. Ltd. 1-2 Shinohozumi 1-chome
Ibaraki-shi Osaka(JP)
Inventor: **Hasegawa, Kenji**
c/o Sunstar Inc 3-1 Asahi-cho
Takatsuki-shi Osaka(JP)
Inventor: **Nakashima, Koichi**
c/o Sunstar Inc 3-1 Asahi-cho
Takatsuki-shi Osaka(JP)
Inventor: **Ysuyoshi, Takashi**
c/o Sunstar Inc 3-1 Asahi-cho
Takatsuki-shi Osaka(JP)

(74) Representative: **Diamond, Bryan Clive**
Gee & Co., Chancery House, Chancery Lane
London WC2A 1QU(GB)

Rank Xerox (UK) Business Services

EP 0 200 508 B1

Description

This invention relates to an oral bandage that can be adhered to the oral mucosa to prevent a drug administered to the oral mucosa from running out and to cover or protect the affected part of the oral mucosa, and to oral preparations comprising such a bandage having incorporated therein a topical drug.

In the field of dental and oral surgery, various topical preparations in the form of ointments or solutions have hitherto been administered to the oral mucosa for prophylaxis and therapy of oral diseases, such as periodontal disease, stomatitis, etc. The most serious problem in administering drugs to the oral mucosa is that the drug runs away in a short time by salivary secretion or through eating or drinking, thereby failing to fully exert its medical effects.

On the other hand, protection of the affected part in the oral cavity has scarcely been conducted because no effective oral bandage has been developed. As mentioned above, the continuous salivary secretion and taking of foods and drinks constitute an insuperable barrier to the protection of the oral mucosa.

In recent years, many proposals have been made in an attempt to effectively administer a drug to the mucosa of the oral cavity, so as to overcome the above-described problems. Among them, proposals relevant to the present invention relate to preparations adhesive to the oral mucosa, which contain water-soluble high-molecular substances as an adhesive. When water-soluble high-molecular substances absorb a small amount of water, they become a viscous aqueous solution or gel having adhesion, though varying in extent with their kind. Making use of this property, various preparations adhesive to the oral mucosa have been proposed, including pastes as disclosed in Japanese Patent Publication No. 27491/81, sponges as disclosed in Japanese Patent Publication No. 25211/81, tablets as disclosed in Japanese Patent Publication No. 7605/83, sheets as disclosed in Japanese Patent Publication No. 16676/69 and Japanese Patent Application (OPI) No. 186913/84 (the term "OPI" has herein used means "unexamined published application").

However, these conventional preparations only are intended to have enough adhesion to allow them to remain in position for a period of time enough to administer the drug to the mucosa. In other words, these preparations do not possess strong adhesion for an extended period of time as required for an oral bandage. On the contrary, an oral bandage is intended to prevent running-off of the administered drug or to provide protection by adhesion to the affected or injured part of the oral cavity. Therefore, it is required to have strong and long-lasting adhesion to the oral mucosa which may be less adherable due to the administered drug or stomatorrhagia. Since both adhesive strength and duration of adhesion of the aforesaid conventional preparations adhesive to the oral mucosa are not so high as demanded for an oral bandage, application of bases used in these preparations to an oral bandage can never satisfy the above-described requirements of an oral bandage. The conventional adhesive tapes which are intended to be applied to the skin cannot be, of course, used as an oral bandage because they have no adhesion to a wet surface such as oral mucosa.

Japanese Patent Application (OPI) No.186913/84 is directed to an invention that four components of gelatin or agar, gluten, carboxyvinyl polymer, and vinyl acetate resin or gum are essential. It is therefore apparent that the cited reference differs from the present application in which a homogeneous state is maintained by a two component system.

In the JPA document a water-soluble material and a water-insoluble material are mixed together with water in such a manner that a water content is 0.5-20 w/w%. From this fact, it is apparent that a homogeneous state cannot be obtained.

Even if a base material having such a state is adhered to the oral mucosa, water at the adhering portion is not absorbed uniformly with respect to the base material, resulting in an ununiform absorption, and as a result, the system of the base material tends to break, and its adhesion is not maintained for a long period of time.

On the other hand, in the homogeneous state as in the present invention, absorption of water from the adhering portion is uniformly conducted over the whole base material. Consequently, it is difficult to proceed breakage of the system, and the adhesion is sufficiently maintained over a long period of time.

An oral bandage is required to have not only strong and long-lasting adhesion to the oral mucosa as described above but also softness sufficient to be adhered to any desired site of complicated shape in the oral mucosa and, in addition, safety from worsening of the injury due to irritation. However, an oral bandage having such performance characteristics has not yet been developed.

The present invention is intended to meet the above-described situations.

Accordingly, an object of this invention is to provide an oral bandage having high adhesive strength for a prolonged period of time and softness with which to adhere to desired site of the oral mucosa or teeth.

Another object of this invention is to provide an oral preparation adhesive to the oral mucosa by which an active ingredient can be surely and effectively administered to the oral mucosa.

According to the invention we provide an oral bandage comprising a soft adhesive film consisting of a mixture of (a) an acrylic acid polymer, methacrylic acid polymer and/or maleic anhydride polymer and (b) a vinyl acetate polymer, the polymers (a) and (b) being uniformly dissolved in each other without regions of phase separation, so as to be substantially water-insolubilized; and optionally a basic substance capable of neutralizing said polymers (a) and an oral preparation comprising such an oral bandage having incorporated therein a topical drug.

The term "compatible state" as herein used means such a state that the polymers (a) and (b) (hereinafter simply referred to as "polycarboxylic acids") and the vinyl acetate polymer (hereinafter referred to as polyvinyl acetate) are uniformly dissolved in each other without forming small individual regions due to phase separation.

Water-soluble high-molecular compounds, such as polycarboxylic acids and polycarboxylic acid anhydrides have per se a shape-retention property. When they absorb a small amount of water, they exhibit strong adhesiveness but soon take up excess water to cause reduction in viscosity and degradation, thus resulting in losing their adhesiveness by being substantially dissolved in water. Moreover, since polycarboxylic acids in a dissolved state are acidic, they heavily irritate the sensitive injured part of the oral mucosa to cause worsening of the condition.

The present inventors have conducted extensive investigations on water-insolubilization of the above-described water-soluble high-molecular compounds, such as polycarboxylic acids, polycarboxylic acid anhydrides, etc., aiming at effective utilization of these compounds exhibiting excellent adhesion upon absorption of water as an oral bandage, while eliminating the above-described disadvantages, i.e., loss of adhesion due to over-absorption of water and irritation of the injured part. As a result, it has now been found that polycarboxylic acids and polyvinyl acetate are compatible with each other, and mixing of these two components in a compatible state substantially realizes water-insolubilization of the polycarboxylic acids without impairing the strong adhesion upon water absorption. Therefore, even if such a compatible mixture of the two components is shaped into a thin and soft film, it can exert strong adhesion for an extended period of time without undergoing degradation due to water absorption in a wet state.

It has further been found that incorporation of a basic substance (salt or base) capable of neutralizing the polycarboxylic acids into the above-described compatible mixture can further relieve the irritation on the injured part of the oral mucosa.

It has furthermore been found that incorporation of topical drugs into adhesive film and/or film support comprising the above-described compatible mixture can provide film-like oral preparations retaining the strong adhesion, by which the drug can be surely, simply and effectively administered to the oral mucosa, thus permitting prevention and treatment of oral diseases.

In the accompanying drawing:

The graph is a characteristic curve of (dissolved amount)/(total dissolved amount) of a drug, over a period of time.

A soft film comprising a compatible mixture of the polycarboxylic acids and polyvinyl acetate according to the present invention does not show adhesion in a dry state but comes to exhibit strong adhesion upon water absorption, such adhesion being substantially unchangeable even when immersed in water. Such a characteristic can first be manifested when the polycarboxylic acids and polyvinyl acetate are in a compatible state, not appearing when they are not in a compatible state.

As described above, the mixture of the polycarboxylic acids and polyvinyl acetate in a compatible state exhibit characteristics unpredictable from those of a mixture in a phase-separated state. More specifically, a film in a phase-separated state is turbid, whereas a film in a compatible state has such a high transparency that no independent small region is observed under an optical microscope. Further, when immersed in water, the polycarboxylic acids is dissolved out from the film in a phase-separated state, resulting in degradation as a whole; while the film in a compatible state only undergoes uniform swelling with very little elution of the polycarboxylic acids into water, which indicates that the polycarboxylic acids is substantially water-insolubilized. The compatible state (compatibility) of the polycarboxylic acids and polyvinyl acetate can be determined by making use of insolubilization of the polycarboxylic acids.

When a basic substance capable of neutralizing polycarboxylic acids is mixed with the above-described compatible mixture, the state of its mixing has no substantial influence on the adhesion property. Therefore, the basic substance may be mixed either in a compatible state or in a coarse dispersion.

Compatibility between the polycarboxylic acids and polyvinyl acetate can be clearly observed if the

mixture consists of only these two components as mentioned above. However, differrences in compatibility become unclear in those mixtures containing a basic substance having a neutralizing effect. In other words, in a mixture containing a basic substance, the mixing state of the basic substance being not restricted, even if the polycarboxylic acids and polyvinyl acetate are in a compatible state, the basic substance, if being mixed in a coarse dispersion, makes the film turbid. Thus, the mixing state of the polycarboxylic acids and polyvinyl acetate cannot always be observed visually or under an optical microscope.

Nevertheless, as described above, it has been confirmed that water-solubility of polycarboxylic acids can be markedly inhibited in a compatible mixture with polyvinyl acetate and that such a compatible mixture is uniformly swollen without degradation even when immersed in water for a considerably long period of time. This property can be recognized irrespective of whether a basic substance having a neutralizing effect be present or not.

Accordingly, this property can be made use of in determination of compatibility between polycarboxylic acids and polyvinyl acetate. This method of determination can be regarded reasonable from the fact that the oral bandage according to the present invention can be adhered to the oral mucosa for a long period of time owing to the limited water-solubility of the polycarboxylic acids.

In the present invention, the compatibility between polycarboxylic acids and polyvinyl acetate is determined from the amount of dissolved polycarboxylic acids. That is, the compatible state as herein referred to specifically means that the dissolution ratio of polycarboxylic acids as obtained by the following method is 40% by weight or less. In the case of an oral bandage containing a salt having a neutralizing effect, it means that the dissolution ratio of polycarboxylic acids as obtained by the following method is 50% by weight or less, taking into account dissolving of the salt.

Method of determing Dissolution Ratio:

A film comprising polycarboxylic acids and polyvinyl acetate is ground and weighed. The ground sample is put in a mesh bag and left to stand still in 300 times or more the weight of pure water at 20 °C for one hour. The bag is then taken out, and the amount of polycarboxylic acids dissolved out into the water is determined by neutralization titration or the like technique. This value is divided by the amount of the polycarboxylic acids initially contained in the film to obtain the dissolution ratio.

In the case when the film contains a basic substance, the dissolution ratio is obtained in the same manner as above except that the bag after the immersion is weighed to obtain the total amount of dissolved polycarboxylic acids and dissolved salt from, for example, weight reduction and this value is divided by the sum of the polycarboxylic acids and the basic substance initially contained in the film to obtain the dissolution ratio.

Since the oral bandage in accordance with the present invention comprises a soft film which is not adhesive in a dry state but shows adhesion only upon absorption of water, it can be stored as such without requiring any special storage conditions. On use, the oral bandage is stuck onto the oral mucosa whereupon it absorbs saliva or moisture of the mucous membrane to rapidly exerts strong adhesion to the mucous membrane. Thus, it firmly adheres to the affected part or injured part of the oral cavity that is less adherable due to the drug administered, stomatorrhagia, and the like. This adhesion lasts for a markedly prolonged period of time, which is a well-marked characteristic of the present invention. Such adhesion of long duration can first be attained by the adhesive film comprising the polycarboxylic acids and polyvinyl acetate in a compatible state as set forth above.

The mechanism accounting for the long-lasting adhesion is not clear, but it is believed that the polycarboxylic acids contributes to adhesiveness to the wet mucosa and the polyvinyl acetate contributes to water resistance in a compatible mixture thereof, thus functioning together to give adhesion of long duration.

The mixing state of the basic substance capable of neutralizing polycarboxylic acids has no influence on the adhesion, but the kind of the basic substance to be used exerts delicate influences on the adhesion and the like. For example, polyvalent metal salts, e.g., zinc oxide, calcium oxide, etc., function to reduce adhesion and to enhance water resistance, while monovalent metal salts, e.g., sodium acetate, etc., or a monovalent base, e.g., sodium hydroxide, triethanolamine, etc., functions to reduce water resistance and to enhance adhesion.

As described above, since the oral bandage in accordance with the present invention has adhesion of long duration, it can prevent the drug administered to the affected part of the oral cavity from running off to accelerate healing with a remarkably increased absorption of the drug and also give protection to the injured part of the oral cavity for a long period of time to expedite recovery.

Further, since the irritation due to eluted polycarboxylic acids can be reduced by adding a basic substance having a neutralizing effect to the adhesive film, a situation wherein the injured part of the oral

cavity becomes worse due to application of the oral bandage can be avoided.

In addition, the adhesive film according to the present invention is not merely composed of a water-soluble high-molecular substance but comprises a substantially water-insoluble soft film, in which polycarboxylic acids and polyvinyl acetate exist in a compatible state. Therefore, adhesion of long duration can be produced in a very thin film. In other words, too a thin film solely made of a water-soluble high-molecular substance is readily dissolved out in saliva in a short time to rapidly lose its adhesiveness so that a film made of such a material should have a considerably large thickness. However, a thick film produces a feeling foreign to the applied part and also reduces softness of the oral bandage. On the contrary, the oral bandage of the present invention does not require such a large thickness, thus giving no uncomfortable feeling.

The oral bandage according to the present invention can be produced by, for example, dissolving polycarboxylic acids and polyvinyl acetate in a solvent common to both and rapidly flow-casting the solution in a thin film, followed by drying.

The oral bandage containing a basic substance having a neutralizing effect according to the present invention can be produced by, for example, dissolving polycarboxylic acids and polyvinyl acetate in a solvent common to both, adding a basic substance capable of neutralizing the polycarboxylic acids to the solution, and rapidly flow-casting the mixture in a thin film, followed by drying. Incorporation of the basic substance may be carried out by dissolving in the solution or by dispersing a powderous basic substance in the solution. The above-described flow casting method is advantageous to easily produce a very thin film.

In the present invention, a topical drug can be incorporated into the oral bandage of the invention to obtain oral preparations. The method of incorporation is not particularly restricted, and usually comprises adding the topical drug directly or in the form of a solution to the solution of polycarboxylic acids and polyvinyl acetate, rapidly casting the composition in a thin film and drying. the acrylic polymers include an acrylic acid homopolymer and copolymers of acrylic acid and acrylic esters, e.g., butyl acrylate, 2-ethylhexyl acrylate,
methacrylic esters, e.g., methyl methacrylate,
or vinyl monomers, e.g., vinyl acetate, and copolymers, e.g., carboxyvinyl polymer. Examples of the methacrylic polymers include a methacrylic acid homopolymer and copolymers of methacrylic acid and comonomers as enumerated for the acrylic polymers. Specific examples of the maleic anhydride polymers include copolymers of maleic anhydride and methyl vinyl ether,

These compounds can be used either individually or in combination of two or more thereof. It is preferable that these Polycarboxylic acids contain 20% by weight or more of a -COOH group in case of methacrylic polymers or 16% by weight or more or a -CO-O-CO- group in case of maleic anhydride polymers.

The vinyl acetate polymer which can be used in the present invention typically includes a vinyl acetate homopolymer. In addition, copolymers of vinyl acetate and vinyl monomers, e.g., acrylic esters, and partial saponification products of a vinyl acetate homopolymer may also be employed. These vinyl acetate polymers may be used either individually or in combinations of two or more thereof. The polyvinyl acetate preferably has an average molecular weight (viscosity-average molecular weight) of not less than 60,000. Use of polyvinyl acetate having an average molecular weight less than 60,000 reduces water resistance of the adhesive, resulting in failing of the expected effects.

The basic substance which can be used for neutralizing polycarboxylic acids includes not only salts but bases. Typical examples of the salt include salts of metals and weak acids, metal oxides, metal hydroxides, amines, and mixtures thereof. Specific examples of the salt of metals and weak acids are salts of sodium, potassium, calcium, magnesium, etc. and carboxylic acids, e.g., acetic acid, lactic acid, citric acid, etc. Specific examples of the metal oxides are zinc oxide, calcium oxide, magnesium oxide, etc. Specific examples of the metal hydroxides are sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, etc. Specific examples of the amines are triethanolamine, diisopropanolamine, etc. These compounds can be used either alone or in combination. A preferred amount of the basic substance to be added varies widely depending on the kind thereof. In the case of using a polyvalent metal salt, for example, it is preferably added in an amount of from 0.2 to 0.8 equivalent based on the polycarboxylic acids. If its amount is less than 0.2 equivalent, the effect to relieve irritation on the injured part of the oral mucosa becomes insufficient. If it exceeds 0.8 equivalent, sufficient duration of adhesion can hardly be attained. In case of using a monovalent metal salt or a monovalent base, it is preferably added in an amount of from 0.03 to 0.2 equivalent based on the polycarboxylic acids. Amounts less than 0.03 equivalent reduce the effect of relieving irritation on the injured part, and amounts exceeding 0.2 equivalent reduce water resistance of the adhesive film, resulting in difficulty in obtaining sufficient adhesion.

The solvent common to the polycarboxylic acids and polyvinyl acetate includes lower alcohols, such as

methanol, ethanol, etc.; mixed solvents comprising a lower alcohol in a larger proportion and a compatible organic solvent, such as acetone, ethyl acetate, etc.; and mixed solvents comprising a lower alcohol or the above-described mixed solvent and water. The mixed solvent of a lower alcohol and an organic solvent preferably contains not more than 30% by weight of the organic solvent because the organic solvent of more than 30% by weight makes it difficult to dissolve polycarboxylic acids. The mixed solvent of a lower alcohol or a lower alcohol-organic solvent mixed solvent and water preferably contains not more than 30% by weight of water because a water content exceeding 30% by weight is liable to make it difficult to dissolve the polyvinyl acetate.

In the preparation of the oral bandage or oral; preparations of the invention, it is preferable that the polycarboxylic acids to polyvinyl acetate mixing ratio fall within such a range that the value A as obtained according to the following formula ranges from 15 to 45:

$$A = \frac{\left(\begin{matrix}\text{Weight of -COOH} \\ \text{in Adhesive Film}\end{matrix}\right) + \frac{5}{4}\left(\begin{matrix}\text{Weight of -CO-O-CO-} \\ \text{in Adhesive Film}\end{matrix}\right)}{\left(\begin{matrix}\text{Weight of Polycarboxylic Acids in Adhesive Film} \\ \text{+ Weight of Polyvinyl Acetate in Adhesive Film}\end{matrix}\right)} \times 100$$

As the value A becomes larger, the adhesion to the mucous membrane increases, but the duration of adhesion tends to decrease. To the contrary, the smaller the value A, the lesser the ahesion, but the duration of adhesion tends to increase. If the value A is less than 15, sufficient adhesion is hard to obtain. If it exceeds 45, it becomes difficult to obtain sufficient duration of adhesion. Accordingly, the mixing ratio of polycarboxylic acids and polyvinyl acetate is preferably adjusted so that the value A falls within a range of from 15 to 45. Taking the case of using polyacrylic acid as a polycarboxylic acid for instance, with the proportion of polyacrylic acid in the adhesive film being between 24 and 72% by weight, the value A falls within the above-recited range to obtain good results.

When the polycarboxylic acids and polyvinyl acetate are dissolved in a common solvent, care should be taken so as to sufficiently dissolve the both components. On this occasion, concentrations of the polycarboxylic acids, polyvinyl acetate, etc. are not particularly limited. However, too a high concentration of the high-molecular substance makes the resulting solution highly viscous, and such a viscous solution is difficult to flow-cast in a film. Therefore, it is preferable to give care that the concentrations of the high-molecular substances may not exceed 40% by weight.

In the preparation of the adhesive film according to the present invention, the solution comprising the polycarboxylic acids and polyvinyl acetate and, if necessary, a basic substance and/or a topical drug is cast on an appropriate film, such as polyethylene-laminated paper, having been subjected to releaseability-imparting treatment, and the casted film is rapidly dried with hot air in a drying oven or a drying tower. Suitable time and temperature in drying vary depending on the composition of a common solvent used, solid content of the solution, thickness of the cast film, the pressure and the like but, in general, preferably range from 60° to 120° C in temperature and from 1 to 20 minutes in time under an atmospheric pressure. A very thin film that can be, as such, used as an oral bandage can be thereby produced. The thickness of the resulting film is preferably be adjusted to a range of from 5 to 100 μm by controlling the amount of the casting solution, and the like. If a film thickness is less than 5 μm, it is difficult to obtain sufficient adhesion. A film having a thickness exceeding 100 μm tends to produce a feeling foreign to the mouth and to impair softness of the film.

As described above, the adhesive film in accordance with the present invention comprises a polycarboxylic acids and a vinyl acetate polymer not in a merely mixed state but in a compatible state with each other, in which the polycarboxylic acids is substantially water-insolubilized. Hence, even being very thin, it exerts strong adhesion for an extended period of time without suffering degradation due to water absorption. Besides, the film can easily be deformed according to the form of the oral mucosa and adhered thereto simply by pressing because of its softness.

The oral bandage and oral preparations according to the present invention may solely comprise the adhesive film but may further comprise a soft film support in combination.

A composite comprising the adhesive film and a support can be produced by laminating the adhesive film on a soft film support in a usual manner, such as hot pressing or by the use of an adhesive. Alternatively, the lamination can be carried out simultaneously with the preparation of the adhesive film by casting the film-forming composition on a soft film support, followed by drying. The latter process has an advantage over the former in simplifying the production procedure since hot pressing or adhesion with an adhesive is unnecessary.

The soft film support which can preferably be used in the present invention is substantially impermeable to water. Such a support typically includes plastic films, such as polyethylene, polyvinyl acetate resin, an ethylene-vinyl acetate copolymer, polyvinyl chloride, polyurethane, etc., metal foils, such as aluminum foil, tin foil, etc., laminates of cloth or paper and a plastic film, and the like. Of these, plastic films are preferred in view of safety and feeling in use. A preferred thickness of the film support is from 10 to 100 μm in view of handling properties and freedom from a foreign feeling on use. A thickness of the composite film, i.e., a total thickness of the adhesive film and the film support, is preferably in the range of from 30 to 150 μm. If it is less than 30 μm, handling properties and operation properties are deteriorated. A thickness exceeding 150 μm is liable to give a foreign feeling on use.

When the oral bandage of the invention contains a topical drug to obtain an oral preparation as described before, the topical drug may be incorporated into the adhesive film and/or the above-described film support. In the latter case, incorporation of the drug can be carried out by kneading with a resin material for the support, mixing the drug in the form of its solution with a resin material, absorbing onto a support, impregnating into a support, or a like method.

The topical drug which can be used in the present invention may be either solid or liquid at room temperature as long as it may be incorporated into the adhesive film or the film support by dissolving or dispersing.

Specific examples of the topical drugs to be used in the present invention are adrenal corticosteroids, e.g., Triamcinolone acetonide, Dexamethasone, Betamethasone, Prednisolone, Fluocinolone, Hydrocortisone, Beclomethasone, etc. and salts thereof; anti-inflammatory agents, e.g., Flurbiprofen, Ibuprofen, Diclofenac, Indomethacin, Bendazac, Flufenamic acid, Bufezamac, Cyclospoline, Clidanac, Glycyrrhizin, Ketoprofen, Piroxicam, Pranoprofen, Benzydamine, Ibuprofenpiconol, Etofenamate, Lysozyme, Chymotrypsin, Epidihydrocholesterine, Hinokitiol, α-Amylase, Azulene, Chlorophllin, Cromoglic acid, Tranilast, Serratiopeptidase, Pronase, Glucanase, Lithospermi Radix extract, etc. and salts thereof; antimicrobial agents, e.g., Acrynol, Cetyl pyridinium, Chlorhexidine, Domifen, Iodine, Monensin, Sanginalline, Metronidazol, Dequalinium, Tetracycline, Minocycline, Ofloxacin, Penicilline, Doxycycline, Oxycycline, Cefatrizin, Nystatin, Clindamycin, Fradiomycin, sulfate, etc. and salts thereof; analgesics, e.g., Ethyl aminobenziate, Camphor, Eugenol, Dibucaine, Phenol, Menthol, Creosote, Diphenhydramine, Lidocaine, Tetracaine, Procaine, Cocaine, Piprocaine, Mepivacaine, Promoxin, Dicronin, Guaiacol, etc. and salts thereof; hemostatics, e.g., Tranexamic acid, ε-Aminocapronic acid, Alginic acid, Bioflavonoide, Ascorbic acid, Thrombin, oxidized Cellulose, Cetraxate, Epinephrine, Ferric chloride, Fibrinogen, Carbazochrome, Adrenochrome, etc. and salts thereof; vasodilators, e.g., Inositol hexanicotinate, Cyclanderate, Cinnarizine, Tolazoline, Acetylcholine, etc. and salts thereof; agents activaing cellular function, e.g., Solcoseryl, Proglumide, Sucralfate, Gefarnate, Nicametate, Glutamine, Aceglutamide aluminum, Ethylcysteine, Chitin, Tocopherol nicotinate, Ubidecarenone, etc. and salts thereof; antiviral agents, e.g., Aciclovir, Idoxuridine, Betrabin, Amantadine, etc. and salts thereof; agents affecting calcium metabolism, e.g., Vitamin D, Endotoxin, Hydroxyapatite, Collagen, Cataboline, 2-Chloroadenosine, Norcardia, Calcitriol, Prostaglandins for alveolar bone, Osteoclast activating factors for alveolar bone, Parathormone for alveolar bone, Calcitonine for alveolar bone, etc. and salts thereof; astringents, e.g., Tannin, Tanninc acid, Zinc fluoride, Sodium fluoride, Strontium fluoride, Potassium nitate, Stannous fluoride, Aluminum potassium sulfate, Berberine, Bismuth compounds, Strontium chloride, Aluminum lactate, etc. and salts thereof.

The amount of these topical drugs to be incorporated in the oral preparation varies depending on the kind thereof, but from considerations of pharmacological effects and adhesion to the mucous membrane, it usually ranges from 0.0001 to 35% by weight, and preferably from 0.0002 to 20% by weight, based on the preparation. When positive administration of the drug to the oral mucosa is expected, the drug is preferably present in the adhesive film side. In the treatment of bad breath, and the like, it may be prevent in the support side.

The composite film composed of the adhesive film and the support has enhanced strength while retaining the excellent adhesion of long duration. As an additional effect, the composite film can present adhesion of foreign matters, such as foods, onto the back side of the oral bandage or oral preparations. Further, use of a substantially water-impermeable support effectively prevents permeation of water through the back side to thereby prolong the duration of adhesion.

The adhesive film or support of the oral bandage or oral preparations according to the present invention may further contain other additives, such as coloring matters, flavoring materials, softening agents, and the like, as long as they do not impair adhesiveness or pharmacological effects. For example, when both the adhesive film and the support are colorless, incorporation of a coloring matter in one of them makes it easy to distinguish the surface or back of the bandage or preparation.

According to the present invention, both of the adhesive film and the composite film composed of the

adhesive film and a support are very soft and, when applied to the oral mucosa, absorb water in the oral cavity to get further softened. Therefore, they can be easily fitted to any site of the oral cavity to thereby produce strong adhesion for an extended period of time. The adhesive strength of the adhesive film or the composite film of the invention was measured using a crosslinked collagen swollen with water as a substitute for the oral mucosa at a peel angle of 180° and, as a result, was found to be from 25 to 200 g/2.5 cm-width. Adhesive strength smaller than 25 g/2.5 cm-width cannot ensure adhesion to the oral mucosa for a long period of time, and that greater than 200 g/2.5 cm-width is liable to injure the mucous membrane upon peeling. Taking these facts into account, the oral bandage or preparations according to the present invention can be reasonably regarded as exhibiting the optimum adhesive strength.

The above-described adhesive strength is naturally subject to variations depending on the kind of adherends. That is, the adhesive film exerts sufficient adhesion to mucous membranes, the teeth, the skin, cross-linked collagen films, and the like, with the adhesive strength being not impaired even when immersed in water. But the adhesive film scarcely shows adhesion to plastics material or regenerated cellulose film, and the adhesion thereto is very weak and rapidly disappears in water. This property is entirely favorable for storage of prodducts. No special moisture-proof packaging is needed because the products do not adhere to packaging materials, storage cases, etc. Further, it is not necessary to cut the oral bandage or oral preparations into small lengths for storage, and they can be formed in a tape and wound on a spool without sticking to each other. They may be stored as they are, but if there is a fear of contamination, the surface that is to be adhered can be protected with paper or a plastic film.

The oral bandage and oral preparations containing a basic substance for neutralization according to the present invention are highly safe from harm to the injured part of the oral cavity due to the irritant polycarboxylic acids which are dissolved out when applied to the injured parts. That is, the adhesive film of the invention containing no basic substance for neutralization may be applied to the skin of shaved guinea pigs, the eye mucous membrane of rabbits, the oral mucosa of healthy persons, etc. without causing any substantial irritation. However, irritation is noted when it is applied to the injured skin of a shaved guinea pig caused by stripping the corneum with an adhesive tape. To the contrary, the products containing a basic substance for neutralization cause substantially no irritation on such an injured skin as well as on the normal mucous membranes.

The oral bandages or preparations according to the present invention possess excellent water resistance attributed to substantial water-insolubilization of the polycarboxylic acids constituting the adhesive film so that they are only swollen but not degraded even when immersed in water. Therefore, they retain adhesiveness for a long period of time, generally 3 to 4 hours or even more, e.g., for one day, onto the oral mucosa.

Further, the oral preparations comprising the oral bandage of the invention having incorporated therein a topical drug are effective in producing pharmacological effects and very easy to handle since they can be adhered to the wet surface of affected parts of the oral cavity simply by pressing thereonto for the prevention or treatment of oral diseases.

This invention will now be illustrated in greater detail with reference to the following examples, are not intended to limit the present invention. In these examples, all the parts and percents are given by weight unless otherwise indicated.

EXAMPLE 1

Five parts of a carboxyvinyl polymer as a polycarboxylic acid and 5 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) were poured in 90 parts of methanol as a common solvent, followed by mixing to form a uniform solution. The resulting solution was flow-casted on a release paper, dried, and peeled off to obtain an adhesive film having a thickness of 30 μm. The value A of this film was 31.3. The dissolution ratio of the polycarboxylic acid, that is a criterion of the compatible state, was 9%, indicating that the film had a compatible state.

The adhesive film thus prepared was laminated on 15 μm thick aluminium foil by hot pressing to obtain an oral bandage.

COMPARATIVE EXAMPLE 1

Five parts of polyvinyl acetate (degree of polymerization: ca. 1,500) were dissolved in 20 parts of toluene, and to the solution was added 5 parts of a toluene-insoluble carboxyvinyl polymer, followed by thoroughly stirring to prepare a uniform suspension. The suspension was then flow-casted on a release paper, dried, hot pressed and peeled off to obtain an adhesive film having a thickness of 30 μm. The

resulting film had the same value A as in Example 1 but a ratio of dissolution of the polycarboxylic acid of 67%, which indicated that the carboxylvinyl polymer and polyvinyl acetate were in a phase-separated state.

The adhesive film thus prepared was laminated on 15 μm thick aluminum foil by hot pressing to obtain an oral bandage.

COMPARATIVE EXAMPLE 2

Five parts of a carboxyvinyl polymer were dissolved in 45 parts of pure water. Separately, 5 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) was dissolved in 20 parts of toluene. The both solutions were mixed and then stirred in a small-sized stirrer at 5,000 rpm for 3 minutes to obtain a suspension. The resulting suspension was flow-casted on a release paper, dried and peeled off to obtain an adhesive film having a thickness of 30 μm. The value A of this film was the same as in Example 1, but the dissolution ratio of the polycarboxylic acid was 79%, indicating that the carboxyvinyl polymer and polyvinyl acetate were in a phase-separated state.

The resulting film was laminated on 15 μm thick aluminum foil by hot pressing to obtain an oral bandage.

The compatible state of each of the samples obtained in the foregoing examples was evaluated by macroscopic observation to see the appearance of the film and also under an optical microscope to observe whether small independent regions of the polycarboxylic acid or polyvinyl acetate were formed or not. Formation of such small regions indicates phase separation.

Further, each of the samples was cut in a size of 5 x 5 cm, immersed in water at 37°C for 10 minutes, dried and weighed to determine weight reduction. The weight reduction (%) as an average of 10 runs was taken as a parameter of solubility of the film.

Furthermore, the dissolution ratio of the polycarboxylic acid after 2 hour- and 4-hour immersion in the same manner as described above for the dissolution ratio after 1 hr-immersion.

The results obtained are shown in Table 1 below. In Table 1, the solubility (weight reduction) is an average of 10 sample pieces. The dissolution ratio after 1 hr-immersion as measured in the foregoing examples is also shown in Table 1.

TABLE 1

	Example 1	Comparative Example 1	Comparative Example 2
Compatible State:			
Appearance	trans-parent	turbid	turbid
Formation of Small Regions	no small regions observed	small regions observed	small regions observed
Solubility (%)	0.1	6.9	7.7
Dissolution Ratio (%):			
1 Hr-Immersion	9	67	79
2 Hr-Immersion	10	-	-
4 Hr-Immersion	12	-	-

As is apparent from Table 1 above, in the adhesive film of Example 1, the polycarboxylic acid and polyvinyl acetate are in a good compatible state, making a contrast to those of Comparative Examples 1 and 2. In particular, the results of polycarboxylic acid dissolution ratios reveal that the most of the

polycarboxylic acid, an adhesive component, in the films of Comparative Examples 1 and 2 is dissolved out into water through immersion for one hour, whereas the dissolution ratio of the film of Example 1 after 1 hour-immersion is as low as 9%, which increases only to 12% even by immersion for 4 hours, said ratio showing no further increase through additional immersion, though not shown in Table 1. It can be seen from these results that a major proportion of the total amount of the dissolved polycarboxylic acid is dissolved out during the first one-hour immersion. The change in the proportion of the dissolved amount to the total dissolved amount with time is shown in Figure 1.

Then, the oral bandages obtained in the foregoing examples were subjected to adhesion test and peel test at a peel angle of 180° C in accordance with the following test methods.

Adhesion Test:

A sample was cut out round to a diameter of 10 mm. The cut piece was attached to a crosslinked collagen film swollen with water which was fixed on a phenolic resin plate and immersed in water at 37° C to observe the state of the film.

Peel Test:

A sample was cut into a strip of 2.5 cm in width and 15 cm in length. The strip was attached to a collagen film and immersed in water in the same manner as in the adhesion test, and a peel strength at a peel angle of 180° C was measured by means of a Schopper type tensile strength tester.

The results obtained are shown in Table 2 below.

TABLE 2

	Example 1	Comparative Example 1	Comparative Example 2
State of Film And Adhesion in Water	No change observed except a swelling of the periphery. Firmly adhered for 5 hrs.	Remarkable swelling from the periphery. Spontaneously separated from the adherend in 0.5 to 1.5 hrs.	Gradual swelling all over the film. Still adhered for 30 mins but with little adhesion. Spontaneously separated from the adherend in 1.5 to 2.0 hrs.
Peel Strength (g/2.5cm-width): Immersion Time:			
10 mins	110	12	20
30 mins.	105	unmeasurable	unmeasurable
60 mins.	95	"	"
120 mins.	85	"	"
240 mins.	90	"	"

As can be seen from Table 2, the samples of Comparative Examples 1 and 2 peel apart from the adherend in the early stage of immersion in water, becoming unmeasurable for peel strength when immersed for 30 minutes. On the contrary, the sample according to the present invention exhibits excellent adhesion in water, with its peel strength after 4 hour-immersion showing about 80% of the initial value. These results prove that the oral bandage of the present invention exerts strong adhesion of extremely long

duration.

EXAMPLE 2

A 10% methanolic solution of a carboxyvinyl polymer (CVP) and a 10% methanolic solution of polyvinyl acetate (PVAc) (degree of polymerization: ca. 2,500) were mixed at a CVP to PVAc ratio as shown in Table 3. The mixed solution was flow-casted on a release paper and dried to obtain an adhesive film having a thickness of 20 μm. The value A of each sample thus prepared is shown in Table 3.

The resulting film was laminated on a 50 μm thick film of polyvinyl acetate (degree of polymerization: ca. 2,500) by hot pressing to obtain an oral bandage.

Each of the samples thus obtained was determined for the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour), adhesiveness in water and peel strength at a peel angle of 180° C after 10 minutes-immersion in accordance with the methods as described in Example 1. The adhesiveness in water was expressed in terms of the time until the sample was spontaneously separated from the adherend. These test results are shown in Table 3.

TABLE 3

Mixing Ratio (CVP:PVAc)	2:8	3:7	5:5	7:3	8:2
Value A	12.5	18.8	31.3	43.8	50.0
Dissolution Ratio (%)	2	5	8	22	35
Adhesion Time (hr)	>8	>8	>8	3.2	1.5
Peel Strength (g/2.5 cm-width)	20	60	110	160	200

It can be seen from Table 3 above that when the value A falls within the range of from 15 to 45 with the CVP:PVAc ratio being from 3:7 to 7:3, the films are excellent in both adhesion time and peel strength as well as in dissolution ratio of the polycarboxylic acid, indicating usefulness as an oral bandage. However, the film having a CVP:PVAc ratio of 2:8 has the value A smaller than 15 and shows poor adhesion. On the other hand, the film having a CVP:PVAc ratio of 8:2 has a short adhesion time and a high polycarboxylic acid dissolution ratio due to the value A exceeding 45. Accordingly, these films out of the scope of the present invention are regarded as hard to use with exceptions for special purposes of use.

EXAMPLE 3

Four parts of an alternating copolymer of methyl vinyl ether and maleic anhydride and 6 parts of polyvinyl acetate (degree of polymerization: ca. 1,000) were dissolved in 90 parts of methanol. The resulting solution was flow-casted on a release paper, dried at 80° C and peeled to obtain an adhesive film having a thickness of 60 μm. The value A of this film was 23.0, and the dissolution ratio (immersion time: 1 hour) was 12%.

The oral bandage thus obtained was cut into a circle having a diameter of 10 mm. The cut piece was adhered to the palatine mucosa of 10 panel members, and the time until the sample was separated apart (peeling time) was determined. As a result, the average peeling time was 4.0 hours.

EXAMPLE 4

Six parts of polyacrylic acid (degree of polymerization: ca. 5000) and 14 parts of partially saponified polyvinyl acetate (degree of saponification: 20 mol%; degree of polymerization: ca. 1,500) were dissolved in 80 parts of methanol, and the resulting solution was flow-casted on a release paper, dried at 80° C and

peeled off to obtain an adhesive film having a thickness of 70 μm. The value A of this film was 37.5, and the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour) was 37%.

Separately, an ethylene-vinyl acetate copolymer (vinyl acetate content: 30 mol%) was hot-pressed to form a film support having a thickness of 80 μm. The above obtained adhesive film and the film support were laminated by the use of a hot laminator to produce an oral bandage.

The resulting oral bandage was cut in a strip of 7 mm in width and 20 mm in length. The cut piece was adhered to the gingival mucosa of 10 panel members, and the time until the strip was separated therefrom (peeling time) was measured. As a result, the average peeling time was 7.6 hours.

EXAMPLE 5

Four parts of a carboxyvinyl polymer and 6 parts of polyvinyl acetate (degree of polymerization: ca. 2,000) were dissolved in 92 parts of isopropanol, and 2 parts of titanium dioxide was added thereto as a coloring matter was added thereto, followed by thoroughly mixing with stirring. The mixture was flow-casted on a release paper, dried at 90° C and peeled off to obtain an adhesive film having a thickness of 15 μm. The value A of this film was 25, and the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour) was 6%. Separately, 0.1 part of Food Red 3 aluminum lake was added to 100 parts of a 20% ethyl acetate solution of polyvinyl acetate (degree of polymerization: ca. 2,000), followed by thoroughly mixing while stirring. The mixture was flow-casted on a release paper, dried at 180° C and peeled off to prepare a film support having a thickness of 30 μm. The above prepared adhesive film and the film support were laminated by hot pressing to obtain an oral bandage.

The thus obtained oral bandage was cut in a circle having a diameter of 20 mm. The cut piece was adhered to the buccal mucosa of 10 panel members, and the time until the bandage was separated therefrom (peeling time) was determined. As a result, an average peeling time was 5.6 hours.

The performance of the oral bandage to prevent running-off of a drug administered was evaluated using a food dye as a model of a drug and a crosslinked collagen film swollen with water as an adherend as follows. That is, 9.5 parts of lactose and 5 parts of Food Red 102 were ground in a mortar, and the mixture was pounched out into tablets of 5.0 mm in diameter and 0.5 mm in thickness. One of the tablets was placed on a water-swollen crosslinked collagen film that was fixed on a phenolic resin plate, and the oral bandage cut round to a diameter of 15 mm was adhered thereonto so as to cover the tablet. The sample was then immersed in water at 37° C. As a result, the time required for the dye in the tablet to be dissolved out into water was 4.1 hours as an average of 10 runs, indicating a sufficient performance property to prevent running-off of a drug administered.

Thereafter, the storage stability of the oral bandage was evaluated as follows. The oral bandage was cut in a tape of 18 mm in width and 3 m in length. The tape was rolled up, wrapped with a cellophane film, packed in a paper box of 6 cm x 6 cm x 2 cm and preserved under ambient conditions for 3 months. As a result, no change in shape or adhesion properties was noted, to confirm excellent storage stability of the oral bandage.

EXAMPLE 6

Three parts of a carboxyvinyl polymer, 2 parts of a methyl vinyl ether-maleic anhydride copolymer and 5 parts of polyvinyl acetate (degree of polymerization: ca. 2,000) were dissolved in 90 parts of methanol. The resulting mixed solution was flow-casted on a release paper, dried at 60° C and peeled off to obtain an adhesive film having a thickness of 15 μm. The value A of this film was 30.3, and the dissolution ratio of the polycarboxylic acid (immersion time: 1 hour) was 10%.

The thus obtained film was laminated on a 30 μm thick film support of polyvinyl acetate (degree of polymerization: ca. 1,500) by hot pressing to obtian an oral bandage.

The resulting oral bandage was cut round to a diameter of 10 mm, adhered to the gingival mucosa of 10 panel members, and the time until the bandage was separated therefrom (peeling time) was measured. As a result, the peeling time was 5.4 hours in average.

EXAMPLE 7

Into 90 parts of methanol were poured 4.7 parts of a carboxyvinyl polymer and 4.7 parts of polyvinyl acetate (degree of polymerization: ca. 1,500), and 0.6 part of diisopropanolamine was further added thereto, followed by mixing to form a uniform solution. The resulting solution was flow-casted on polyethylene-laminated paper dried in a drier at 80° C for 8 minutes and peeled off to prepare an adhesive film having a

thickness of 40 μm. The value A of this film was 31, and the dissolution ratio of the polycarboxylic acid was 12%, which value indicated the compatible state of the film.

The thus obtained adhesive film was laminated on a 40 μm polyvinyl acetate film (degree of polymerization: ca. 2,000) by hot pressing at 100 °C to obtain an oral bandage.

COMPARATIVE EXAMPLE 3

In 30 parts of toluene were dissolved 4.7 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) and 0.6 parts of diisopropanolamine, and 5 parts of a toluene-insoluble carboxyvinyl polymer powder was added to the solution, followed by sufficiently mixing while stirring to prepare a uniformly dispersed suspension. The resulting suspension was flow-casted on polyethylene-laminated paper dried in a drier at 100 °C for 10 minutes and peeled off to obtain an adhesive film having a thickness of 40 μm. The value A of this film was equal to that of the adhesive film of Example 7, but the dissolution ratio of the polycarboxylic acid was 72%, indicating that the carboxyvinyl polymer and the polyvinyl acetate were in a phase-separated state.

The adhesive film thus obtained was laminated on a 40 μm thick polyvinyl acetate film by hot pressing at 100 °C in the same manner as in Example 7 to obtain an oral bandage.

COMPARATIVE EXAMPLE 4

In 45 parts of pure water were dissolved 4.7 parts of a carboxyvinyl polymer and 0.6 part of diisopropanolamine. Separately, 4.7 parts of polyvinyl acetate (degree of polymerization: ca. 1,500) was dissolved in 30 parts of toluene. The two solutions were mixed and stirred in a small-sized stirrer at 5,000 rpm for 5 minutes to prepare a suspension. The resulting suspension was flow-casted on polyethylene-laminated paper, dried in a drier at 100 °C and peeled off to obtain an adhesive film having a thickness of 40 μm. The value A of this film was equal to that of the film of Example 7, but the dissolution ratio of the polycarboxylic acid was 77%, indicating that the carboxyvinyl polymer and the polyvinyl acetate were in a phase-separated state.

The film thus obtained was laminated on a 40 μm thick polyvinyl acetate film by hot pressing at 100 °C in the same manner as in Example 7 to obtain an oral bandage.

Each of the samples obtained in Example 7 and Comparative Examples 3 and 4 was evaluated for the compatible state, the adhesiveness (adhesion time) and the peel strength. The compatible state was observed in the same manner as in Example 1, and the adhesiveness and peel strength were determined in the same manner as in Example 2. Further, each sample cut round to a diameter of 10 mm was adhered to the palatine mucosa of 5 healthy male panel members, and the time until the sample was separated therefrom was measured. The adhesion was effected after lunch, and the panel members were allowed to drink and talk, ad lib. The results obtained are shown in Table 4 below.

TABLE 4

	Example 7	Comparative Example 3	Comparative Example 4
Compatible State:			
Appearance	trans-parent	turbid	turbid
Formation of Small Regions	no small regions observed	small regions observed	small regions observed
Adhesiveness (Adhesion Time) (min)	185[1)]	70[2)]	55[2)]
Peel Strength (g/2.5 cm-width)	35	10	12
Peeling Time (min)	210	25	40

Note: 1): Strong adhesion was retained for 60 minutes.

2): Only slight adhesion was noted with insubstantial adhesive strength after 60 minutes.

As is apparent from the results of Table 4, the polycarboxylic acid and the polyvinyl acetate in the film of Example 7 are in a good compatible state, making a contrast to the films of Comparative Examples 3 and 4. More specifically, the films of Comparative Examples 3 and 4 are separated from the adherend in the early stage of the adhesion test and undergo great reduction in adhesion through immersion in water for 10 minutes in the peel test. Further, these comparative samples are separated from the adherend in the test using a panel. To the contrary, the oral bandage according to the present invention exhibits excellent results in the adhesion test, peel test and panel test, demonstrating strong adhesion of long duration.

COMPARATIVE EXAMPLE 5

In order to ascertain high safety of the oral bandage of the present invention, a comparative adhesive film containing no diisopropanolamine was prepared as follows.

Carboxyvinyl polymer	5.0 parts
Polyvinyl acetate (degree of polymerization: ca. 2,000)	5.0 parts
Methanol	90.0 parts

The above components were mixed while stirring to prepare a uniform solution. The solution was flow-casted on polyethylene-laminated paper, dried in a drier at 80° C for 8 minutes and peeled off to obtain an

adhesive film having a thickness of 40 μm. The resulting film was laminated on a 40 μm thick polyvinyl acetate film (degree of polymerization: ca. 2,000) by hot pressing at 100 °C to obtain a comparative oral bandage.

Irritation of the oral bandage as obtained in Example 7 on the normal skin and injured skin of a guinea pig was determined as compared with the above obtained comparative sample in accordance with the following test method.

The back of female Hartley guinea pigs (body weight: 300 to 400 g) was shaved with an electric clipper and an electric shaver to expose the normal skin. An adhesive tape was attached to the normal skin followed by peeling 7 times, whereby the stratum corneum was removed therefrom to form injured skin.

The sample was cut round to a diameter of 10 mm, dipped in water and adhered to each of the normal skin and the injured skin. The adhered sample was covered with absorbent cotton and further closely covered thereon with an adhesive tape for tight covering. Six hours later, the sample was removed, and irritation score was judged after 1 hour and 24 hours from the removal according to the following four grades:

0 : No change
0.5: Slight Erythema
1 : Moderate Erythema
2 : Severe erythema with edema

The results obtained are shown in Table 5 below. Each score shown in Table 5 is an average of 6 runs.

TABLE 5

	Normal Skin		Injured Skin	
	1 Hr	24 Hrs	1 Hr	24 Hrs
Example 7	0.3	0.3	0.5	0.5
Comparative Example 5	0.3	0.4	0.4	2.0
Non-Treated Group	0.1	0.2	0.2	0.3

The results of Table 5 above demonstrate that the sample according to the present invention causes no irritation on not only the normal skin but the injured skin as compared with the comparative sample, although there is no difference in irritation on the normal skin between the sample of the invention and the comparative sample.

EXAMPLE 8

Carboxyvinyl polymer	8.0 parts
Polyvinyl acetate (degree of polymerization: ca. 1,500)	2.0 parts
ZnO	3.6 parts
Methanol	26.4 parts

The above components were kneaded to obtain a uniform mixture. The mixture was flow-casted on polyethylene-laminated paper having been subjected to releasability-imparting treatment, dried in a drier at 100 °C for 3 minutes and peeled off to obtain an adhesive film having a thickness of 10 μm. The value A of this film was 50. The resulting film was then laminated on a 40 μm thick film of a mixture of polyvinyl acetate (degree of polymerization: ca. 800) and polybutene (95:5) by hot pressing at 100 °C to obtain an oral bandage.

The sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 60 g/2.5 cm-width
Peeling Time: 186 minutes
Irritation Score: 0.6

EXAMPLE 9

Carboxyvinyl polymer	3.4 parts
Polyvinyl Acetate (Degree of polymerization: ca. 1,000)	8.4 parts
Sodium citrate ($Na_3C_6H_5O_7$)	0.2 part
Methanol	71.0 parts
Pure water	17.0 parts

The above components were mixed to obtain a uniform solution, and the solution was flow-casted on a polyethylene terephthalate film, dried in a drier at 80° C for 15 minutes and peeled off to obtain an adhesive film having a thickness of 80 μm. The value A of this film was 18. The resulting film was then laminated on 15 μm thick aluminum foil by hot pressing at 100° C to obtain an oral bandage.

The sample was evaluated for peel strength, peel time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 25 g/2.5 cm-width
Peeling Time: 258 minutes
Irritation Score: 0.3

EXAMPLE 10

Methyl vinyl ether/maleic anhydride alternating copolymer	4.0 parts
Polyvinyl acetate (degree of polymerization: ca. 1,500)	6.0 parts
Sodium hydroxide	0.5 part
Methanol	67.5 parts
Ethyl acetate	22.0 parts

The above components were mixed to prepare a uniform solution, and the solution was flow-casted on 15 μm thick aluminum foil and dried in a drier at 60° C for 15 minutes to obtain a composite oral bandage having a total thickness of 35 μm. The value A of the adhesive film constituting the composite oral bandage was 23.

The sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 54 g/2.5 cm-width
Peeling Time: 222 minutes
Irritation Score: 0.5

EXAMPLE 11

Polyacrylic acid	7.0 part
Saponified polyvinyl acetate (saponification degree: 20 mol%)	3.0 parts
ZnO	0.8 part
Methanol	89.2 parts

The above components were mixed to prepare a uniform solution. The solution was flow-casted on polyethylene-laminated paper, and dried in a drier at 80 °C for 10 minutes to obtain a composite oral bandage having a thickness of 50 μm. The value A of the adhesive film constituting the composite was 44.

The sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 70 g/2.5 cm-width
Peeling Time: 166 minutes
Irritation Score: 1.0

EXAMPLE 12

Carboxyvinyl polymer	4.0 parts
Polyvinyl acetate (degree of polymerization: ca. 2,000)	6.0 parts
Diisopropanolamine	0.7 part
ZnO	1.4 parts
Methanol	87.9 parts

The above components were mixed to prepare a uniform solution. The solution was flow-casted on a polyethylene terephthalate film, dried in a drier at 80 °C for 15 minutes and peeled off to obtain an adhesive film having a thickness of 30 μm. The value A of this film was 25.

Polyvinyl acetate (degree of polymerization: ca. 2,000)	80.0 parts
Titanium white	19.5 parts
Food Red 3 aluminum lake	0.5 part

The above components were mixed and formed into a film of 30 μm in thickness, and the above prepared adhesive film was laminated thereon by hot pressing at 100 °C to obtain an oral bandage.

The resulting sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results obtained are as follows:

Peel Strength: 35 g/2.5 cm-width
Peeling Time: above 300 minutes
Irritation Score: 0.4

EXAMPLE 13

Carboxyvinyl polymer	3.0 parts
Methyl vinyl ether/maleic anhydride alternating copolymer	2.0 parts
Polyvinyl acetate (degree of polymerization: ca. 1,500)	4.3 parts
Triethanolamine	0.7 part
Methanol	80.0 parts
Pure water	10.0 parts

The above components were mixed to prepare a uniform solution. The solution was flow-cast on polyethylene-laminated paper, dried in a drier at 80 °C for 10 minutes and peeled off to obtain an adhesive film having a thickness of 25 μm. The value A of this film was 33.

The resulting film was laminated on a 30 μm thick polyvinyl acetate film (degree of polymerization: ca. 1,500) by hot pressing at 100 °C to obtain an oral bandage.

The resulting sample was evaluated for peel strength, peeling time (panel test) and irritation on the injured skin in the same manner as for the sample of Example 7. The results are as follows:

Peel Strength: 42 g/2.5 cm-width
Peeling Time: 190 minutes
Irritation Score: 0.4

EXAMPLES 14 to 19

Oral preparations comprising an adhesive film or a composite of an adhesive film and a support, in which the adhesive film and/or the support contained a topical drug as shown in Table 6 below, were prepared using the materials shown in Table 6. In each example, the adhesive film and the support were prepared in the same manner as described in the corresponding example shown in the column of "material" in Table 6 except for film thickness.

TABLE 6

Example No.	Adhesive Film Material	Drug and Its Content (wt%)	Thickness (μm)	Support Material	Drug and Its Content (wt%)	Thickness (μm)
14	Example 1	Mepivacaine 5	30	Example 1	-	15
15	Example 2 (CVP/PVAc= 5/5)	-	20	Example 2	Cetylpyridinium chloride 2 ℓ-Menthol 3	50
16	Example 3	Lithospermi Radix extract	60	PVAc*	-	30
17	Example 4	Chlorhexidine-hydrochloride 2	100	-	-	-
18	Example 5	Predonisolone 0.2	40	Example 5	-	30
19	Example 6	Sodium azulene-sulfonate 0.5	20	Example 6	-	30

Note: *: Polyvinyl acetate having a degree of polymerization of about 2,000.

EXAMPLES 20 to 37

Oral preparations comprising an adhesive film and a support, in which the adhesive film or both the adhesive film and the support contained a topical drug as shown in Table 7 below, were prepared using the film materials shown in Table 7. In each example, the adhesive film and the support were prepared in the same manner as described in the corresponding example shown in the column of "material" in Table 7 except for film thickness.

TABLE 7

Example No.	Adhesive Film Material	Drug and Its Content (wt%)	Thickness (μm)	Support Material	Drug and Its Content (wt%)	Thickness (μm)
20	Example 7	Triamcinolone acetonide 0.05	30	Example 7	-	40
21	Example 7	Dipotassium glycyrrhetinate 1.0	30	Example 7	-	40
22	Example 7	Fradiomycin sulfate 1.0 Hydrocortisone acetate 0.5	30	Example 7	-	40
23	Example 7	Ethyl aminobenzoate 10.0	30	Example 7	-	40
24	Example 7	Tocopherol nicotinate 2.0 Cetylpyridinium chloride 0.2	30	Example 7	-	40
25*	Example 8	Tetracycline hydrochloride 3	20	Example 8	-	30
26*	Example 8	Strontium chloride 5	20	Example 8	-	30
27*	Example 8	Tranexamic acid 0.1	20	Example 8	-	30

* Dried at 70°C for 15 minutes

EP 0 200 508 B1

TABLE 7 (cont'd)

Example No.	Adhesive Film: Material	Adhesive Film: Drug and Its Content (wt%)	Adhesive Film: Thickness (μm)	Support: Material	Support: Drug and Its Content (wt%)	Support: Thickness (μm)
28	Example 9	Dexamethasone 0.1	60	Example 9	-	9
29	Example 9	Sodium fluoride 5	60	Example 9	-	9
30	Example 9	Lysozyme chloride 0.5	60	Example 9	-	9
31	Example 11	Lidocaine 5	50	Ethylene-vinyl acetate copolymer (vinyl acetate content: 28 wt%)	-	60
32	Example 12	Aluminum lactate 5	60	Example 12	-	30
33	Example 13	Dibucaine hydrochloride 0.5	30	Example 13	Dibucaine hydrochloride 0.5	30
34	Example 13	Dequalinium hydrochloride 2	30	Example 13	Dequalinium hydrochloride 2	30
35	Example 13	Calcitriol 0.001	40	Example 13	-	30
36	Example 13	1α,(OH)-vitamin D_3 0.005	40	Example 13	-	30
37	Example 13	1α,24(R)-$(OH)_2$-vitamin D_3 0.005	40	Example 13	-	30

The effects of the oral preparations obtained in Example 14 to 37 were evaluated by the following clinical examples.

CLINICAL EXAMPLE 1

Effect on Stomatitis

A patient (50-year-old, female) suffered from stomatitis of 5 mm in diameter on her buccal mucosa. The oral preparation of Example 20 was applied on the affected part three times a day. The inflammation subsided on the third day.

CLINICAL EXAMPLE 2

Effect on Stomatitis

A patient (27-year-old, male) with stomatitis of 6 mm in diameter on his gingival mucosa had much pain at meals. The oral preparation of Example 3 was prescribed to him with a direction to apply to the affected part at meals. He had no pain on the injured site during a meal.

CLINICAL EXAMPLE 3

Effect on the injured site by toothbrushing

A patient (8-year-old, female) had a injured site on her gingival mucosa due to brushing with a toothbrush. The oral preparation of Example 21 was applied to the injured part three times a day, while toothbrushing instructions were given to the patient. The wound healed on the 2nd day.

CLINICAL EXAMPLE 4

Effect on Halitosis

A patient (21-year-old, female) complained of bad breath. Ten oral bandages of Example 15 were prescribed to her with directions to apply to the cervix dentis of the jaw twice a day. On re-examination after 1 week, subjective symptoms disappeared.

CLINICAL EXAMPLE 5

Prophylactic Effect on Infection

⌊456 Flap operation was performed on a patient (39-year-old, male) with adult periodontitis having deep pockets. The oral preparation of Example 22 was applied on the operated part, and a pack was further applied thereon. When the pack was removed on the third day, granulation was found to be normal. The patient further received only the oral preparation twice a day for 4 days, and the postoperative course was uneventful.

CLINICAL EXAMPLE 6

Effect on Periodontal Disense

The oral preparation of Example 24 was applied to ⌊345 of a patient (45-year-old, male) with adult periodentitis having deep pockets once a day for 4 weeks. As a control, ⌊345 were not treated with the oral preparation.

As a result, in the treated part, the gingival index decreased from 2 to 1 and the pocket depth decreased from 5.5 mm to 4.0 mm. On the other hand, almost no improvement of symptoms was noted in the control part.

CLINICAL EXAMPLE 7

Effect on Dentin Hyperesthesia

A patient (36-year-old, female) complained of dentin hyperesthesia accompanied by sharp pain in ⌊4. Thirty units of the oral preparation of Example 26 were prescribed to her with a direction to apply to the affected part twice a day.

On re-examination after 3 weeks, the symptoms completely disappeared.

CLINICAL EXAMPLE 8

Effect on dentin hyperesthesia

A patient (56-year-old, female) complained of dentin hyperesthesia accompanied by sharp pain in ⌊2. The oral preparation of Example 9 were applied to the affected part twice a day.

On re-examination after four weeks, the symptoms completely disappered.

CLINICAL EXAMPLE 9

Local Anesthetic Effect

The oral preparation of Example 31 was preoperatively applied to the gingiva of a patient (41-year-old, female) with proliferative gingivitis. Thereafter, gingivectomy was performed on the patient, but the patient experienced neither pain during the operation nor paresthesia in the part where the oral preparation was not administered. Further, the postoperative course was uneventful.

Claims

1. An oral bandage comprising a soft adhesive film consisting of a mixture of (a) an acrylic acid polymer, methacrylic acid polymer and/or maleic anhydride polymer and (b) a vinyl acetate polymer, the polymers (a) and (b) being uniformly dissolved in each other without regions of phase separation, so as to be substantially water-insolubilized; and optionally a basic substance capable of neutralizing said polymers (a).

2. An oral bandage as claimed in Claim 1, wherein the weight ratio of the polymer(s) (a) to polymer (b) in the film is such that the value obtained from the following formula is from 15 to 45:

$$\frac{(\text{weight of } -COOH) + \frac{5}{4}(\text{Weight of } -CO-O-CO-)}{\text{Total weight of polymers (a) and (b)}} \times 100$$

3. An oral bandage as claimed in Claim 1 or 2, wherein said vinyl acetate polymer has an average molecular weight determined by viscosity of at least 60,000.

4. An oral bandage as claimed in any preceding claim, wherein said acrylic or methacrylic polymer contains 20% by weight or more of -COOH group and said maleic anhydride polymer contains 16% by weight or more of -CO-O-CO- group.

5. An oral bandage as claimed in any preceding claim, wherein said mixture was obtained by dissolving the polymers (a) and (b) in a solvent common to both.

6. An oral bandage as claimed in Claim 5, wherein said solvent is selected from lower alcohols, mixtures of a lower alcohol in a larger proportion and a compatible organic solvent, mixtures of a lower alcohol in a larger proportion and water, and mixtures of a lower alcohol in a larger proportion, a compatible organic solvent and water.

7. An oral bandage as claimed in Claim 6, wherein said mixture of a lower alcohol and an organic solvent contains not more than 30% by weight of the organic solvent.

8. An oral bandage as claimed in Claim 6, wherein said mixture of a lower alcohol and water or of a lower alcohol, an organic solvent and water contains not more than 30% by weight of water.

9. An oral bandage as claimed in any preceding claim wherein said basic substance (c) is at least one salt or base.

10. An oral bandage as claimed in Claim 9, wherein said basic substance is a monovalent metal salt or monovalent base and is present in an amount of from 0.03 to 0.2 equivalent based on the said

polymers (a).

11. An oral bandage as claimed in any preceding claim, wherein said oral bandage further comprises a soft film support.

12. An oral preparation comprising an oral bandage as defined in any preceding claim and a topical drug incorporated therein.

Revendications

1. Emplâtre pour la cavité buccale comprenant un film adhésive souple consistant en un mélange de (a) un polymère d'acide acrylique, un polymère d'acide méthacrylique et/ou un polymère d'anhydride maléique et (b) un polymère d'acétate de vinyle, les polymères (a) et (b) étant uniformément dissous l'un dans l'autre sans régions de séparation de phase de manière à être substantiellement rendus insolubles dans l'eau, et à choix une substance basique capable de neutraliser les dits polymères (A).

2. Emplâtre buccal selon la revendication 1, dans lequel le rapport du poids du/des polymère(s) (a) au polymère (b) dans le film est tel que la valeur obtenue par la formule ci-jointe va de 15 à 45:

$$\frac{(\text{poids du } -COOH) + \frac{5}{4}(\text{poids du } -CO-O-CO-)}{\text{poids total des polymères (a) et (b)}} \times 100$$

3. Emplâtre buccal selon la revendication 1 ou 2, dans lequel le dit polymère d'acétate de vinyle a un poids moléculaire moyen déterminé par la viscosité d'au moins 60'000.

4. Emplâtre buccal selon l'une quelconque des revendications précédentes, dans lequel le dit polymère acrylique ou méthacrylique contient 20% en poids ou plus du groupe -COOH et le dit polymère d'anhydride maléique contient 16% en poids ou plus du groupe -CO-O-CO.

5. Emplâtre buccal selon l'une quelconque des revendications précédentes, dans lequel le dit mélange a été obtenu par dissolution des polymères (a) et (b) dans un solvant qui leur est commun à tous deux.

6. Emplâtre buccal selon la revendication 5, dans lequel le dit solvant est sélectionné parmi les alcools inférieurs, les mélanges d'un alcool inférieur dans une proportion plus grande et d'un solvant compatible, les mélanges d'un alcool inférieur dans une proportion plus grande et d'eau, et les mélanges d'un alcool inférieur dans une portion plus grande, d'un solvant organique compatible et d'eau.

7. Emplâtre buccal selon la revendication 6, dans lequel le dit mélange d'un alcool inférieur et d'un solvant organique ne contient pas plus de 30% en poids de solvant organique.

8. Emplâtre buccal selon la revendication 6, dans lequel le dit mélange d'un alcool inférieur et d'eau ou d'un alcool inférieur, d'un solvant organique et d'eau ne contient pas plus de 30% en poids d'eau.

9. Emplâtre buccal selon l'une quelconque des revendication précédentes, dans lequel la substance basique (c) est au moins un sel ou une base.

10. Emplâtre buccal selon la revendication 9, dans lequel la dite substance basique est un sel de métal monovalent ou une base monovalente et est présente dans une quantité allant de 0,03 à 0,2 équivalente sur la base des dits polymères (a).

11. Emplâtre buccal selon l'une des revendications précédentes, dans lequel le dit emplâtre buccal comprend de plus un support souple de film.

12. Préparation pour la cavité de la bouche comprenant un emplâtre buccal selon l'une quelconque des revendications précédentes et un médicament topique qui lui est incorporé.

Patentansprüche

1. Oraler Verband, enthaltend einen weichen Klebefilm, bestehend aus einer Mischung von (a) einem Acrylsäurepolymer, Methacrylsäurepolymer und/oder Maleinanhydridpolymer und (b) einem Vinylacetatpolymer, wobei die Polymere (a) und (b) einheitlich ineinander aufgelöst sind, ohne Zonen von Phasentrennung, so dass sie im wesentlichen wasserinsolubilisiert sind; und gegebenenfalls eine basische Substanz, die fähig ist, die genannten Polymere (a) zu neutralisieren.

2. Oraler Verband gemäss Anspruch 1, worin das Gewichtsverhältnis des (der) Polymer(e) (a) zu Polymer (b) im Film so ist, dass der Wert, der von folgender Formel erhalten wird, 15 bis 45 ist:

$$\frac{(\text{Gewicht von } -COOH) + \frac{5}{4}(\text{Gewicht von } -CO-O-CO)}{\text{Gesamtgewicht der Polymere (a) und (b)}} \times 100$$

3. Oraler Verband gemäss Anspruch 1 oder 2, worin das genannte Vinylacetatpolymer ein mittleres durch Viskosität bestimmtes Molekulargewicht von mindestens 60'000 besitzt.

4. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin das genannte Acryl- oder Methacrylpolymer 20 Gew.-% oder mehr -COOH-Gruppen aufweist und das genannte Maleinanhydridpolymer 16 Gew.-% oder mehr -CO-O-CO-Gruppen aufweist.

5. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin die genannte Mischung durch Auflösen der Polymere (a) und (b) in einem für beide üblichen Lösungsmittel erhalten wurde.

6. Oraler Verband gemäss Anspruch 5, worin das genannte Lösungsmittel ausgewählt ist aus niederen Alkoholen, Mischungen von niederen Alkohlen in einem grösseren Anteil und einem verträglichen organischen Lösungsmittel, Mischungen eines niederen Alkoholes in einem grösseren Anteil und Wasser, Mischungen eines niederen Alkoholes in einem grösseren Anteil, einem verträglichen organischen Lösungsmittel und Wasser.

7. Oraler Verband gemäss Anspruch 6, worin die genannte Mischung eines niederen Alkohols und einem organischen Lösungsmittel nicht mehr als 30 Gew.-% des organischen Lösungsmittels enthält.

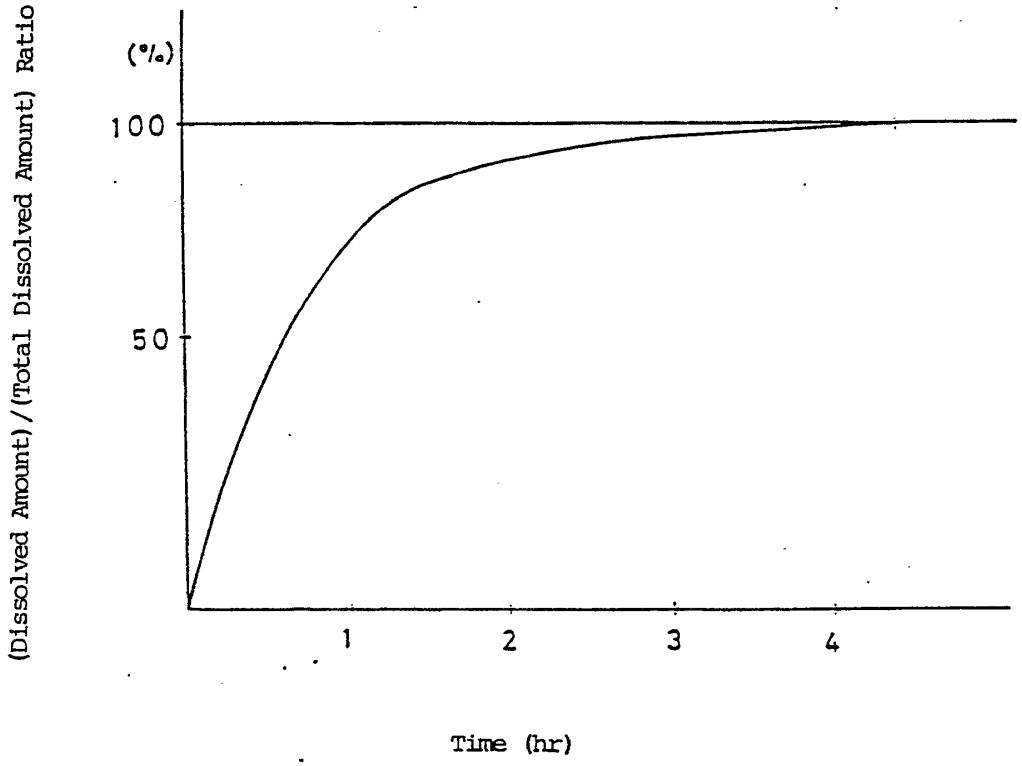
8. Oraler Verband gemäss Anspruch 6, worin die genannte Mischung eines niederen Alkohols und Wasser oder eines niederen Alkohols, eines organischen Lösungsmittels und Wasser nicht mehr als 30 Gew.-% Wasser enthält.

9. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin die genannte basische Substanz (c) mindestens ein Salz oder eine Base ist.

10. Oraler Verband gemäss Anspruch 9, worin die genannte basische Substanz ein monovalentes Metallsalz oder eine monovalente Base ist und in einem Anteil von 0,03 bis 0,2 Aequivalenten auf Basis des genannten Polymers (a) vorhanden ist.

11. Oraler Verband gemäss einem der vorhergehenden Ansprüche, worin der genannte orale Verband im weiteren einen weichen Trägerfilm aufweist.

12. Orale Zubereitung, enthaltend einen oralen Verband gemäss der Definition eines der vorhergehenden Ansprüche und eines einverleibten topischen Medikamentes.



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Veröffentlichungsnummer: **0 219 762**
B1

(12) # EUROPÄISCHE PATENTSCHRIFT

(45) Veröffentlichungstag der Patentschrift: **27.12.90**

(51) Int. Cl.[5]: **A61K 9/24**, A61K 9/70

(21) Anmeldenummer: **86113919.4**

(22) Anmeldetag: **07.10.86**

(54) **Verfahren zur Herstellung einer Darreichungs- und Dosierungsform für Arzneimittel-Wirkstoffe, Reagentien oder andere Wirkstoffe.**

(30) Priorität: **09.10.85 DE 3536024**

(43) Veröffentlichungstag der Anmeldung: **29.04.87 Patentblatt 87/18**

(45) Bekanntmachung des Hinweises auf die Patenterteilung: **27.12.90 Patentblatt 90/52**

(84) Benannte Vertragsstaaten: **AT BE CH DE ES FR GB GR IT LI LU NL SE**

(56) Entgegenhaltungen:
DE-A- 2 746 414
GB-A- 139 077
GB-A- 1 061 557

CHEMICAL ABSTRACTS, Band 85, Nr. 10, 6. September 1976, Seite 364, Zusammenfassung Nr. 68303m, Columbus, Ohio, US; & JP-A-76 54 917 (TOPPAN PRINTING CO. LTD.) 14.05.1976

(73) Patentinhaber: **Desitin Arzneimittel GmbH, Weg beim Jäger 214, D-2000 Hamburg 63(DE)**

(72) Erfinder: **Schmidt, Wolfgang, Dr., Reembroden 44, D-2000 Hamburg 63(DE)**

(74) Vertreter: **UEXKÜLL & STOLBERG Patentanwälte, Beselerstrasse 4, D-2000 Hamburg 52(DE)**

EP 0 219 762 B1

ACTORUM AG

Beschreibung

Arzneimittel können in Form von Pulvern, Tropflösungen oder Säften oral verabreicht werden. Da bei diesen Abgabeformen eine genaue Dosierung jedoch schwierig ist, werden vom Hersteller dosierte Applikationsformen wie Tabletten, Dragees oder Kapseln generell bevorzugt. Auch Reagentien und andere Wirkstoffe, z.B. Süßstoffe oder Aromastoffe, werden für eine genaue dosierte Anwendung häufig tablettiert. Die Herstellungstechnik für Tabletten, Dragees, Kapseln und dergleichen ist zwar weitgehend ausgereift, doch sind eine Reihe von systembedingten Nachteilen nicht zu übersehen.

Für niedrig dosierte Wirkstoffe muß ein großer Anteil an Hilfsstoffen zugesetzt werden, um zu einer handhabbaren Größe der Einzeldosis zu gelangen. Weiterhin ist eine genaue Kennzeichnung einzelner Tabletten oder Dragees praktisch nicht möglich. Es haben sich deshalb Durchdrückpackungen durchgesetzt, welche eine Mehrzahl von Tabletten, Dragees oder auch Kapseln enthalten und welche mit den notwendigen Informationen, insbesondere dem Namen des Präparates bedruckt sind. Die Herstellung solcher Verpackungen erfordert naturgemäß einen zusätzlichen Arbeitsgang und es werden Umverpackungen in Form von Faltschachteln benötigt, welche ein beträchtliches Leervolumen aufweisen und dadurch zusätzlich Lagerraum beanspruchen. Ein besonders gravierender Nachteil von Dragees und Kapseln besteht darin, daß eine Zerteilung praktisch unmöglich ist, die kleinste Dosis somit vorgegeben ist. Auch bei Tabletten ist eine genaue Zerteilung schwierig, lediglich größere Tabletten mit einer Kerbe als Sollbruchstelle lassen sich allenfalls teilen, wobei häufig ungleichgroße Bruchstücke entstehen.

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekannt geworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-A 637 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. durch Auftragen oder -streuen beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Die Wirkstoffdosierung ist dabei zwangsläufig äußerst ungenau. Aus den DE-A 2 432 925 und DE-A 2 449 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Daneben können die Folien Füllstoffe und Trennmittel enthalten. Die DE-A 2 746 414 beschreibt ebenfalls die Verarbeitung von wirkstoffhaltigen Folienmassen auf Basis von beispielsweise Gelatine oder Zellulosederivaten und weiteren Zusätzen wie Stärke zu Folien, in die der Wirkstoff eingearbeitet ist. Die erhaltenen wirkstoffhaltigen Folien lassen sich zur Dosierung durch Perforation in einzelne Abschnitte aufteilen.

Aus der GB-A 1 061 557 ist es bekannt, Gelatinefolien oder Reispapier mit einer Wirkstofflösung zu imprägnieren oder mit einer Wirkstofflösung bzw. -schmelze zu beschichten. Die Beschichtung erfolgt durch Besprühen mit der Lösung oder durch Laminieren von zwei Trägerfolien mit der dazwischen liegenden Wirkstoffschmelze. Diese Herstellungsverfahren ermöglichen keine exakte Dosierung des Wirkstoffes: Beim Aufsprühen einer Wirkstofflösung kann ebenso wie beim Beschichten mit einer Schmelze eine völlig gleichmäßige Schichtdicke nicht sichergestellt werden. Darüber hinaus haftet die nur aus dem Wirkstoff bestehende Beschichtung häufig schlecht auf der Trägerfolie.

Die JA-A 76/54 917 erwähnt die Möglichkeit, eßbare Folien, z.B. Gelatinefolien, mit Wirkstofflösungen zu bedrucken, welche Verdickungsmittel wie Hydroxylpropylzellulose enthalten. Auch bei dieser Vorgehensweise erhält man häufig nur schlecht haftende Beschichtungen.

Alle diese Vorschläge haben keinen Eingang in die Praxis gefunden und in dem neuesten Lehrbuch der "Arzneiformenlehre" von P.H. List, 4. Auflage, Stuttgart, 1985, finden sie keine Erwähnung. Dies beruht ersichtlich darauf, daß die bislang bekanntgewordenen Vorschläge es nicht ermöglichen, die geforderte Gewichtskonstanz und gleichmäßige Wirkstoffverteilung zu erreichen, welche heute gefordert werden. Die Pharmakopoea Europae setzt zum Beispiel Maßstäbe für die Gleichförmigkeit des Gewichtes einzeldosierter Arzneiformen, wobei diese dem jeweiligen Durchschnittsgewicht entsprechend nach höchstzulässigen Abweichungen in % gestattelt sind. Die Forderung liegt im allgemeinen bei +/– 5 bis max. 10%. Entsprechende Werte für feste Arzneiformen bestehen auch hinsichtlich anderer Parameter wie Zerfallzeit und Lösungsgeschwindigkeit.

Die oben erwähnten Vorschläge des Standes der Technik führen zu Produkten ungenügender Akzeptanz durch die Patienten (z.B. lassen sich Papierabschnitte nur schlecht einnehmen) und erlauben keine exakte Dosierung pro Flächeneinheit, wie sie unbedingt gefordert werden muß. Bei Inkorporieren des Wirkstoffes in eine Folie bereitet nicht nur die genaue Dosierung Schwierigkeiten, sondern ein wesentlicher weiterer Nachteil besteht darin, daß für jeden Wirkstoff eine entsprechende Folie gesondert hergestellt werden muß, so daß die Wirtschaftlichkeit des Herstellungsverfahrens nicht gegeben ist.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine "zweidimensionale" Darreichungs- und Dosierungsform zu schaffen, welche die genannten Nachteile nicht aufweist, sich leicht herstellen läßt und mit großer Flexibilität an die Anforderungen des Marktes und verschiedener Wirkstoffe angepaßt werden kann.

Gegenstand der Erfindung ist ein Verfahren zur Herstellung einer Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder andere Wirkstoffe in Form einer wasserlöslichen Folie auf Basis von Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen, welches dadurch gekennzeichnet ist, daß man

a) eine wäßrige Zusammensetzung, deren Rezeptur derjenigen der Trägerfolie entspricht, aus dem Wirkstoff sowie Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen hergestellt, und

b) diese Beschichtungsmasse kontinuierlich mittels eines Walzenauftragsverfahrens in genau vorbestimmter Menge (Schichtdicke) auf mindestens eine Seite der wasserlöslichen wirkstofffreien Folie aufbringt.

Die erfindungsgemäß hergestellte Darreichungsform weist eine Reihe wesentlicher Vorteile auf:

– Eine Trägerfolie kann für die verschiedensten Wirkstoffe verwendet werden und somit in größerer Menge wirtschaftlich produziert werden,

– die wirkstoffhaltige Schicht kann bei hochwirksamen Arzneimitteln sehr dünn sein, da das Trägermaterial die ausreichende mechanische Festigkeit gewährleistet,

– die Beschichtung haftet hervorragend auf der Trägerfolie, weil beide dieselbe Rezeptur aufweisen,

– mit Hilfe der modernen Walzen-Auftragverfahren läßt sich die wirkstoffhaltige Beschichtung mit konstanter Schichtdicke aufbringen, so daß die erforderlichen Toleranzen eingehalten werden können,

– falls eine Sterilisierung erforderlich ist, kann diese wegen der geringen Schichtdicke problemlos mittels Strahlenbehandlung erreicht werden,

– der Träger läßt sich auf der Vorder- und insbesondere der Rückseite unter Verwendung physiologisch verträglicher Druckfarben mit verschiedenen Informationen bedrucken,

– aufgrund der relativ großen Fläche von beispielsweise 4 bis 10 cm^2 lassen sich ausführliche Informationen für den Benutzer auf das unbeschichtete Trägermaterial oder auch nachträglich aufdrucken,

– die Dosiereinheiten lassen sich durch entsprechende Vorzerteilung, z.B. eine Perforierung, flexibel gestalten, so daß für verschiedene Dosierungen (z.B. für Erwachsene und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

Mit den früher beschriebenen Darreichungsformen in Folienform hat die erfindungsgemäße darüberhinaus den Vorteil des äußerst geringen Platzbedarfes gemeinsam. Statt Faltschachteln können daher beispielsweise Taschen oder Beutel aus Kunststoffolie oder kunststoffbeschichtetem Papier verwendet werden, in welche das Produkt eingesiegelt wird, ähnlich wie feuchte Erfrischungstücher.

Die Herstellung der Trägerfolie erfolgt in an sich bekannter Weise mit einer kontinuierlich arbeitenden Folienmaschine auf Rollenbasis. Das Streichverfahren zur Herstellung der Trägerfolie arbeitet nach dem Walzenprinzip, d.h. die wasserhaltige Zusammensetzung für die Trägerfolie wird mittels Rollen und Rakel angetragen und zu dünnen Bahnen ausgestrichen, auf der Rolle vorgetrocknet und im Haupttrockengang auf die gewünschte Endfeuchte nachgetrocknet. Das erhaltene Endprodukt ist so fest und elastisch, daß es auf Rollen gewickelt werden kann und lagerfähig ist, wenn die Restfeuchtigkeit nicht zu hoch ist (Gefahr der Schimmelbildung).

Die Folienbreite kann beliebig sein und wird günstigerweise auf die Breite der Beschichtungsmaschine zugeschnitten. Es bietet sich jedoch an, bereits bei der Herstellung beide Breiten aufeinander abzustimmen.

Es ist technisch auch möglich, die Folienherstellung und die Beschichtung zeitlich nacheinander auf derselben Anlage vorzunehmen, wodurch die Wirtschaftlichkeit wesentlich erhöht werden kann.

Die verwendete Zusammensetzung wird unter Umpumpen bei der gewünschten Temperatur, Viskosität und Homogenität gehalten. Die Trocknung der Folie erfolgt anschließend in einem Wärmetunnel. Die so gewonnene Trägerfolie stellt den indifferenten Träger für die spätere Beschichtung mit verschiedene Wirkstoffe enthaltenden Beschichtungsmassen dar.

Zur Herstellung der wasserlöslichen Trägerfolie dient eine physiologisch unbedenkliche Zusammensetzung. Die "Wasserlöslichkeit" soll dabei so definiert sein, daß die Herstellung der Folie aus einer wäßrigen Zusammensetzung erfolgt und daß sich die fertige Folie später bei der Anwendung wiederum in Wasser bzw. im Magensaftmilieu löst oder darin quillt.

Als Folienbildner kommen insbesondere Gelatinen sowie Stärken (Kartoffelstärke, Weizenstärke, Maisstärke) sowie ferner Poly-N-vinylpyrrolidon (PVP), Methyl- und Ethylzellulose sowie Polyvinylalkohol (PVA) infrage. Ferner können wässerlösliche Acrylharzdispersionen Verwendung finden. Geeignete Weichmacher sind insbesondere polyfunktionelle Alkohole wie Glycerin und Sorbit (Karion®).

Die Komponenten werden in geeigneter Weise mit Wasser kalt angemischt und unter leichtem Erwärmen und ständigem Rühren zu einem streichfähigen Schleim verarbeitet. Das Einrühren von Luft muß soweit wie möglich vermieden werden, um eine klare, allenfalls leicht opaleszierende Masse zu erhalten.

Die Stärke der Trägerfolie beträgt vorzugsweise zwischen etwa 50 und 250 µm. Sie ist in weitem Maße steuerbar. Auch die Eigenschaften der Trägerfolie lassen sich durch entsprechende Kombination der Folienbildner und Weichmacher qualitativ stark beeinflussen. Die Trägerfolie soll eine möglichst gleichmäßige Stärke aufweisen (vorzugsweise z.B. 100 µm), leicht elastisch und knickfähig sein, ohne zu brechen. Dabei sollte der Stärkeanteil ausreichend hoch sein, damit beim Aufbringen der Beschichtungsmasse Feuchtigkeit aufgenommen wird, ohne daß es zu einem Kleben der Oberfläche oder zum Erweichen der ganzen Folie kommt.

Folgende Rahmenrezeptur hat sich für die Trägerfolie bewährt:

Gelatine 8 bis 10 g
Stärke 4 bis 8 g
Glycerin 1 bis 2 g

Polyvinyl-pyrrolidon 1 bis 2 g
Wasser 30 bis 50 g

Wasserlösliche natürliche und/oder synthetische Harze, z.B. Acrylharze, und Gumme sind ebenfalls geeignet. Ggf. können der Masse noch übliche weitere Stoffe zugefügt werden, z.B. Konservierungsmittel wie p-Hydroxybenzoesäure-Ester, inerte lösliche oder unlösliche Füllstoffe, Geschmackstoffe, Zucker oder andere Süßungsmittel, weitere Weichmacher, insbesondere Polyole, Wachse oder Farbstoffe.

Die Möglichkeit der vorder- und rückseitigen Bedruckung der Trägerfolie ist ein besonderer Vorteil der erfindungsgemäßen Darreichungsform. Beispielsweise können die Kennzeichnung, Angaben über die Inhaltsstoffe sowie Dosierungsangaben aufgedruckt werden. Gegebenenfalls läßt sich sogar der ganze Inhalt eines Beipackzettels rückseitig aufdrucken mit der Folge, daß ein separater Beipackzettel, der auch häufig verlorengeht, überflüssig wird. Bei Arzneimitteln, welche regelmäßig genommen werden müssen, beispielsweise bei hormonalen Contrazeptiva, kann der gesamte Verabreichungsplan so angebracht werden, daß eine einfache Einnahmekontrolle gewährleistet ist. Zur Bedruckung müssen physiologisch verträgliche Farben (Lebensmittelfarben) verwendet werden, da die Trägerfolie einen Teil der oral verabreichten Darreichungsformen bildet.

Für die wirkstoffhaltige Beschichtungsmasse findet eine wäßrige Zusammensetzung Verwendung, die physiologisch inert ist und deren Einzelkomponenten für Arzneimittel bzw. Lebensmittel geeignet sind. Wesentlich ist die gegenseitige physikalisch-chemische Affinität und Verträglichkeit zwischen Beschichtungsmasse und Trägerfolie, welche besonders gut ist, weil die verwendeten Komponenten gleich sind bzw. sehr ähnliche Eigenschaften besitzen. Unter Berücksichtigung des zugeführten Wirkstoffes entspricht die Rezeptur der Beschichtungsmasse demgemäß der oben für die Trägerfolie genannten, wobei die genaue Einstellung auf Feststoffgehalt und Viskosität mittels indifferenter Quell- und Füllstoffe erfolgt.

Die Masse enthält somit einmal polymere Filmbildner, vorzugsweise Gelatine und quellende oder lösliche Stärken sowie ggf. Zellulosen oder Hemizellulosen. Ferner werden Weichmacher zugesetzt, insbesondere mehrwertige Alkohole wie Glycerin oder Sorbit. Zur Einstellung der erwünschten Viskosität der Beschichtungsmasse, welche die Konsistenz eines Schleimes aufweist, finden polymere Quellstoffe Verwendung, vorzugsweise Alginate, Pectine, Chitine, Lecithine oder Polyethylenglykole. Diese letzteren Stoffe können gleichzeitig als Haftvermittler dienen. Andererseits können auch wasserlösliche synthetische oder natürliche Harze oder Gumme oder Gummi arabicum zugesetzt werden, um die Haftung der Beschichtung auf dem Trägermaterial zu verbessern. Schließlich können noch Konservierungsmittel wie z.B. p-Hydroxybenzoesäureester, Farbstoffe (Lebensmittelfarbstoffe), Pigmente wie Titandioxid oder Aroma- und Süßstoffe zugesetzt werden.

Coatingmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10 000 cPs haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

In dieser Grundmasse wird der Wirkstoff gelöst bzw. dispergiert. Im Fall der Verwendung einer Dispersion muß der Wirkstoff für eine gleichmäßige Verteilung äußerst feinteilig sein. Vorzugsweise liegt die mittlere Teilchengröße im Bereich von etwa 1 bis 20 µm.

Die gewünschte Dosis des Wirkstoffes und die angestrebte Fläche der Dosiseinheiten bestimmen letztlich die Dicke der Schicht, wobei der Feuchtigkeitsgehalt der Beschichtungsmasse und der fertigen Beschichtung zu berücksichtigen sind.

Die erfindungsgemäße Darreichungsform ist besonders geeignet für Arzneimittel, welche niedrig dosiert verabreicht werden, d.h. bei welchen die Einzeldosis für die orale Applikation zwischen 0 mg (Placebo) und etwa 20 mg liegt. Geeignete Arzneimittelwirkstoffe finden sich in allen Bereichen der oralen Therapie; hervorzuheben sind u.a. Analeptika, Antibiotika, Antidiabetika, Antiemetika, Antiepileptika, Antihypertonika, Cortikoide, Geriatrika, Hypnotika, Cardiaka, Hypostatika und Biowirkstoffe.

In einem Beschichtungsgang lassen sich ca. 4 bis 20 g Wirkstoff je m^2 (= 10.000 cm^2) Trägerfolie aufbringen, so daß 10 cm^2 (= 2 übliche Briefmarken) bis zu 20 mg Wirkstoff aufnehmen können.

Die Beschichtungsmasse wird normalerweise auf eine Seite der Trägerfolie aufgebracht, doch ist auch eine beidseitige Beschichtung, insbesondere bei zwei verschiedenen Wirkstoffen möglich. Jede Beschichtung kann einen oder mehrere Arzneimittelwirkstoffe enthalten. Falls bei Verwendung mehrerer Wirkstoffe diese nicht ohne weiteres miteinander verträglich sind und in einer Beschichtungsmasse enthalten sein können, ist es bei der erfindungsgemäßen Darreichungsform möglich, die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufzubringen und die Wirkstoffe dadurch voneinander zu trennen, wobei erforderlichenfalls eine wirkstofffreie Zwischenschicht vorgesehen werden kann. Weiterhin ist es möglich, über der wirkstoffhaltigen Schicht noch eine weitere Schutzschicht vorzusehen, welche den/die Wirkstoff(e) genen eine Berührung mit der Atmosphäre und/oder gegen Licht schützt. In diesen Fällen muß die Schutzschicht demgemäß luft- und feuchtigkeitsundurchlässig und/oder durch Zusatz entsprechender Farbstoffe bzw. Pigmente lichtundurchlässig sein.

Weiterhin kann durch entsprechenden Aufbau der Beschichtung die Wirkstoffabgabe nach Verabreichung des Arzneimittels gesteuert werden. Beispielsweise ist es möglich, eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten anzuordnen, welche die Wirkstoffresorption im Magen/Darmtrakt in an sich bekannter Weise steuern.

Dabei kann die Wirkstoffschicht z.B. zwischen zwei säureunlöslichen Schichten angeordnet werden, so daß bei Verabreichung der Magen passiert wird und die Resorption erst im Darmtrakt erfolgt. In ähnlicher Weise können unterschiedliche Wirkstoffe in verschiedenen Schichten übereinander auf die Trägerfolie aufgebracht werden, damit die Resorption nacheinander und/oder verzögert erfolgt.

Ähnliche pharmakokinetische Effekte lassen sich durch das Einarbeiten (z.B. Suspendieren) von unterschiedlich vorbehandelten mikroverkapselten Wirkstoffen erzielen.

Die Beschichtung des Trägermaterials mit der wirkstoffhaltigen Beschichtungsmasse erfolgt mittels eines Walzenauftragverfahrens. Dieses für die quantitative Beschichtung besonders geeignete Verfahren arbeitet nach einem dem Tiefdruck ähnlichen Verfahren, welches als "Akkugravur" bezeichnet wird. Hierfür geeignete Maschinen sind im Handel (Fa. Pagendarm, Hamburg) und erlauben Auftragsgewichte bis zu 80 g/m² bei Bahngeschwindigkeiten von mehreren 100 m/min. Die reproduzierbare Gewichtskonstanz liegt für 20 g/m² bei nur +/- 2,5% für 1 g/m² und für ca. +/- 10% über die gesamte Fläche. Der Auftrag der Beschichtungsmasse erfolgt kontinuierlich über Walzen mit spezieller Feingravur, wobei die eingravierten Rillen zur Laufrichtung der Trägerfolie vorzugsweise einen Winkel von 30 bis 60, insbesondere 45° bilden. In die Walzen können 27 bis 80 Rillen/cm eingeätzt sein. Entsprechend ihrer Form und Tiefe kann die Gravur eine definierte Menge der Beschichtungsmasse aufnehmen und anschließend an die Trägerfolie weitergeben. Durch Variation der Vorlaufgeschwindigkeit, der Laufrichtung und der Gravur sowie durch indirektes Auftragen über eine weitere geschwindigkeitsvariable Walze lassen sich die Beschichtungsmengen sehr exakt einstellen.

Eine zweiseitige Beschichtung ergibt häufig Vorteile, da Probleme durch Verwerfen des Trägermaterials und durch unterschiedliche Hygroskopizität ausgeglichen werden. Mehrfach- und auch Streifenbeschichtungen, ja sogar Druckbildbeschichtungen, sind möglich und bieten bei der Verarbeitung von inkompatiblen Wirkstoffen eine große Variabilität.

Ein anderes geeignetes Auftragverfahren entspricht dem Streichen von Papier oder von Folien. Dabei werden Rohpapiere dadurch verbessert, daß sie ein- oder zweiseitig mit Coatingmaterialien beschichtet werden. Die wässrigen Beschichtungsmassen gelangen zunächst auf ein Walzwerk, welches sie mittels einer rotierenden Walze aufnimmt, mit einen Rakel bestimmten Abstandes auf eine definierte Schichtdicke abstreift, worauf die Walze die Beschichtungsmasse auf den Träger abgibt. Die Trägerfolie, welche 0,30 bis 7,50 m breit sein kann, durchläuft anschließend einen Trockentunnel und wird dann auf Rollen aufgewickelt. Dieser Vorgang ist in einem oder mehreren Schritten ein- oder zweiseitig wiederholbar, wobei auch eine bereits beschichtete Fläche nochmals beschichtet werden kann. Das Gewicht des Trägermaterials nimmt um das der Trockenmasse zu. Die Genauigkeit des Auftragverfahrens mittels dieses Rakel-Verfahrens liegt reproduzierbar bei +/- 5%. Sie ist abhängig von der jeweiligen Schichtdicke, die variabel zwischen 4 und 40 g/m² betragen kann. Innerhalb der einzelnen Fertigungen kann eine Gewichtstoleranz pro Flächeneinheit bis unter +/- 1 % erreicht werden.

Bei Aufbringung mehrerer Schichten, wie dies oben bereits beschrieben wurde, werden diese nacheinander aufgebracht, wobei ggf. jede Beschichtung zuvor eine Trocknungsstation durchläuft. Diese kann beispielsweise aus einem temperierten Walzenpaar und einem in Sektionen steuerbaren Trockentunnel bestehen. Nach dem letzten Beschichtungsvorgang wird das beschichte Material auf Rollen aufgewickelt.

Die wirkstoffbeschichtete Trägerfolie wird anschließend in Dosiseinheiten vorzerteilt, welche ähnlich wie Briefmarken abtrennbar sind. Normalerweise wird diese Vorzerteilung beim Arzneimittelhersteller erfolgen, es ist jedoch auch denkbar, das beschichtete Material beispeilsweise an Krankenhäuser oder Apotheken auszuliefern, wo dann die Vorzerteilung dosisabhängig oder auch individuell nach ärztlicher Vorgabe durchgeführt werden kann.

Die Vorzerteilung erfolgt in besonders einfacher Weise durch Perforierung oder Stanzung, wobei es möglich ist, diesen Schritt mit der Bedruckung des Trägermaterials zu kombinieren. In vielen Fällen wird es allerdings günstiger sein, die Bedruckung des Trägermaterials vor der Beschichtung vorzunehmen.

Vor oder besser nach Vorzerteilung der wirkstoffhaltigen Beschichtung in Dosiseinheiten wird das beschichtete Trägermaterial zu gebrauchsfertigen Abschnitten zerschnitten, welche eine bestimmte Anzahl von Dosiseinheiten enthalten. Es ist auch denkbar, das Material auf Rollen zu schmalen Bändern zu zerschneiden. Von einer solchen Einzelrolle können dann die einzelnen Dosiseinheiten ähnlich wie einzelne Briefmarken abgetrennt werden.

Da als Grundstoffe für die Herstellung der erfindungsgemäßen Darreichungsform überwiegend Naturstoffe wie Stärken und Gelatine verwendet werden, erhält man insgesamt Produkte, welche den bekannten Oblaten ähneln und deren orale Einnahme keinerlei Schwierigkeiten bereitet. Wichtig ist, daß das Fertigprodukt weitgehend von Wasser befreit ist, d.h. einen Wassergehalt von wengier als 10 und vorszugsweise von weniger als 2% aufweist, da sonst Schimmelbildung auftreten kann.

Vorstehend wurde die Erfindung im wesentlichen im Zusammenhang mit Arzneimitteln beschrieben, worauf sie jedoch keineswegs beschränkt ist. Beispielsweise lassen sich in derselben Weise auch Dosierungsformen für chemische Reagentien, Aromastoffe und dergleichen herstellen.

Zur näheren Erläuterung der Erfindung soll das nachfolgende Ausführungsbeispiele dienen.

Beispiel

Herstellung einer Arzneimittel-Darreichungsform in Form einer beschichteten Folie.

Zur Herstellung einer wasserlöslichen Trägerfolie wurde von folgender Zusammensetzung ausgegangen:
Gelatine 10,0 Gew.-Teile = 25%
Kartoffelstärke 8,0 Gew.-Teile = 20%
Glycerin 1,5 Gew.-Teile = 3,75%
gereinigtes Wasser 20,5 Gew.-Teile = 51,25%

Die Viskosität der schleimartigen Zusammensetzung betrug bei 50°C ca. 3000 cPs. Mit Hilfe des Streichverfahrens wurde die Masse zu einer Folie verarbeitet, welche nach dem Trocknen noch 9,3% Restwasser enthielt.

Unter Verwendung derselben Grundstoffe wie für die Trägerfolie wurde die Beschichtungsmasse gemäß folgender Rezeptur hergestellt:
Gelatine 10,0 Gew.-Teile = 18,2%
Kartoffelstärke 5,0 Gew.-Teile = 9,1%
Glycerin 1,0 Gew.-Teile = 1,8%
Wirkstoff 5,0 Gew.-Teile = 9,1%
gereinigtes Wasser 34,0 Gew.-Teile = 61,8%

Die Viskosität der schleimartigen Zusammensetzung betrug temperatur- und wirkstoffabhängig zwischen 4.000 und 10.000 cPs. Zur Herstellung der Beschichtungsmasse wurde zunächst die Gelatine in einer ausreichenden Menge Wasser gelöst. Dazu wurde Wasser von 90 bis 95°C vorgelegt, in das die Gelatine unter Rühren eingetragen wurde. In einem getrennten Ansatz wurde der Wirkstoff zusammen mit dem Glycerin in Wasser gelöst. Schließlich wurde die Kartoffelstärke bei 50 bis 60°C unter Rühren in einer ausreichenden Menge Wasser angerührt. Die Gelatinelösung und die Kartoffelstärkesuspension wurden zusammengegeben und die Wirkstoffsuspension wurde in die Mischung langsam eingerührt, wobei Lufteinschlüsse vermieden wurden. Die Temperatur wurde auf 55 bis 60°C gehalten. Zuletzt wurde der gewünschte Wassergehalt durch Zugabe von weiterem Wasser eingestellt.

Die Beschichtungsmasse wurde mittels Akkugravur mit einem Naßbeschichtungsgewicht von 55 g/m² auf die Trägerfolie aufgebracht. Nach dem Trocknen betrug das Beschichtungsgewicht 23 g/m² entsprechend einem Wirkstoffgehalt von 5 g/m². Die wirkstoffbeschichtete Folie wurde anschließend kastenartig perforiert, so daß die einzelnen Abschnitte bei Abmessungen von 2 x 2,5 cm eine Fläche von 5 cm² aufwiesen. Ein solcher Abschnitt enthielt 2.5 mg Wirkstoff.

Nach dem Trocknen lag die Restfeuchtigkeit des Produktes bei 8,6%.

Es wurde eine Darreichungsform erhalten, welche bei oraler Einnahme im Mund rasch quillt und zergeht und sich demgemäß leicht schlucken läßt.

Patentansprüche

1. Verfahren zur Herstellung einer Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder andere Wirkstoffe in Form einer wasserlöslichen Folie auf Basis von Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen, dadurch gekennzeichnet daß man
a) eine wässrige Zusammensetzung, deren Rezeptur derjenigen der Trägerfolie entspricht, aus dem Wirkstoff sowie Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen herstellt, und
b) diese Beschichtungsmasse kontinuierlich mittels eines Walzenauftragsverfahrens in genau vorbestimmter Menge (Schichtdicke) auf mindestens eine Seite der wasserlöslichen wirkstofffreien Folie aufbringt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man der Zusammensetzung für die Trägerfolie und die Beschichtung zusätzlich inerte lösliche und/oder unlösliche Füllstoffe, Zucker und/oder andere Süßungsmittel, weitere Weichmacher, insbesondere Polyole, Wachse, Farbstoffe, Geschmacksstoffe und/oder Konservierungsmittel zusetzt.

3. Verfahren nach einem der Ansprüche 1 oder 2, dadurch gekennzeichnet, daß man für die Herstellung der Trägerfolie und der Beschichtungsmasse eine Zusammensetzung verwendet, die 8 bis 10 Gew.-Teile Gelatine, 4 bis 8 Gew.-Teile Stärke, 1 bis 2 Gew.-Teile Glycerin und 20 bis 50 Gew.Teile Wasser enthält.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß man eine Beschichtungsmasse einsetzt, die bis zu 10 Gew.-Teile des Wirkstoffes enthält.

5. Verfahren nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß man der Beschichtungsmasse zur Einstellung der Viskosität indifferente Quell- und Füllstoffe zusetzt.

6. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß man die Beschichtungsmasse kontinuierlich mittels Rasterwalzen, welche eine genau definierte Menge der Beschichtungsmasse aufnehmen und wieder abgeben, auf die Trägerfolie aufbringt.

7. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß man die Beschichtungsmasse kontinuierlich mittels glatter Walzenpaare, welche in geschwindigkeitsversetztem Gleichlauf die Masse aufnehmen und in definierter Menge abgeben, auf die Trägerfolie aufbringt.

8. Verfahren nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß man zur Herstellung eines Kombinationspräparates auf die Ober- und die Unterseite der Trägerfolie unterschiedliche Wirkstoffe aufbringt.

Claims

1. Process for the manufacture of a presentation and dosage form for pharmaceutical active substances, reagents or other active substances in the form of a water-soluble foil based on starches, gelatines, glycerin and/or sorbite and also in some cases on natural and/or synthetic resins and gums, characterized in that
a) an aqueous composition, the formulation of which corresponds to that of the carrier foil, is manufactured from the active substance and from starches, gelatines, glycerin and/or sorbite and also in some cases from natural and/or synthetic resins and gums, and that

b) this coating substance is applied continuously in a precise pre-determined quantity (layer thickness) to at least one side of the active-substance-free-water-soluble foil by means of a roller coating process.

2. Process according to claim 1, characterized in that inert, soluble and/or insoluble fillers, sugars and/or other sweeteners, other softeners, particularly polyols, waxes, colorants, flavouring agents and/or preservatives are also added to the composition for the carrier foil and the coating.

3. Process according to one of claims 1 or 2, characterized in that, for the manufacture of the carrier foil and the coating substance, a composition is used which contains 8 to 10 parts by weight of gelatine, 4 to 8 parts by weight of starch, 1 to 2 parts by weight of glycerin and 20 to 50 parts by weight of water.

4. Process according to claim 3, characterized in that a coating substance is used which contains up to 10 parts by weight of the active substance.

5. Process according to one of claims 1 to 4, characterized in that inert swelling agents and fillers are added to the coating substance to regulate the viscosity.

6. Process according to one of claims 1 to 5, characterized in that the coating substance is continuously applied by means of grid rollers which take up and then release a precisely defined quantity of the coating substance.

7. Process according to one of claims 1 to 5, characterized in that the coating substance is applied to the carrier foil continuously by means of smooth pairs of rollers synchronized but out of phase which take up the substance and release a pre-defined quantity.

8. Process according to one of claims 1 to 7, characterized in that different active substances are applied to the top and bottom of the carrier foil for the manufacture of a compound preparation.

Revendications

1. Procédé de fabrication d'une forme d'administration et de dosage pour des principes actifs de médicaments, des réactifs ou d'autres substances actives, sous forme d'une feuille hydrosoluble à base d'amidons, de gélatines, de glycérol et/ou de sorbitol, et éventuellement de résines et gommes naturelles et/ou synthétiques, procédé caractérisé en ce que l'on

a) fabrique une composition aqueuse, dont la formulation correspond à celle de la feuille support, à partir de la substance active ainsi que d'amidons, de gélatines, de glycérol et/ou de sorbitol, et éventuellement de résines et gommes naturelles et/ou synthétiques, et

b) dépose en continu, à l'aide d'un cylindre d'enduction, cette masse, en quantité exactement prédéterminée (épaisseur de couche), sur au moins une des faces de la feuille hydrosoluble dépourvue de substance active.

2. Procédé selon la revendication 1, caractérisé en ce que l'on ajoute en plus, à la composition pour la feuille support et le revêtement, des charges inertes solubles et/ou insolubles, des sucres et/ou d'autres édulcorants, en outre des plastifiants, en particulier des polyols, des cires, des colorants, des aromatisants et/ou des conservateurs.

3. Procédé selon l'une des revendications 1 ou 2, caractérisé en ce que, pour la fabrication de la feuille support et du revêtement, on utilise une composition qui renferme de 8 à 10 parties en poids de gélatine, 4 à 8 parties en poids d'amidon, 1 à 2 parties en poids de glycérol et 20 à 50 parties en poids d'eau.

4. Procédé selon la revendication 3, caractérisé en ce que l'on met en œuvre une masse d'enduction qui renferme jusqu'à 10 parties en poids de la substance active.

5. Procédé selon l'une des revendications 1 à 4, caractérisé en ce que l'on ajoute des agents gonflants et charges inertes à la masse d'enduction, pour ajuster la viscosité.

6. Procédé selon l'une des revendications 1 à 5, caractérisé en ce que l'on dépose en continu la masse d'enduction sur la feuille support, à l'aide de cylindres à trame, qui prennent puis rétrocèdent une quantité exactement définie de la masse d'enduction.

7. Procédé selon l'une des revendications 1 à 5, caractérisé en ce que l'on dépose en continu la masse d'enduction sur la feuille support, à l'aide de paires de cylindres lisses, qui prennent la masse avec un syndrome décalé de la vitesse et la rétrocèdent en quantité définie.

8. Procédé selon l'une des revendications 1 à 7, caractérisé en ce que, pour fabriquer une préparation combinée, on dépose différentes substances actives sur la face supérieure et sur la face inférieure de la feuille support.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 250 187 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **29.09.93** (51) Int. Cl.5: **A61K 9/20**, A61K 9/70

(21) Application number: **87305280.7**

(22) Date of filing: **15.06.87**

(54) **Bioadhesive extruded film for intra-oral drug delivery and process.**

(30) Priority: **16.06.86 US 874904**

(43) Date of publication of application:
23.12.87 Bulletin 87/52

(45) Publication of the grant of the patent:
29.09.93 Bulletin 93/39

(84) Designated Contracting States:
AT CH DE FR GB IT LI

(56) References cited:
EP-A- 0 063 604
EP-A- 0 155 229
FR-A- 2 450 610

PATENT ABSTRACTS OF JAPAN, vol. 7, no. 185 (C-181)[1330], 13th August 1983; & JP-A-58 90 507 (NIPPON SODA K.K.) 30-05-1983

CHEMICAL ABSTRACTS, vol. 102, no.24, June 1985, page 366, abstract no. 209484e, Columbus, Ohio, US; & JP-A-60 05 159 (LION CORP.) 11-01-1985

(73) Proprietor: **JOHNSON & JOHNSON CONSUMER PRODUCTS, INC.**
Grandview Road
Skillman, New Jersey 08558(US)

(72) Inventor: **Schiraldi, Michael Thomas**
24 Overhill Road
East Brunswick, NJ 08816(US)
Inventor: **Perl, Martin Monroe**
1382 East 49th Street
Brooklyn, NY 11234(US)
Inventor: **Rubin, Howard**
4 Carla Court
Rockaway, NJ 07866(US)

(74) Representative: **Jones, Alan John et al**
CARPMAELS & RANSFORD 43 Bloomsbury Square
London, WC1A 2RA (GB)

Rank Xerox (UK) Business Services
(3.10/3.6/3.3.1)

EP 0 250 187 B1

Description

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a controlled-releasing medicament-containing preparation for intra-oral use. In particular it is more especially concerned with such a preparation (and the process of using it) in the form of a very thin extruded thermoplastic film (which can be in single layer or laminated multi-layer form) having at least one bioadhesive layer containing 22.4-68.3% by weight of a specified thermoplastic cellulose ether and 23.75-60% by weight of a specified homopolymer of ethylene oxide which can adhere to the mucosa of the oral cavity. The extruded film drug delivery system of the present invention, which has incorporated therein the medicament to be dispensed, is so thin and flexible when wet as to be unobtrusive to the patient after it has been properly positioned and placed in the mouth.

Description of the Prior Art

Several systems have previously been described which pertain to the delivery of drugs into the oral cavity. These include:

1. Treatment of periodontal disease with tetracycline. chlorhexidine or metronidazole loaded into hollow cellulose acetate fibers. These fibers are packed in the periodontal pockets and provide controlled release of the drug to the infected area.
2. Cast films containing ethyl cellulose/propylene glycol with chlorhexidine or metronidazole for treatment of periodontal disease.
3. An orthodontic appliance with a hydroxyethyl methacrylate/methyl methacrylate copolymer (HEMA/MMA) matrix. Sodium fluoride is incorporated into the HEMA/MMA matrix to provide sustained fluoride release and enhanced anticaries activity. HEMA/MMA with fluoride may also be attached to the tooth in the form of a wafer-like tablet.
4. Silicone/ethyl cellulose/polyethylene glycol films containing sodium fluoride are applied as coatings on orthodontic bands or in chewing gum. Controlled release of fluoride and anticaries activity is claimed.

The above systems are discussed in the "The Compendium of Continuing Education" Vol VI, No. 1, Jan.1985 p. 27-36 review article "Controlled Drug Delivery: A New Means of Treatment of Dental Disease", by J. Max Goodson, D.D.S., Ph.D. of the Forsyth Dental Center. Other systems, described in GB patent application 2,042,888 and U.S. Patents 4,292,299/4,226,848 (Teijin Ltd., Japan), use combinations of cellulosic and polyacrylate polymers. The preferred materials are hydroxypropyl cellulose ("Klucel") and a copolymer of acrylic acid ("Carbopol") that is administered in the form of thin tablets (discs), granules or powder. Other polymers that might be added are vinyl copolymers, polysaccharides, gelatin and collagen. U.S. patent 4,517,173 (Nippon Soda Co. Ltd, Japan) uses various celluloses in a multi-layered non-extruded cast film preparation.

Examples of prior art products currently on the market include ointments such as ORABASE* with Benzocaine (Squibb), Kenalog* (Triamcinolone Acetonide) in ORABASE* (Squibb) and Mycostatin* (Nystatin) ointment (Squibb).

The prior art products and delivery systems described above are useful but have the following disadvantages:

Tablets, appliances, hollow fibers are "bulky" in the mouth, are difficult to keep in place and inconvenient to apply.

Ethyl cellulose and/or silicone films do not adhere to mucosal tissue.

Ointments (i.e., ORABASE*) have an unpleasant feel and do not last very long.

Except for ORABASE*, all the foregoing systems require professional application to the tooth or periodontal pockets.

The bioadhesive film of the present invention alleviates many of the above problems. It may be applied easily by the consumer. It has very little or no mouthfeel, it has good adhesion to the mucosal tissues, and provides controlled release of the medicament.

Also EP-A-0 063 604 discloses a mucous membrane-adhering film preparation in which the one surface of water-soluble high polymer film containing pharmaceutical agents is treated to be made difficultly water-soluble. JP-A-5 890 507 discloses a film formed by an injection moulding machine or an extrusion moulding machine, the film comprising a mixture of a water-soluble polymer (water-soluble cellulose derivative), an active component (drug absorbable through the mucous membrane) arbitrary additives (diluent, taste or

scent improvers, colorants etc) and a plasticizer (polyethylene glycol).

Object of the Invention

It is an object of this invention to provide an extruded film that is an effective and convenient intra-oral drug delivery system and method for applying and delivering controlled dosages of therapeutic agents into the oral cavity. This technology may also be extended for controlled drug delivery in skin care, gynecological applications, wound care and like uses.

Summary of the Invention

The invention involves a pharmaceutically acceptable controlled-releasing medicament-containing extruded single or multi-layered thin film, capable of adhering to a wet mucous surface, comprising a water soluble or swellable polymer matrix bioadhesive layer which can adhere to a wet mucous surface and which bioadhesive layer consists essentially of 22.4-68.3% by weight of hydroxypropyl cellulose of molecular weight above 100,000 23.75-60% of a homopolymer of ethylene oxide of molecular weight above 100,000, 0-12.5%, of a water-insoluble polymer selected from ethyl cellulose, propyl cellulose, Carboxy methyl cellulose free acid, polyethylene and polypropylene, and 2.85-5% of a plasticizer, said film having incorporated therein a pharmaceutically effective amount of said medicament, the presence of medicament and optional components making the total 100%.

The present invention is directed to an extruded single or multi-layered laminated thin (1-10 mils or 0.025-0.25 mm) film, composed of selected water soluble and/or insoluble polymers. Various therapeutic agents are incorporated into the film during manufacture which are useful for treatment of oral disorders (i.e., denture discomfort, caries, periodontal disease, aphthous ulcers, etc.).

The extruded film of the present invention must have at least one bioadhesive layer, but may also have a reservoir layer and/or an outer protective barrier membrane layer. The therapeutic agent may be incorporated into any or all of the layers. When properly formulated and fabricated, these films will adhere to wet mucosal surfaces, provide a protective barrier for injured tissue and deliver controlled/sustained dosages of medication to the infected areas. The film may be designed for localized drug delivery (i.e., the periodontal pocket, an aphthous lesion), or may allow diffusion of the drug into the oral cavity.

An example of a non-localized system would be the delivery of sodium fluoride for caries prevention. A single or laminated film with good adhesion to the tooth or mucosal tissue may be employed in which the fluoride release rates may be controlled by varying film solubilities and/or concentration of fluoride in a multi-layered film.

An example of a localized application of medication would be in the treatment of aphthous lesions. A laminated two layer film with benzocaine incorporated into the adhesive layer would directly contact the injured mucosa. The outer layer would consist of non-soluble/non-adhesive polymers that provide durability, protection and directs the delivery of benzocaine toward the lesion.

The film forming polymers that are useful in this invention are selected from pharmaceutical grade materials, or those that are considered generally regarded as safe (GRAS) as food additives. They include, hydroxypropyl cellulose, and polyethylene oxide homopolymers. Small amounts of other polymers. e.g., polyvinyl ether-maleic acid copolymers and the like may be used in small amounts as well, replacing a small portion of the other polymers. The above materials are either water soluble or swellable and are most useful in the bioadhesive layer of the film. Various non-soluble polymers may also be incorporated for modification of the film's permeability properties, such as ethyl cellulose, propyl cellulose, polyethylene, polypropylene and carboxymethylcellulose (free acid) in an amount of up to 12.5% by weight. By varying the ratios of the above polymers both the solubility and the adhesive properties of each layer of film may be controlled. Therefore, depending on the desired delivery rate, the type of disorder to be treated, the area to be treated and the medication being administered it is possible to custom design the film by selecting and blending various polymers. The final film product may also be fabricated into flexible tapes of varied thickness and width, "spots" of different sizes and shapes or other pre-shaped forms.

The medicaments and pharmaceutical agents set forth in the prior art discussed above may generally be delivered by the drug delivery system of the present invention. Usable medicaments are those which are capable of withstanding the heats and pressures generated in the extrusion process involved in making the film of the present invention. Preferred medicaments include:

Anesthetics/Analgesics - benzocaine, dyclonine HCl, phenol, aspirin, phenacetin, acetaminophen, potassium nitrate, etc.

Anticaries Agents - sodium fluoride, sodium monofluorophosphate, stannous fluoride, etc.

Anti-inflammatories - hydrocortisone acetate, triamcinolone acetonide, dipotassium, glycyrrhizinate, etc.
Antihistamines - chlorpheniramine maleate, ephedrine HCL, diphenhydramine HCL, etc.
Antibiotics - i.e., tetracycline, doxycycline hyclate, meclocycline, minocycline, etc.
Antibacterials - chlorhexidine, cetyl pyridinium chloride, benzethonium chloride, dequalinium chloride, silver sulfadiazene, phenol, thymol, hexedine, hexetidine, alexidine, etc.
Fungistats - nystatin, miconazole, ketoconazole, etc.

The above are illustrative examples of therapeutic agents that are used to treat oral disorders. The present invention is not to be limited to these specific materials especially where it is intended to deliver drug outside of the oral cavity e.g. to skin where other drugs may be desirable.

The film of the present invention has the advantage of being an extruded film, rather than a cast film. When a multi-layered film is involved, the different layers can be coextruded and then laminated together, or else each layer can be separately extruded one on the other, and then laminated together, so that the final multi-layered film is still very thin. The films of the present invention can be made in thicknesses of only 1-10 mils or 0.025-0.25 mm. The films are so thin that when placed in the mouth after they become wet they soon become unobtrusive, and hardly noticeable by most patients.

The film must always have a bioadhesive layer, which enables it to adhere to wet mucosal surfaces. The bioadhesive layer has 22.4-68.3 wt % of hydroxpropyl cellulose, 23.75-60 wt % of a homopolymer of ethylene oxide and 2.85-5 wt % of a glycol plasticizer (all percents are % by weight).

The Hydroxypropyl cellulose (HPC), useful for purposes of the present invention is commercially available from Hercules, Inc. (Wilmington, DE) under the tradename KLUCEL*. Preferred grades include Klucel MF, with a molecular weight around 600,000 and having a viscosity of 4,000-6,000 cps (Brookfield) in 2 percent water solutions, or Klucel HP, having a molecular weight around 1,000,000 and viscosity of 1500-2500 cps in 1 percent water solution. Any HPC having a Molecular Weight above about 100,000 is useful for purposes of this invention.

The homopolymer of ethylene oxide useful for purposes of the present invention has a relatively high molecular weight, i.e., above 100,000 and preferably above 3,000,000. Such polymers are commercially available from various sources. The Union Carbide Corporation material, "Polyox WSR-301", which has a molecular weight of approximately 4,000,000 - 5,000,000 is most preferred for purposes of the present invention.

The "plasticizer" useful for purposes of the present invention are selected from glycols such as propylene glycol and polyethylene glycol; polyhydric alcohols such as glycerin and sorbitol; glycerol esters such as glycerol triacetate; fatty acid triglycerides such as NEOBEE* M-5 and MYVEROLS*; mineral oil; vegetable oils such as castor oil, etc.

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.

The preferred plasticizer for use in the present invention is either propylene glycol or polyethylene glycol (such as is available from Union Carbide Corporation as their series of Carbowaxes which runs from 200 to 600 molecular weight, of which we prefer to use Carbowax 400, which has a molecular weight of 400, average.

In addition to the polymers and plasticizer which are required ingredients of the films of the present invention, minor amounts of other non-essential but customary ingredients will often be used if desired, e.g., antioxidants, preservatives, flavors, colorants.

Detailed Description

The following examples will serve to illustrate the present invention in greater detail. The units shown in the examples are parts by weight. The thickness of the layers is expressed in either mils (.001 inches) or millimeters. For easy conversion, 4 mils is approximately equal to 0.1 mm.

EXAMPLE 1 - TRIPLE LAYERED LAMINATE CONTAINING SODIUM FLUORIDE FOR ANTICARIES PROTECTION:

This three layered film laminate is comprised of a "bioadhesive" layer, a sodium fluoride "reservoir" layer and, an "outer protective barrier membrane" layer, in which the composition and thickness of each layer are as shown below:

Ingredients	Bioadhesive Layer (4 mils) (0.1 mm)	% w/w Reservoir Layer (1 mil) (0.025 mm)	Outer Protective Barrier Membrane Layer (1 mil) (0.025 mm)
Polyethylene oxide homopolymer (Union Carbide-Polyox* WSR-301)	60.0	-	-
Hydroxypropyl Cellulose (Hercules, Inc.-Klucel* MF)	30.0	20.0	24.0
Polyethylene (Allied Chemical-6A) (Low Density)	5.0	-	-
Propylene Glycol, U.S.P.	3.0	-	-
Polyethylene Glycol 400 (Union Carbide)	2.0	-	-
Ethyl Cellulose (Hercules, Inc.-N100F)	-	59.0	69.6
Caprylic/Capric Triglyceride (PVO Incorporated-Neobee M-5)	-	5.0	6.0
Sodium Fluoride, U.S.P.	-	16.0	0.4
	100.0	100.0	100.0

The process used to make the above laminate was :

a) Powder Blending - Each layer is made separately and all ingredients used therein except propylene glycol and Neobee M-5 (liquid plasticizers) are placed in a Patterson Kelley (PK) V-blender equipped with liquid addition capabilities. The ingredients which are all powders are blended for approximately 10-15 minutes while the liquid plasticizer is slowly added to the mix. Three separate powder blends are made, one for each layer.

b) Extrusion Process - A standard Johnson 2-1/2 inch (0,0635 m) vinyl/polyolefin extruder equipped with a single three stage screw was used to extrude the "powder blend". The temperature conditions for the water soluble powders are however quite different from those used for vinyls and polyolefins. The

temperature (°C) profile for the "reservoir" and "membrane layers" of the triple laminate was as follows:

Barrel Zone 1	100
Barrel Zone 2	125
Barrel Zone 3	135
Barrel Zone 4	145
Barrel Zone 5	160
Barrel Zone 6	170
Adapter -	180
Die Zone 1	180
Die Zone 2	180
Die Zone 3	180

The films which had a width of 18 inches (0,45 m), were extruded at approximately 20 feet/minute (6 m/min) through a flat lipped die. The temperature profile for the "bioadhesive layer" was:

Barrel Zone 1	125
Barrel Zone 2	140
Barrel Zone 3	165
Barrel Zone 4	170
Barrel Zone 5	185
Barrel Zone 6	185
Adapter -	185
Die Zone 1	185
Die Zone 2	185
Die Zone 3	185

Each layer is extruded separately with the first layer extruded as a "free film". Successive layers are extruded onto each other and laminated by passing them through heated stainless steel rollers.

Test Results:

In vitro fluoride ion release studies were conducted on samples of the above described triple laminate film measuring 0.5 cm x 1.25cm (0.625 cm^2) according to the following procedures:
The test sample is adhered to a glass slide by prewetting the film and placing the bioadhesive layer on the glass surface. The slide is then immersed in a beaker containing 100 ml of distilled water with continuous stirring. Five milliliter aliquots are withdrawn from the solution, at prescribed time intervals, and analyzed for fluoride content with an Orion Ionanlyzer equipped with a fluoride specific electrode. Release rates are then calculated from the data.

The results obtained indicated fluoride release rates in the order of 0.05-0.2 mgs/cm^2/hr for 24 hours. This falls within the desirable range for maintaining constant low levels of fluoride in the mouth and enhanced anticaries activity. Release rates may be tailored to desired use levels by modification of the film composition and construction.

EXAMPLE 2 - SINGLE LAYER ADHESIVE FILM CONTAINING HYDROCORTISON ACETATE (0.5%) AS AN ANTI-INFLAMMATORY AGENT:

The composition of the film, which was 0.1 mm. thick, was as follows:

Ingredients	% w/w
Ethylene Oxide Homopolymer (Polyox* WSR-301)	59.4
Hydroxypropyl Cellulose (Klucel* MF)	30.0
Polyethylene (AC-6A)	5.0
Propylene Glycol	3.0
Polyethylene Glycol 400	2.0
Butylated Hydroxy Toluene (BHT) FCC (preservative)	0.1
Hydrocortisone Acetate	0.5
	100.0

The powder blending process and extruder conditions used were the same as those described in Example I for the "bioadhesive layer" of the sodium fluoride trilaminate. In vitro tests were performed on the above film and demonstrated a prolonged drug release pattern.

EXAMPLE 3 - SINGLE LAYER ADHESIVE FILM CONTAINING TRIAMCINOLONE ACETONIDE (0.1%) AS AN ANTI-INFLAMMATORY:

The composition of the film, which was 0.1 mm. thick, was as follows:

Ingredients	% w/w
Ethylene Oxide Homopolymer (Polyox WSR-301)	59.9
Hydroxypropyl Cellulose (Klucel MF)	29.9
Polyethylene (AC-6A)	5.0
Propylene Glycol	3.0
Polyethylene Glycol 400	2.0
BHT	0.1
Triamcinolone Acetonide	0.1
	100.0

The powder blending process and extruder conditions used to make the film of this Example 3 were the same as those of the "bioadhesive layer" of Example I.

Other desired active medicament ingredients may be incorporated into the adhesive films of any of Examples 1-3 in place of the particular medicament used in said examples. These include Benzocaine (analgesic), Potassium nitrate (analgesic), Silver sulfadiazene (antimicrobial).

Chlorhexidine (antimicrobial), miconazole nitrate (antifungal), Benzethonium chloride (antimicrobial), Tetracycline (antibiotic) and other similar therapeutic compounds.

EXAMPLE 4 - ANALGESIC FILMS WITH POTASSIUM NITRATE

This example shows 5 variations of the film having different solubilities, resulting in different release rates.

Ingredients	% w/w 1	2	3	4	5
Polyethylene oxide homopolymer (Polyox* WSR-301)	23.75	57.00	55.00	55.00	57.00
Hydroxypropyl Cellulose, N.F. (Klucel* HF)	68.30	-	-	-	-
Hydroxypropyl Cellulose, N.F. (Klucel* MF)	-	28.40	29.90	22.40	22.40
Ethyl Cellulose	-	4.75	5.00	12.50	12.50
Polyethylene Glycol 400	1.90	1.90	2.00	2.00	2.00
Polyethylene Glycol 8000	0.95	-	-	-	-
Propylene Glycol, U.S.P.	-	2.85	3.00	3.00	3.00
BHT, F.C.C.	0.10	0.10	0.10	0.10	0.10
Potassium Nitrate, F.C.C.	5.00	5.00	5.00	5.00	3.00

The above ingredients are blended in a Patterson-Kelly powder blender equipped with liquid addition capabilities. The resulting powder blend is then extruded into film on a Killion or Johnson vinyl extruder using processing procedures similar to those of the bioadhesive layer of Example I.

EXAMPLE 5 - ANESTHETIC FILMS WITH BENZOCAINE (LAMINATE)

This is an example of a two-layer laminate. The processing conditions used were similar to those of the bioadhesive layer and outer protective barrier membrane layer of Example I.

A. Inner medicated bioadhesive layer

Polyoxyethylene Homopolymer (Polyox* WSR-301)	57.00
Hydroxypropyl Cellulose, N.F. (Klucel* MF)	28.40
Polyethylene (AC-6A)	4.75
Propylene Glycol, U.S.P.	2.85
Polyethylene Glycol 400	1.90
BHT, F.C.C.	0.10
Benzocaine, U.S.P.	5.00
	100.00

B. Outer protective/barrier layer

Hydroxypropyl Cellulose (Klucel* MF)	78.00
Ethyl Cellulose	20.00
Polyethylene Glycol 400	2.00
	100.00

Part A was extruded on a Johnson extruder followed by subsequent extrusion and lamination of Part B to A.

Samples were applied to oral lesions, and provided profound anesthetic effects (lasting several hours) within minutes of application.

The identical two-layer laminate may also be made by coextruding the inner medicated bioadhesive layer (Part A) and the outer protective barrier layer (Part B) through separate die slots within a coextruder and laminating the two layers together.

EXAMPLE 6 - ANESTHETIC FILMS WITH PHENOL AND DYCLONINE HCl

Four variations of a single layer bioadhesive film were made as shown below:

Ingredients	1	2	3	4
Polyethylene oxide homopolymer (Polyox* WSR-301)	59.10	54.00	59.70	58.20
Hydroxypropyl Cellulose (Klucel HF)	29.45	26.91	29.75	29.00
Ethyl Cellulose	4.93	4.50	4.98	4.85
Propylene Glycol, U.S.P.	2.96	2.70	2.99	2.91
Polyethylene Glycol 400	1.97	1.80	1.99	1.94
BHT, F.C.C.	0.09	0.09	0.09	0.10
Phenol, U.S.P.	1.50	-	-	-
Dyclonine HCl	-	10.00	0.50	3.00

Following the procedures for the bioadhesive layer of Example I, the powders were blended in P-K blender equipped with liquid addition capabilities. Resulting powders were extruded on a Killion laboratory-sized extruder.

EXAMPLE 7 - SILVER SULFADIAZENE FILMS - ANTIMICROBIAL

Three different single-layered bioadhesive films containing 1.0% 0.5% and 0.5% respectively of silver sulfadiazene (SSD) were prepared on a heated Carver laboratory press (designed to simulate extruded conditions) as shown below.

Ingredients	% w/w A	% w/w B
Polyethylene oxide homopolymer (Polyox* WSR-301)	60.00	60.00
Hydroxypropyl Cellulose (Klucel* HF)	28.9	29.4
Polyethylene (AC-6A)	5.0	5.0
Propylene Glycol, U.S.P.	3.0	3.0
Polyethylene Glycol 400	2.0	2.0
BHT, F.C.C.	0.1	0.1
Silver Sulfadiazine	1.0	0.5
	100.0	100.0

Effects on wound repair and activity against Staphylococcus aureus were evaluated in the guinea pig model. Full-thickness excisions were inoculated with 3.8×10^5 organisms, (Staph. aureus) and wound surface microbiology samples taken 10 minutes and 24 hours after treatment. Test films were placed on the wound and covered with BIOCLUSIVE* Transparent Dressings secured with elastic tape. Wound contraction was measured over an eight-day period using OPTOMAX* Computer-Assisted Image Analysis. The three films tested were the following:

A. 1.0% Silver Sulfadiazene, 125 ° C/2 minutes/4 tons
B. 0.5% Silver Sulfadiazene, 125 ° C/2 minutes/4 tons
C. 0.5% Silver Sulfadiazene, 150 ° C/3 minutes/4 tons

SILVADENE Cream and un untreated occluded control. The results indicated that:

1. SILVADENE* treated wounds significantly inhibited full-thickness wound contraction.
2. Film A, B and C inhibited wound contraction relative to that of BIOCLUSIVE* dressed wounds.
3. The three SSD films each permitted substantially faster wound contraction than that of wounds treated daily with SILVADENE* cream.
4. All films were very active against S. aureus 24 hours after inoculation.

The films may be scaled up by using an extruder. This example demonstrates the feasibility of such a film to perform its intended purpose. Use of a press for larger samples would result in a non-uniform and lower-quality film than an extruded film.

Based on the above findings, the films were very effective antibacterial agents, while mildly inhibiting wound contraction. They offer clinicians a convenient and more effective delivery system for antimicrobials which can be place in wounds beneath any dressing or can be laminated to any acceptable dressing face.

Claims

1. A pharmaceutically acceptable controlled-releasing medicament-containing extruded single or multilayered thin film, capable of adhering to a wet mucous surface, comprising a water soluble or swellable polymer matrix bioadhesive layer which can adhere to a wet mucous surface and which bioadhesive layer consists essentially of 22.4-68.3% by weight of a hydroxypropyl cellulose having a molecular weight above 100,000, 23.75-60% by weight of a homopolymer of ethylene oxide having a molecular weight above 100,000, 0-12.5% by weight of a water-insoluble polymer selected from ethyl cellulose, propyl cellulose, carboxymethyl cellulose free acid, polyethylene and polypropylene, and 2.85-5% of a plasticizer, said film having incorporated therein a pharmaceutically effective amount of said medicament, the presence of medicament and optional components making the total 100%.

2. The extruded film of claim 1, made in a form which is so thin and flexible when wet as to be unobtrusive to the patient when properly positioned and placed in the patient's mouth.

3. The extruded film of claim 2 having a thickness no greater than 0.25 millimeters.

4. The extruded film of claim 3 wherein, in the bioadhesive layer the homopolymer of ethylene oxide has a molecular weight from 3,000,000 to 5,000,000.

5. The extruded film of Claim 3, in multi-layer laminated form, which in addition to the bioadhesive layer also contains a reservoir layer in which at least a major portion of the medicament is contained.

6. The extruded multi-layer film of Claim 5 in which the reservoir layer consists essentially of a polymer matrix comprised of both a water soluble or swellable polymer and a non-water soluble polymer selected from ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and also hydroxypropyl cellulose.

7. The extruded film of Claim 4 in multi-layer laminated form, which in addition to the bioadhesive layer also contains an outer protective-barrier membrane layer.

8. The extruded multi-layer film of Claim 7 in which the outer protective-barrier membrane layer is thinner than the bioadhesive layer, and said outer protective barrier layer consists essentially of a polymer matrix of a major proportion of a non-water-soluble polymer selected from ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and a minor proportion of hydroxypropyl cellulose.

9. The extruded multi-layer film of Claim 1 in the form of a triple layered laminate containing sodium fluoride for anticaries protection having the following composition:

Ingredients	Bioadhesive Layer (0.1 mm)	% w/w Reservoir Layer (0.025 mm)	Outer Protective Barrier Membrane Layer (0.025 mm)
Polyethylene oxide homopolymer (MW 3,000,000 minimum)	60.0	-	-
Hydroxypropyl Cellulose (MW 1,000,000)	30.0	20.0	24.0
Polyethylene (Low Density)	5.0	-	-
Propylene Glycol, U.S.P.	3.0	-	-
Polyethylene Glycol (MW 400)	2.0	-	-
Ethyl Cellulose	-	59.0	69.6
Caprylic/Capric Triglyceride	-	5.0	6.0
Sodium Fluoride	-	16.0	0.4
	100.0	100.0	100.0

Patentansprüche

1. Ein pharmazeutisch verträglicher, dünner extrudierter Film, der ein Medikament enthält und kontrolliert freisetzt, mit einer einzigen oder mit mehreren Schichten, der die Fähigkeit aufweist, daß er auf der nassen Schleimhautoberfläche festkleben kann, umfassend eine wasserlösliche oder quellbare Polymermatrix einer bioadhäsiven Schicht, die auf der nassen Oberfläche der Schleimhaut kleben kann, wobei die bioadhäsive Schicht im wesentlichen aus 22,4 - 68,3 Gew.-% Hydroxypropyl-Cellulose mit einem Molekulargewicht von oberhalb 100 000, 23,75 - 60 Gew.-% eines Homopolymers von Ethylenoxid mit einem Molekulargewicht von oberhalb 100 000, 0 - 12,5 Gew.-% eines wasserunlöslichen Polymers, ausgewählt aus Ethyl-Cellulose, Propyl-Cellulose, Carboxymethyl-Cellulose in Form der freien Säure, Polyethylen und Polypropylen und 2,85 - 5 % eines Weichmachers besteht, wobei der Film eine pharmazeutisch wirksame Menge des Medikamentes inkorporiert enthält und das Medikament und die wahlweise enthaltenen Komponenten insgesamt 100 % ergeben.

2. Extrudierter Film nach Anspruch 1, der in einer Form hergestellt ist, die so dünn und flexibel ist, daß er, wenn er naß ist, den Patienten nicht stört, wenn er im Mund des Patienten an die richtige Stelle gelegt und eingebracht worden ist.

3. Extrudierter Film nach Anspruch 2 mit einer Dicke, die nicht größer als 0,25 mm ist.

4. Extrudierter Film nach Anspruch 3, bei dem die bioadhäsive Schicht des Homopolymers von Ethylenoxid ein Molekulargewicht von 3 000 000 bis 5 000 000 aufweist.

5. Extrudierter Film nach Anspruch 3 in einer mehrschichtigen laminierten Form, die zusätzlich zur bioadhäsiven Schicht noch eine Reservoir-Schicht enthält, in der zumindest ein Hauptanteil des Medikamentes enthalten ist.

6. Extrudierter mehrschichtiger Film nach Anspruch 5, in dem die Reservoir-Schicht im wesentlichen aus einer polymeren Matrix besteht, die sowohl aus einem wasserlöslichen und quellbaren Polymer und einem nichtwasserlöslichen Polymer besteht, das ausgewählt ist aus Ethyl-Cellulose, Propyl-Cellulose, Polyethylen und Polypropylen und auch Hydroxypropyl-Cellulose.

7. Extrudierter Film nach Anspruch 4 in Form eines mehrschichtigen Laminates, das zusätzlich zur bioadhäsiven Schicht auch eine äußere Schicht aus einer protektiven Membranbarriere enthält.

8. Extrudierter mehrschichtiger Film nach Anspruch 7, bei dem die äußere Schicht mit einer protektiven Membranbarriere dünner ist als die bioadhäsive Schicht und in dem die protektive Barriereschicht im wesentlichen aus einer Polymermatrix aus einem Hauptanteil eines nichtwasserlöslichen Polymers, das ausgewählt ist aus Ethyl-Cellulose, Propyl-Cellulose, Polyethylen und Polypropylen und einem geringeren Anteil von Hydroxypropyl-Cellulose, besteht.

9. Extrudierter mehrschichtiger Film nach Anspruch 1 in Form eines dreischichtigen Laminats, das Natriumfluorid zum Antikariesschutz enthält und das die folgende Zusammensetzung aufweist:

Bestandteile	bioadhäsive Schicht (0,1 mm)	% Gew./Gew. Reservoirschicht (0,025 mm)	äußere protektive Schicht der Membranbarriere (0,025 mm)
Homopolymer des Polyethylenoxids (MG mindestens 3 000 000)	60,0	-	-
Hydroxypropyl-Cellulose (MG 1 000 000)	30,0	20,0	24,0
Polyethylen (geringe Dichte)	5,0	-	-
Propylen-Glycol, U.S.P.	3,0	-	-
Polyethylen-Glycol (MG 400)	2,0	-	-
Ethyl-Cellulose	-	59,0	69,6
Capryl/Caprinsäure-Triglycerid	-	5,0	6,0
Natriumfluorid	-	16,0	0,4
	100,0	100,0	100,0

Revendications

1. Film mince extrudé mono- ou multicouche pharmaceutiquement acceptable contenant un médicament à libération contrôlée pouvant adhérer sur une surface de muqueuse humide, comprenant une couche bioadhésive de matrice de polymère gonflable ou soluble dans l'eau qui peut adhérer sur une surface de muqueuse humide et cette couche bioadhésive est constituée essentiellement de 22,4-68,3 % d'hydroxypropylcellulose ayant un poids moléculaire supérieur à 100 000, de 23,75-60% en poids d'un homopolymère d'oxyde d'éthylène ayant un poids moléculaire supérieur à 100 000, 0-12,5 % en poids d'un polymère insoluble dans l'eau choisi parmi l'éthylcellulose, la propylcellulose, la carboxyméthylcellulose exempte d'acide, le polyéthylène et le polypropylène, et 2,85-5 % d'un plastifiant, ledit film

contient une quantité pharmaceutiquement efficace du médicament qui y est incorporée, la présence du médicament et de composants éventuels faisant le complément du total de 100 %.

2. Film extrudé de la revendication 1, d'une forme suffisamment fine et souple quand il est humide de façon à ne pas gêner le patient quand il est placé et positionné correctement dans la bouche du patient.

3. Film extrudé de la revendication 2 ayant une épaisseur non supérieure à 0,25 millimètre.

4. Film extrudé de la revendication 3 dans lequel, dans la couche bioadhésive l'homopolymère d'oxyde d'éthylène a un poids moléculaire de 3 000 000 à 5 000 000.

5. Film extrudé de la revendication 3 sous forme feuilletée multicouche, qui contient aussi en plus de la couche bioadhésive une couche réservoir dans laquelle se trouve au moins une portion majeure du médicament.

6. Film multicouche extrudé de la revendication 5 dans lequel la couche réservoir est constituée essentiellement d'une matrice polymère contenant à la fois un polymère gonflable ou soluble dans l'eau et un polymère non soluble dans l'eau choisi parmi l'ethylcellulose, la propylcellulose, le polyéthylène et le polypropylène, et aussi de l'hydroxypropylcellulose.

7. Film extrudé de la revendication 4 sous forme feuilletée multicouche, qui contient en plus de la couche bioadhésive une couche membrane barrière de protection externe.

8. Film extrudé multicouche de la revendication 7 dans lequel la membrane barrière protectrice externe est plus mince que la couche bioadhésive, et ladite couche barrière protectrice externe est constituée essentiellement d'une matrice polymère composée en proportion majoritaire d'un polymère non soluble dans l'eau choisi dans le groupe de l'éthylcellulose, de la propylcellulose, du polyéthylène et du polypropylène, et d'une proportion mineure d'hydroxypropylcellulose.

9. Film multicouche extrudé de la revendication 1 sous forme d'un lamifié à triple couche contenant du fluorure de sodium pour la protection anticaries qui a la composition suivante :

Ingrédients	couche Bioadhésive 0,1 mm	% pds/pds Couche Réservoir (0,025 mm)	couche Membrane Barrière Protectrice Externe (0,025 mm)
Oxyde de Polyéthylène homopolymère (PM 3 000 000 minimum)	60,0	-	-
Hydroxypropylcellulose (PM 1 000 000)	30,0	20,0	24,0
Polyéthylène (basse densité)	5,0	-	-
Propylèneglycol, U.S.P.	3,0	-	-
Polyéthylèneglycol (PM 400)	2,0	-	-
Ethylcellulose	-	59,0	69,6
Triglycéride caprylique/caprique	-	5,0	6,0
Fluorure de sodium	-	16,0	0,4
	100,0	100,0	100,0

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Veröffentlichungsnummer: **0 259 749 B1**

(12) # EUROPÄISCHE PATENTSCHRIFT

(45) Veröffentlichungstag der Patentschrift: **14.08.91**

(51) Int. Cl.[5]: **A61K 9/20**, A61K 9/70

(21) Anmeldenummer: **87112712.2**

(22) Anmeldetag: **01.09.87**

(54) **Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder dergleichen sowie Verfahren zu deren Herstellung.**

(30) Priorität: **09.09.86 DE 3630603**

(43) Veröffentlichungstag der Anmeldung:
16.03.88 Patentblatt 88/11

(45) Bekanntmachung des Hinweises auf die Patenterteilung:
14.08.91 Patentblatt 91/33

(84) Benannte Vertragsstaaten:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) Entgegenhaltungen:
EP-A- 0 019 929
EP-A- 0 219 762
DE-A- 1 947 684
DE-A- 2 746 414
FR-A- 1 382 158
GB-A- 2 022 999

(73) Patentinhaber: **Desitin Arzneimittel GmbH**
Weg beim Jäger 214
W-2000 Hamburg 63(DE)

(72) Erfinder: **Schmidt, Wolfgang, Dr.**
Reembroden 44
W-2000 Hamburg 63(DE)

(74) Vertreter: **UEXKÜLL & STOLBERG Patentanwälte**
Beselerstrasse 4
W-2000 Hamburg 52(DE)

EP 0 259 749 B1

Beschreibung

Arzneimittel können in Form von Pulvern, Tropflösungen oder Säften oral verabreicht werden. Da bei diesen Abgabeformen eine genaue Dosierung jedoch schwierig ist, werden vom Hersteller dosierte Applikationsformen wie Tabletten, Dragees oder Kapseln generell bevorzugt. Auch Reagentien und andere Wirkstoffe, z.B. Süßstoffe, werden für eine genaue dosierte Anwendung häufig tablettiert. Die Herstellungstechnik für Tabletten, Dragees, Kapseln und dergleichen ist zwar weitgehend ausgereift, doch sind eine Reihe von systembedingten Nachteilen nicht zu übersehen.

Für niedrig dosierte Wirkstoffe muß ein großer Anteil an Hilfsstoffen zugesetzt werden, um zu einer handhabbaren Größe der Einzeldosis zu gelangen. Weiterhin ist eine genaue Kennzeichnung einzelner Tabletten oder Dragees praktisch nicht möglich. Es haben sich deshalb Durchdrückpackungen durchgesetzt, welche eine Mehrzahl von Tabletten, Dragees oder auch Kapseln enthalten und welche mit den notwendigen Informationen, insbesondere dem Namen des Präparates bedruckt sind. Die Herstellung solcher Verpackungen erfordert naturgemäß einen zusätzlichen Arbeitsgang und es werden Umverpackungen in Form von Faltschachteln benötigt, welche ein beträchtliches Leervolumen aufweisen und dadurch zusätzlich Lagerraum beanspruchen. Ein besonders gravierender Nachteil von Dragees und Kapseln besteht darin, daß eine Zerteilung praktisch unmöglich ist, die kleinste Dosis somit vorgegeben ist. Auch bei Tabletten ist eine genaue Zerteilung schwierig, lediglich größere Tabletten mit einer Kerbe als Sollbruchstelle lassen sich allenfalls teilen, wobei häufig ungleichgroße Bruchstücke entstehen.

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekannt geworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-PS 637 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Aus den DE-OS 24 32 925 und 24 49 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Auch die so erhaltenen wirkstoffhaltigen Folien lassen sich zur Dosierung durch Perforation in einzelne Abschnitte aufteilen. Aus DE-A-2746414 ist es ferner bekannt, derartige Dosierfolien mit weiteren Wirkstoffhaltigen oder- freien folien zu Dosierlaminaten zu vereinigen. Dadurch lassen sich inkompatible Wirkstoffe verarbeiten oder die Lösungsgeschwindigkeit bereinflussen. Diese Laminate insgesamt werden in form von Dosiereinheiten verwendet. Diese Vorschläge haben keinen Eingang in die Praxis gefunden und in dem neuesten Lehrbuch der "Arzneiformenlehre" von P.H. List, 4. Auflage, Stuttgart, 1985, finden sie keine Erwähnung. Dies beruht ersichtlich darauf, daß die bislang bekanntgewordenen Vorschläge es nicht ermöglichen, die geforderte Gewichtskonstanz und gleichmäßige Wirkstoffverteilung zu erreichen, welche heute gefordert werden. Die Ph. Eur. setzt zum Beispiel Maßstäbe für die Gleichförmigkeit des Gewichtes einzeldosierter Arzneiformen, wobei diese dem jeweiligen Durchschnittsgewicht entsprechend nach höchstzulässigen Abweichungen in % gestaffelt sind. Die Forderung liegt im allgemeinen bei +/- 5 bis max. 10%. Entsprechende Werte für feste Arzneiformen bestehen auch hinsichtlich anderer Parameter wie Zerfallzeit und Lösungsgeschwindigkeit.

Die oben erwähnten Vorschläge des Standes der Technik führen zu Produkten ungenügender Akzeptanz durch die Patienten (Papierabschnitte lassen sich nur schlecht einnehmen) und erlauben keine exakte Dosierung pro Flächeneinheit, wie sie unbedingt gefordert werden muß. Bei Inkorporieren des Wirkstoffes in eine Folie bereitet nicht nur die genaue Dosierung Schwierigkeiten, sondern ein wesentlicher weiterer Nachteil besteht darin, daß für jeden Wirkstoff eine entsprechende Folie gesondert hergestellt werden muß, so daß die Wirtschaftlichkeit des Herstellungsverfahrens nicht gegeben ist.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine "zweidimensionale" Darreichungs- und Dosierungsform zu schaffen, welche die genannten Nachteile nicht aufweist, sich leicht herstellen läßt und mit großer Flexibilität an die Anforderungen des Marktes und verschiedener Wirkstoffe angepaßt werden kann.

Gegenstand der Erfindung ist eine Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder dergleichen in Form eines folienförmigen Trägermaterials mit einer wirkstoffhaltigen Beschichtung, wobei diese Darreichungsform dadurch gekennzeichnet ist, daß das Trägermaterial ein Release-Papier, ein Release-Film oder eine Release-Folie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

Die erfindungsgemäße Darreichungsform weist mehrere wesentliche Vorteile auf:

- Da der Träger im Gegensatz zu den vorbekannten Ausführungsformen keinen Teil der Darreichungsform bildet, kann er die erforderliche Festigkeit aufweisen, ohne die Akzeptanz des Arzneimittels

durch Patienten zu beeinträchtigen,

- die wirkstoffhaltige Schicht kann bei hochwirksamen Arzneimitteln sehr dünn sein, da das Trägermaterial die mechanische Festigkeit gewährleistet,
- mit Hilfe moderner Auftragverfahren läßt sich die wirkstoffhaltige Beschichtung mit konstanter Schichtdicke aufbringen, so daß die erforderlichen Toleranzen eingehalten werden können,
- falls eine Sterilisierung erforderlich ist, kann diese wegen der geringen Schichtdicke problemlos mittels Strahlenbehandlung erreicht werden,
- der Träger läßt sich auf der Vorder- und insbesondere der Rückseite mit verschiedenen Informationen bedrucken,
- aufgrund der relativ großen Fläche von beispielsweise 4 bis 10 cm^2 lassen sich ausführliche Informationen für den Benutzer auf das unbeschichtete Trägermaterial oder auch nachträglich aufdrucken,
- die Dosiseinheiten lassen sich durch entsprechende Vorzerteilung flexibel gestalten, so daß für verschiedene Dosierungen (z.B. für Erwachsene und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

Mit den vorbekannten Darreichungsformen in Folienform hat die erfindungsgemäße Darreichungsform darüberhinaus den Vorteil des äußerst geringen Platzbedarfes gemeinsam. Statt Faltschachteln können daher beispielsweise Taschen oder Beutel aus Kunststoffolie oder kunststoffbeschichtetem Papier verwendet werden, in welche das Produkt eingesiegelt wird, ähnlich wie feuchte Erfrischungstücher.

Als Trägermaterialien eignen sich die verschiedensten Materialien, beispielsweise Papiere mit einem Gewicht von etwa 80 bis 120, vorzugsweise 100 g/m^2, Kunststoffilme bzw. -folien auf Basis von Polyethylen, Polyvinylchlorid, Polyvinylidenchlorid, Polyester und anderen indifferenten Polymeren oder dünne Metallfolien, beispielsweise solche aus Aluminium. Bevorzugt werden siliconisierte Papiere, welche in unterschiedlichen Qualitäten im Handel erhältlich sind, und welche insbesondere zur Abdeckung von selbstklebenden Produkten wie Pflastern, Klebebändern oder Haftetiketten Verwendung finden. Die an sich auch geeigneten mit Wachs oder Paraffin beschichten Release-Papiere sind dagegen in der Praxis weitgehend durch die mit inerten Siliconen beschichteten Papiere ersetzt worden. Bei einem Auftrag der wirkstoffhaltigen Beschichtung auf nur eine Seite der Trägerfolie reicht es aus, wenn nur diese mit einer nicht haftenden Beschichtung versehen ist. Die Rückseite sollte dagegen vorzugsweise so beschaffen sein, daß sie mit Informationen unterschiedlicher Art gut und dauerhaft bedruckbar ist.

Die Möglichkeit der vorder- und rückseitigen Bedruckung ist ein besonderer Vorteil der erfindungsgemäßen Darreichungsform. Beispielsweise können die Kennzeichnung, Angaben über die Inhaltsstoffe sowie Dosierungsangaben aufgedruckt werden. Gegebenenfalls läßt sich sogar der ganze Inhalt eines Beipackzettels rückseitig aufdrucken mit der Folge, daß ein separater Beipackzettel, der auch häufig verlorengeht, überflüssig wird. Bei Arzneimitteln, welche regelmäßig genommen werden müssen, beispielsweise bei hormonalen Contrazeptiva, kann der gesamte Verabreichungsplan so angebracht werden, daß eine einfache Einnahmekontrolle gewährleistet ist. Da die einzelnen Dosiseinheiten von dem Träger abgezogen werden, bleibt dieser bis zum vollständigen Aufbrauch des Arzneimittels erhalten und es gehen keine der aufgedruckten Informationen verloren.

Für die wirkstoffhaltige Beschichtung findet vorzugsweise eine wässrige Beschichtungsmasse Verwendung, die physiologisch inert ist und deren Einzelkomponenten für Arzneimittel bzw. Lebensmittel geeignet sind. Dabei handelt es sich zum einen um wasserlösliche Quellstoffe in der Art polymerer Filmbildner, vorzugsweise Gelatine, Zellulosen oder Hemizellulosen, quellende oder lösliche Stärken. Vorzugsweise werden ferner Weichmacher zugesetzt, insbesondere mehrwertige Alkohole wie Glycerin oder Sorbitol. Zur Einstellung der erwünschten Viskosität der Beschichtungsmasse, welche etwa die Konsistenz eines Schleimes aufweist, finden polymere Quellstoffe Verwendung, vorzugsweise Alginate, Pectine, Chitine, Lecithine oder Polyethylenglykole. Diese letzteren Stoffe können gleichzeitig als Haftvermittler dienen. Andererseits können auch wasserlösliche Gumme oder Gummi arabicum zugesetzt werden, um die Haftung der Beschichtung auf dem Trägermaterial zu verbessern. Schließlich können noch Konservierungsmittel wie z.B. p-Hydroxybenzoesäureester, Farbstoffe (Lebensmittelfarbstoffe), Pigmente wie Titandioxid oder Aroma- und Süßstoffe zugesetzt werden.

Coatingmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10000 cPs haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

Folgende Rahmenrezeptur hat sich bewährt:

Gelatine	8 bis 10 g
Stärke	3 bis 8 g
Glycerin	1 bis 2 g
Wasser	30 bis 50 g

In dieser Grundmasse wird der Wirkstoff gelöst bzw. dispergiert. Im Fall der Verwendung einer Dispersion muß der Wirkstoff für eine gleichmäßige Verteilung äußerst feinteilig sein. Vorzugsweise liegt die mittlere Teilchengröße im Bereich von etwa 1 bis 20 µm.

Die gewünschte Dosis des Wirkstoffes und die angestrebte Fläche der Dosiseinheiten bestimmen letztlich die Dicke der Schicht, wobei der Feuchtigkeitsgehalt der Beschichtungsmasse und der fertigen Beschichtung zu berücksichtigen sind.

Im Rahmen der Erfindung ist es auch möglich, die Beshichtungsmasse zu einer wirkstoffhaltigen Folie zu verarbeiten und diese anschließend, gegebenenfalls unter Verwendung eines physiologisch einsetzbaren inerten Klebstoffes, auf das Trägermaterial aufzukaschieren. Diese Ausführungsform kommt insbesondere dann in Betracht, wenn die wirkstoffhaltige Beschichtung eine größere Dicke aufweisen soll, so daß die Verarbeitung zu einer Folie möglich und sinnvoll ist.

Die erfindungsgemäße Darreichungsform ist besonders geeignet für Arzneimittel, welche niedrig dosiert verabreicht werden, d.h. bei welchen die Einzeldosis für die orale Applikation zwischen 0 mg (Placebo) und etwa 20 mg liegt. Geeignete Arzneimittelwirkstoffe finden sich in allen Bereichen der oralen Therapie; hervorzuheben sind u.a. Analeptika, Antibiotika, Antidiabetika, Antiemetika, Antiepileptika, Antihypertonika, Cortikoide, Geriatrika, Hypnotika, Cardiaka, Hypostatika und Biowirkstoffe.

Die Beschichtung kann einen oder mehrere Arzneimittelwirkstoffe enthalten. Falls bei Verwendung mehrerer Wirkstoffe diese nicht ohne weiteres miteinander verträglich sind, ist es bei der erfindungsgemäßen Darreichungsform möglich, die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufzubringen und die Wirkstoffe dadurch voneinander zu trennen, wobei erforderlichenfalls eine wirkstofffreie Zwischenschicht vorgesehen werden kann. Weiterhin ist es möglich, über der wirkstoffhaltigen Schicht noch eine weitere Schutzschicht vorzusehen, welche den/die Wirkstoff(e) gegen eine Berührung mit der Atmosphäre und/oder gegen Licht schützt. In diesen Fällen muß die Schutzschicht demgemäß luft- und feuchtigkeitsundurchlässig und/oder durch Zusatz entsprechender Farbstoffe bzw. Pigmente lichtundurchlässig sein.

Weiterhin kann durch entsprechenden Aufbau der Beschichtung die Wirkstoffabgabe nach Verabreichung des Arzneimittels gesteuert werden. Beispielsweise ist es möglich, eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten anzuordnen, welche die Wirkstoffresorption im Magen/Darmtrakt in an sich bekannter Weise steuern. Dabei kann die Wirkstoffschicht z.B. zwischen zwei säureunlöslichen Schichten angeordnet werden, so daß bei Verabreichung der Magen passiert wird und die Resorption erst im Darmtrakt erfolgt. In ähnlicher Weise können unterschiedliche Wirkstoffe in verschiedenen Schichten übereinander auf die Trägerfolie aufgebracht werden, damit die Resorption nacheinander und/oder verzögert erfolgt. Ähnliche pharmakokinetische Effekte lassen sich durch das Einarbeiten (z.B. Suspendieren) von unterschiedlich vorbehandelten mikroverkapselten Wirkstoffen erzielen.

Die Aufbringung der wirkstoffhaltigen Beschichtungen auf den Träger, z.B. ein Release-Papier oder eine Release-Kunststoffolie, erfolgt vorzugsweise mit Hilfe eines Glattwalzen-Beschichtungsverfahrens. Die vorzugsweise auf ca. 60 bis 80 °C erwärmte Beschichtunsmasse wird dabei au einem geschlossenen Auftragsystem auf eine beheizte Walze in dünner Schicht übertragen. Mit verzögertem Gleichlauf in bestimmten wählbaren Verhältnissen wird die Masse auf eine parallel angeordnete Walze übertragen, wobei eine Reduzierung der Schichtdicke im Verhältnis 1:2 bis 1:10 erfolgen kann, wodurch gleichzeitig die Toleranzen bei der Auftragung um diese Faktoren verringert werden. Im Gleichlauf erfolgt dann über ein weiteres Walzensystem die Beschichtung des Trägermaterials. Bei einer Anpassung der Wirkstoffbeschichtungsmasse an den Release-Wert des Trägermaterials kann auf den Zusatz eines Klebemittels völlig verzichtet werden. Gegebenenfalls können jedoch auch geeignete Haftvermittler zugesetzt werden.

Bei Aufbringung mehrerer Schichten, wie dies oben bereits beschrieben wurde, werden diese nacheinander aufgebracht, wobei ggf. jede Beschichtung zuvor eine Trocknungsstation durchläuft. Diese kann beispielsweise aus einem temperierten Walzenpaar und einem in Sektionen steuerbaren Trockentunnel bestehen. Nach dem letzten Beschichtungsvorgang wird das beschichte Material auf Rollen aufgewickelt.

Die wirkstoffhaltige Beschichtung wird anschließend in Dosiseinheiten vorzerteilt, welche ähnlich wie Haftetiketten vom Trägermaterial abziehbar sind. Normalerweise wird diese Vorzerteilung beim Arzneimittelhersteller erfolgen, es ist jedoch auch denkbar, das beschichtete Material beispielsweise an Krankenhäuser oder Apotheken auszuliefern, wo dann die Vorzerteilung dosisabhängig oder auch individuell nach ärztlicher Vorgabe durchgeführt werden kann.

Die Vorzerteilung erfolgt in besonders einfacher Weise durch Stanzung, wobei es möglich ist, diesen

Schritt mit der Bedruckung des Trägermaterials zu kombinieren. In vielen Fällen wird es allerdings günstiger sein, die Bedruckung des Trägermaterials vor der Beschichtung vorzunehmen.

Vor oder besser nach Vorzerteilung der wirkstoffhaltigen Beschichtung in Dosiseinheiten wird das beschichtete Trägermaterial zu gebrauchsfertigen Abschnitten zerschnitten, welche eine bestimmte Anzahl von Dosiseinheiten enthalten. Es ist auch denkbar, das Material auf Rollen zu schmalen Bändern zu zerschneiden. Von einer solchen Einzelrolle können dann die einzelnen Dosiseinheiten ähnlich wie einzelne Haftetiketten abgezogen werden.

Vorstehend wurde die Erfindung im wesentlichen im Zusammenhang mit Arzneimitteln beschrieben, worauf sie jedoch keineswegs beschränkt ist. Beispielsweise lassen sich in derselben Weise auch Dosierungsformen für chemische Reagentien, Aromastoffe und dergleichen herstellen.

Zur näheren Erläuterung der Erfindung sollen die nachfolgenden Ausführungsbeispiele dienen.

Beispiel 1
Herstellung eines Cardiakum

Zum Naßauftrag auf ein Releasepapier (Silikonpapier mit einem Flächengewicht von 100 g/m²) wurde eine Beschichtungsmasse gemäß folgender Rezeptur hergestellt:

Gelatine	10,0	Gew.-Teile	= 22,22%
Kartoffelstärke	3,0	-"- -"-	= 6,67%
Glycerin	1,5	-"- -"-	= 3,33%
Titandioxid	0,3	-"- -"-	= 0,67%
α-Acetyldigoxin	0,2	-"- -"-	= 0,44%
Wasser	30,0	-"- -"-	= 66,67%

Diese Beschichtungsmasse wurde in einer Schichtdicke von 90 g/m² mittels Walzen auf das Releasepapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Das Beschichtungsgewicht lag bei 34 g/m², was einem Arzneimittelanteil von 0,4 g/m²entspricht. Ein Abschnitt von 2 × 2,5 cm = 5 cm² (entsprechend den Abmessungen einer üblichen Briefmarke) enthält 0,2 mg α-Acetyldigoxin, was mit dem Gehalt der handelsüblichen Tabletten übereinstimmt.

Beispiel 2
Herstellung eines Contrazeptivum

Zum Naßauftrag auf ein Releasepapier (einseitig siliconisiertes Papier von 110 g/m²) wurde eine Beschichtungsmasse von schleimartiger Konsistenz nach folgender Rezeptur hergestellt:

Gelatine	10,00	Gew.-Teile	= 22,222%
Maisstärke	3,17	-"- -"-	= 7,044%
Glycerin	1,50	-"- -"-	= 3,333%
Titandioxid	0,30	-"- -"-	= 0,667%
Levonorgestrel	0,03	-"- -"-	= 0,067%
Wasser	30,00	-"- -"-	= 66,663%

Die Beschichtungsmasse wurde mittels eines Walzenübertragungsverfahrens mit einem Beschichtungsgewicht von 45 g/m² auf das Releasepapier aufgebracht. Nach dem Trocknen wies die Beschichtung einen Restwassergehalt von 11,76% auf. Bei einem Beschichtungsgewicht von 17 g/m² betrug der Arzneimittelanteil 0,03 g/m².

Ein Abschnitt von 2,5 × 4 cm bzw. zwei Abschnitte von 2,5 × 2 cm = 10 cm² enthalten somit 0,03 mg Levonorgestrel, was dem Gehalt der handelsüblichen Dragees entspricht.

Patentansprüche

1. Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien, Aromastoffe oder dergleichen in Form eines folienförmigen Trägermaterials mit einer wirkstoffhaltigen Beschichtung, dadurch gekennzeichnet, daß das Trägermaterial ein Releasepapier, ein Releasefilm oder eine Releasefolie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

2. Darreichungsform nach Anspruch 1, dadurch gekennzeichnet, daß das Trägermaterial ein silicon- oder wachsbeschichtetes Releasepapier ist.

3. Darreichungsform nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die wirkstoffhaltige Beschichtung durch Stanzung in Dosiseinheiten vorzerteilt ist.

4. Darreichungsform nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die Beschichtung einen oder mehrere Arzneimittelwirkstoffe enthält.

5. Darreichungsform nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Beschichtung wasserlösliche Quellstoffe als polymere Filmbildner und gegebenenfalls Weichmacher enthält.

6. Darreichungsform nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß sie zur Viskositätseinstellung polymere Quellstoffe enthält, welche gleichzeitig als Haftvermittler dienen können.

7. Darreichungsform nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die Beschichtung in mehreren Schichten unterschiedlicher Zusammensetzung aufgebracht ist.

8. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß miteinander inkompatible Wirkstoffe in getrennten Schichten nacheinander auf das Trägermaterial aufgebracht sind.

9. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten angeordnet ist, welche die Wirkstoff-Resorption im Magen/Darmtrakt in an sich bekannter Weise steuern.

10. Darreichungsform nach Anspruch 7, dadurch gekennzeichnet, daß über der Wirkstoffschicht eine weitere Schicht aufgebracht ist, die den Wirkstoff gegen Berührung mit der Atmosphäre und/oder gegen Licht schützt.

11. Darreichungsform nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß die Rückseite des Trägermaterials mit die Wirkstoffzusammensetzung und/oder deren Einnahme betreffenden Informationen bedruckbar ist.

12. Verfahren zur Herstellung der Arzneimitteldarreichungsform der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß man eine wirkstoffhaltige Zusammensetzung mit Hilfe von Walzen auf die nichthaftend ausgerüstete Seite eines Releasepapiers, eines Releasefilms oder einer Releasefolie aufbringt.

Claims

1. Presentation and dosage form for pharmaceutical active substances, reagents, aromas or the like in the form of a foil-like carrier material with an active-substance-containing coating, characterized in that the carrier material is a release paper, a release film or a release foil and that the carrier material is provided on one side with the active-substance-containing coating, which can be removed dosewise from the carrier material following prior division into dosage units.

2. Presentation form according to claim 1, characterized in that the carrier material is a silicone or wax-coated release paper.

3. Presentation form according to claims 1 or 2, characterized in that the active-substance-containing coating substance is pre-divided into dosage units by punching.

4. Presentation form according to one of claims 1 to 3, characterized in that the coating contains one or more pharmaceutical active substances.

5. Presentation form according to one of claims 1 to 4, characterized in that the coating contains water-soluble swelling substances as polymeric foil formers and optionally softeners.

6. Presentation form according to one of claims 1 to 5, characterized in that it contains, to set the viscosity, polymeric swelling substances, which can simultaneously serve as adhesion promoters.

7. Presentation form according to one of claims 1 to 6, characterized in that the coating is applied in the form of several layers having differing composition.

8. Presentation form according to claim 7, characterized in that incompatible active substances are applied one after the other as separate layers to the carrier material.

9. Presentation form according to claim 7, characterized in that an active substance layer is arranged between at least two other layers which control the absorption of the active substance in the gastro-intestinal tract in a manner known per se.

10. Presentation form according to claim 7, characterized in that a further layer is applied onto the active substance layer, said layer protecting the active substance against contact with the atmosphere and/or against light.

11. Presentation form according to one of claims 1 to 10, characterized in that the back of the carrier material can be printed with the active substance composition and/or information concerning the intake thereof.

12. Process for preparing the pharmaceutical presentation form according to claims 1 to 11, characterized in that an active-substance-containingcomposition is applied with the aid of rollers to the non-adhesively finished side of a release paper, a release film or a release foil.

Revendications

1. Forme de présentation ou de dosage de principes actifs médicamenteux, réactifs, substances aromatisantes ou similaires, sous la forme d'un matériau support en forme de feuille muni d'un revêtement contenant le principe actif, caractérisée en ce que le matériau support est un papier détachable, un film détachable ou une feuille détachable et, le matériau support est muni d'un côté du revêtement contenant le principe actif, que l'on peut détacher par doses du matériau support après l'avoir préalablement divisé en doses unitaires.

2. Forme de présentation selon la revendication 1, caractérisée en ce que le matériau support est un papier détachable revêtu de silicone ou de cire.

3. Forme de présentation selon la revendication 1 ou 2, caractérisée en ce que le revêtement contenant le principe actif est préalablement divisé en doses unitaires par poinçonnage.

4. Forme de présentation selon l'une quelconque des revendications 1 à 3, caractérisée en ce que le revêtement contient un ou plusieurs principe(s) actif(s) médicamenteux.

5. Forme de présentation selon l'une quelconque des revendications 1 à 4, caractérisée en ce que le revêtement contient des substances épaississantes, comme des agents filmogènes polymères et, le cas échéant, des plastifiants.

6. Forme de présentation selon l'une quelconque des revendications 1 à 5, caractérisée en ce qu'elle contient des substances épaississantes polymères pour ajustement de la viscosité, celles-ci pouvant servir en même temps d'agents adhésifs.

7. Forme de présentation selon l'une quelconque des revendications 1 à 6, caractérisée en ce que le

revêtement est constitué de plusieurs couches de compositions différentes.

8. Forme de présentation selon la revendication 7, caractérisée en ce que des principes actifs incompatibles entre eux sont appliqués successivement sur le matériau support, dans des couches séparées.

9. Forme de présentation selon la revendication 7, caractérisée en ce qu'une couche de principe actif est placée entre au moins deux autres couches qui règlent, par des moyens connus par eux-mêmes, la résorption du principe actif dans l'estomac/le tractus intestinal.

10. Forme de présentation selon la revendication 7, caractérisée en ce que l'on étale, sur la couche de principe actif, une couche supplémentaire qui préserve le principe actif, une couche supplémentaire qui préserve le lumière.

11. Forme de présentation selon l'une quelconque des revendications 1 à 10, caractérisée en ce que l'on peut imprimer au verso du matériau support la composition du principe actif et/ou des informations concernant sa prise.

12. Procédé pour préparer la forme de présentation de médicament des revendications 1 à 11, caractérisé en ce que l'on étale, à l'aide de cylindres, une composition contenant le principe actif sur le côté laissé non adhésif d'un papier détachable, d'un film détachable ou d'une feuille détachable.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 273 069 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **14.10.92**

(51) Int. Cl.[5]: **C08B 37/14**, A22C 13/00, A61L 15/28, B01D 71/08

(21) Application number: **86118163.4**

(22) Date of filing: **30.12.86**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **Glucomannan/polyhydric alcohol composition and film prepared therefrom.**

(43) Date of publication of application:
06.07.88 Bulletin 88/27

(45) Publication of the grant of the patent:
14.10.92 Bulletin 92/42

(84) Designated Contracting States:
DE FR GB

(56) References cited:
EP-A- 0 109 269
DE-B- 2 148 159
GB-A- 853 378
GB-A- 2 048 642

CHEMICAL ABSTRACTS, vol. 97, 1982, page 487, abstract no. 4931e, Columbus, Ohio, US

CHEMICAL ABSTRACTS, vol. 100, 1984, page 530, abstract no. 137715q, Columbus, Ohio, US

PATENT ABSTRACTS OF JAPAN, vol. 6, no. 98 (C-106)[976], 8th June 1982

(73) Proprietor: **UNI COLLOID KABUSHIKI KAISHA**
No. 7-8, Sakurayama 1-chome
Zushi-shi Kanagawa-ken(JP)

(72) Inventor: **Kubodera, Masao**
203, Shiba-cho Kanazawa-ku
Yokohama-shi Kanagawa-ken(JP)

(74) Representative: **Glawe, Delfs, Moll & Partner Patentanwälte**
Postfach 26 01 62 Liebherrstrasse 20
W-8000 München 26(DE)

Rank Xerox (UK) Business Services

EP 0 273 069 B1

Description

BACKGROUND OF THE INVENTION

The present invention relates to a composition having a complex network structure that is formed by mixing glucomannan and optionally another natural polysaccharide with a polyhydric alcohol such as glycerin or a concentrated solution thereof in the presence of absence of an alkali. The present invention also relates to a film prepared from this composition.

The composition of the present invention can be dissolved in water to form a viscous solution. A film formed of this composition is water-resistant and may be given greater strengthand heat-resisting property. The film finds utility in various applications such as edible films, semipermeable membranes for separating low-molecular weight materials from those having high molecular weights ; wound dressings, and the shells of soft capsules.

The principal use of glucomannan has been to produce konjak by reacting it with an alkali in an aqueous solution, then heating the reaction product to form a gel. The gel formed bythis method has an inhomogeneous structure and finds no utility other than as konjak. Other natural polysaccharides have been used in an aqueous solution as thickeners, gelling agents, water retainers, stabilizers, dispersants, emulsifiers, binders, etc.

Compounds having multiple hydroxyl groups as exemplified by polyhydric alcohols, sugar alcohols, monosaccharides, dissaccharides and oligosaccharides have been used solely as additives such as sweeteners, humectants, softening agents and plasticizers. Moreover, these compounds have been used singly and no attempt has been made to allow the natural polysaccharidesto react directly with polyhydric alcohols in the presence of a small amount of water.

Edible films currently available include starch-based waters, gelatin-based collagen film, and pullulan films. All of these films except those based on gelatin lack resistance to water. Even gelatin films lack high resistance to acid, alkalies and heat. Films formed of cyclodextrins or special proteins obtained by extracting nucleic acids, cell membranes, etc. from yeasts are expensive and their high cost is not justified by corresponding improvements in water resistance, heat resistance and strength.

In the production of smoked meat products such as hams and sausages, semipermeable membranes such as those made of animal guts, regenerated cellulose or cellulose derivatives are used to allow the fragrant and seasoning components in the smoke to penetrate into the meat. However, the supply of animal guts is not abundant and, in addition, they lack strength and are not uniform in size. The supply of regenerated cellulose and cellulose derivatives is also limited because strict regulations against pollution has rendered the construction of new plants practically impossible.

Gelatin has heretofore been used as the shell matereal of soft capsules for cunfining drugs, flavors or seasonings but the user of gelatin is limited to applications where oily substances are employed.

Electrolytes or low-molecular weight materials have been separated from high-molecular weight materials by such means as electrodialysis, reverse osmosis, and ion-exchange membrane technology. However, these methods use a large number of electrodes or require high pressures so that the equipment for practicing these methods is becoming more and more complex. In order to desalt foods by these methods, large-sized equipmentis necessary and it often occurs that other seasoning componentsare eliminated as well as the sodium salt with the result that the taste of the food is impaired.

In the treatment of skin losses due to burns or other external injuries, the affected area is temporarily covered to prevent loss of water or body fluids from the wound, or any exudate from the wound is desplaced to prevent bacterial infection so that the formation of granulations and the epidermis is promoted. The films which have been used or attempted to be used for these purposes are formed of such materials as silicone rubber, poly -E -caprolactone, poly (vinyl alcohol) , polyamino acids,fibrin membranes, collagen, polyurethane and pigskin.

However, freeze-dried pigskin and other polyamino acid based wound dressings are all made of polypeptides which are subject to biochemical decomposition. In order to avoid the adverse effects of the degradation products which are liberated, these wound dressings have to be replaced at short intervals, typically every other day. However, replacement of the wound dressing involves much pain for the patient. Furthermore, the film itself has insufficient strength to attain satisfactory coverage. Wound dressings made of synthetic resins such as polyurethane and silicone rubber do not have sufficient affinity for the wound surface to achieve satisfactory permeation to oxygen and water. Nomal skin generally allows water to be evaporated in an approximate amount of 350g/m^2 per day, but it has been difficult to prepare synthetic resin films that exhibit this amount of water evaporation and which yet has sufficient strength.

It has been proposed to prepare a composite wound dressing by laminating a polyamino acid based

film with a synthetic resin film but this composite film still suffers from the defects of the respective film components.

SUMMARY OF THE INVENTION

The present inventors have found that if glucomannan, either independently or in combination with other natural polysaccharides, is mixed with a compound having multiple hydroxyl groups or with a concentrated solution thereof in the presence of absence ofan alkali, the respective components react with each other to form a composition having a dense three-dimensional structure. The present inventors have also found that a viscous solution formed by dissolving this composition in water has unique physicochemical properties that have been unattainable by glucomannan, other natural polysaccharides or polyhydric alcohols, and that various products having the characteristics shown below can be prepared from this composition. The present invention has been accomplished on the basis of these findings.

Firstly, edible films having desirable properties s such as water resistance, heat resistance and strength can be prepared from the above-described viscous aqueous solution either directly or after being mixed with other foods or food materials. The so prepared films may be eaten as such or used as edible food packages.

Secondly, the viscous aqueous solution may be dried into film form and the resulting film may be used in the production of processed meat products (e.g. hams and sausages) as semipermeable membranes having sufficient strength and heat resistance to withstand smoking condition.

Thirdly, the viscous aqueous solution may be processed to form a film that is suitable for use as the shell of a soft capsule, and using this film, soft capsules capable of confining non-oily drugs, health foods, seasonings or flavors can be prepared.

Fourthly, the film made from the viscous aqueous solution also serves as a high-performance filter medium that is capable of efficient separation of low-molecular weight substances from high-molecular weight substances at reasonably low pressures.

Fifthly, the membrane formed by drying the viscous aqueous solution into film form is a superior wound dressing that achieves close contact with the skin and exhibits superior vapor and oxygen permeation without undergoing any biodegradation during prolonged attachment to the skin.

Sixthly, the viscous aqueous solution cools to provide a gel-like or semifluid foodstuff having unique properties.

DETAILED DESCRIPTION OF THE INVENTION

The glucomannan used in the preparation of the composition of the present invention is the polysaccharide naturally occurring in Amorphophallus Koniac K. Koch which is the rhizome of a plane belonging to Colocasia antiquorum; it is composed of particles referred to as idioblasts which range from 0.5 to 1.05 mm in length and from 0.37 to 0.5 mm in breadth. The chemical structure of glucomannan is a chain of a 1 : 2 mixture of glucose and mannose with acetyl and phosphate groups forming pendant ester linkages.

Illustrative polyhydric alcohols that can be used in the present invention are polhydric alcohols in the narrow sense of the term such as propylene glycol and glycerin. These polyhydric alcohols are liquid and may be directly used; however, because of their high hygroscopicity they contain water and are in the form of concentrated aqueous solutions. Moreover they can be used as water solution of concentration in the range of 30 to 90 %. Illustrative sugar alcohols include sorbital, mannitol, maltitol, xylytol and saccharified products of reducing sugar. Illustrative monosaccharides include glucose, fructose, galactose and xylose. Illustrative disaccharides are saccharose, maltose and lactose. Starches such as sweet potato, potato and corn that have been decomposed with enzymes or acids are usable as oligosaccharides, and include di-, tri-, tetra-, penta- and hexasaccharides. The polyhydric alcohols listed above, both in the broad and narrow sense of the term, which are in a powder form at ordinary temperatures, are used as aqueous solutions having concentrations in the range of 30-90 wt %, preferably 50-80 wt %, more preferable 65-75wt%.

Other natural polysaccharides that may be used in the present invention include the following:

alginic acid which are intracellular polysaccharides in brown algae,

sodium alginate,

propylene glycol ester of alginic acid, and

agar;

carrageenan which is an intracellular polysaccharide in red algae and is hydrolyzed into D-galactose and D-galactose sulfate ester ;

locust bean gum which is a polysaccharide that is present in the seeds of leguminous locust bean and

carob and which is chiefly composed of glucomannan;

guar gum that is a polysaccharide present in the seed of leguminous guar and which is hydrolyzed into galactose and mannose ;

tamarind seed polysaccharide which is a polysaccharide present in the seed of leguminous Tamarindus indica and which is hydrolyzed into glucose, xylose and galactose ;

pectin which is a generic term for a group of polysaccarides that are the materials of construction of the cell walls of plants such as fruit and vegitables and which are hydrolyzed in to galacturonic acid;

xanthan gum is a polysaccharide produced by the microorganism Xanthomonas campestris during fermantation in the present of glucose and other appropriate essential elements;

chitin which is one kind of mucopolysaccharides;

pullulan which has a repeating unit of α -1,6 linkage derived from maltotriose ; and

cellulose,

cyclodextrin and

starches.

These natural polysaccharides are optionally used in amounts of 0.05 - 20 parts by weight, preferably from 0.1 to 10 parts by weight, per part by weight of glucomannan.

In the present invention, reaction is preferably carried out in the presence of an alkali. Ordinary inorganic or organic alkaline substances may be employed and suitable ones inclueded: sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, ammonium carbonate, magnesium carbonate, sodium bicarbonate, ammonium bicarbonate, basic amino acids and amines. The addition of these alkalis is generally effective in providing films with improved strength and heat resistance.

Part of the glucomannan and optionally used natural polysaccharides may be replaced by proteins to provide composition which generally have improved heat resistance. Solutions of these compositions in warm water have good mouth feel and can be readily eaten. Illustrative proteins are soybeen protein, wheat protein, milk protein, egg white, collagen, decomposed collagen and microbial proteins. Decomposition products of these proteins, such as polypeptides and amino acids, may also be used.

The present invention is characterized by reacting glucomannan directly with at least one compound selected from among the polyhydric alcohols, sugar alcohols, monosaccharides, disaccharides and oligosaccharides. The component made of at least one compound selected from polyhydric alcohols, sugar alcohols, monosaccharides, disaccharides and oligosaccharides is used in an amount which ranges from 0.05 to 10 parts by weight, preferably from 0.10 to 5.0 parts by weight, more preferably from 0.15 to 1.0 part by weight, per part by weight of the powder component made of glucomannan and optionally of other natural polysaccharides and proteins. Generally, a higher content of the polyhydric alcohol renders it difficult for a three-dimensional network to develop.

The reactants are mixed at a temperature ranging from 5 to 150 °C, preferably from 10 to 100 °C, more preferably from 20 to 80 °C. Mixing at low temperatures will cause no problem because the intended reaction can be allowed to proceed satisfactorily by heating the mixture in a subsequent step such as drying. Generally, mixing at high temperatures provides a composition having a dense structure whereas a brittle composition having a coarse network results if low mixing temperatures are used.

The composition formed by mixing the starting materials described above is a powder that is usually moist to some extent. A solution of this composition in water is viscous and will solidify irreversibly when left to stand at ordinary temperatures, frozen, refrigerated or heated. The properties, in particular the strength, heat resistance and the temperature for dissolution in water, of the solidified product can be altered by proper adjustment of the combination of the starting materials used. Therefore, the solidified product can be used as a base for semifluid or gel-like foods such as jelly and jam. Films may be formed from the viscous solution by shaping it into a soldified form of a suitable thickness between 1 and 1,000 μm by any of the known techniques such as wet casting, freeze-drying and extrusion molding. Some of the films formed by these methods are heat-resistant and heat-sealable. If desired, the viscous solution may be coated or sprayed onto a foodstuff and dried to form an edible film on the food.

Films having thicknesses in the range of 1-1,000 μm, preferably 2- 300 μm, are useful as semipermeable membranes. In a more preferable embodiment, a thin and reinforced semipermeable membrane can be formed by preparing a thin fibrous product from an appropriate material such as paper, nonwoven fabric, woven fabric or net, then filling the voids in the fibrous product with the filter film of the present invention. Filling of the voids in the thin fibrous product may also be achieved by coating the film with the viscous solution or submerging the film in the solution, followed by drying of the film.

Filtration may be achieved by any known technique such as simple filtering under gravity, ultrafiltration or reverse osmosis. The filter medium may be an assembly of hollow fibers or a module of a spirally wound

sheet.

In the simplest way, afoodstuff having high sodium chloride concentration is placed on top of the semipermeable membrane of the present invention which is in contact with an underlying water layer; in the absence of any applied pressure, sodium chloride and other low-molecular weight substances in the upper layer will permeate through the membrane to enter the underlying aqueous layer.

Soy sauce, miso and pickled products contain a large amount of sodium chloride in order to ensure that they can be transported long distances or to achieve various purposes such as storage, preservation or good manufacturing practice. The filter film of the present invention is capable of allowing the sodium chloride content of these food products to be lowered without impairing their taste.

In producing processed meat products such as hams and sausages, the meat wrapped in a semipermeable membrane must be smoked. Conventionally, the semipermeable membrane is formed of regenerated cellulose, cellulose derivatives, alginates, collagen, or sheep or bovine gut. However, as already mentioned, these materials have problems in terms of their physical strength and heat resistance, and in particular, sheep and bovine guts are not uniform in size and shape and suffer from instability in supply.

Fibrous products are usually porous and the films prepared by impregnating or coating them with the edible composition of the present invention serve as ideal casing materials wherein the semipermeable membrane formed of the edible material isreinforced with the fibrous product. Such casing materials may be prepared as follows: a fibrous product of a given width is shaped into a tubular base, which is continuously impregnated with an aqueous solution of the composition of the present invention and dried to form a strong fibrous casing.

The shell of conventional soft capsules is formed from an aqueous solution of gelatin and glycerin and is only capable of confining oily products. The soft capsules formed from an aqueous solution of the composition of the present invention are capable of confining not only oily products but also water-soluble substances and, hence, are applicable to enlarged areas of use, for instance: (1) water-soluble vitamins such as vitamins B_1, B_2, B_5, B_6, B_{12}, niacin folic acid and vitamin C; (2) nutrients such as liquid glycides, proteins and minerals; (3) diets formed of soft capsules that incorporate liquid seasonings or flavors and which are readily edible after cooking ; and (4) cosmetics in soft capsules that are to be punctured with a needle to allow the contents to be used.

Soft capsules may be prepared from the composition of the present invention as follows : the composition is dissolved in water and the solution is allowed to flow out of a spreader box to form a gel which is subsequently shaped into a film form, two sheets of the film thus obtained are passed through a pair of die rolls to adhere to each other ; a predetermined amount of the content (ie, fill) is forced with a pump to obtain a caplule form, which is subsequently dried to form a soft capsule.

The film prepared in accordance with the present invention is also useful as an ideal wound dressing. It swells readily upon absorbing body fluids from a wounded site of the human body but its three-dimensional network will remain intact. The film increases in thickness but its area remains the same so as to allow the absorbed moisture to be evaporated from its furface. The film supplies the wound surface not only with moisture but also with the drug applied onto the outer surface of the film ; at the same time, the film allows the unwanted exudate to be liberated on its surface. Therefore, the film does not have to be peeled off until after the wound has healed. The thickness of the film used as a wound dressing generally ranges from 1 to 1,000μm, preferably form 5 to 200 μm, more preferably from 7 to 50 μm.

When the composition of the present invention is dissolved in water, a vicous solution or slurry with a solids content of 2-10 % will form and this can be incorporated in a large amount in suitable food materials. The incorporated composition will solidify irreversibly be being left to stand at ordinary temperatures, frozen, refrigerated or heated. The properties, in particular the strength, heat resistance and the temperature for dissolution in water of the solidified product can be altered by properly adjusting the combination of starting materials used. Furthermore, the solidifed product retains the tast flavor of the food material present.

The food materials that can be mixed with the viscous solution or paste of the composition of the present invention are diverse and include: seaweeds ; marine products such as shrimp, cuttlefish, fish (e.g. bonito, tuna and salmon) , and fish roe; vegitables such as spinach, cabbage, carrot and pumpkin; fruits such as orange, grape, apple and pineapple ; meats such as beef, pork, chicken, and corned beef ; processed foods such as cheese, jam, mayonnaise and miso ; seasonings such as soy sauce and sodium glutamate ; as well as spices and flavors such as peanut, almond, mustard, pepper, curry, cocoa, coffee an chocolate.

These food materials may be mixed with the viscous solution or slurry of the composition of the present invention either directly, or after being conditioned for a given particle size or shape, or after being formed into a paste. The mixing ratio of these food material to the glucomannan /polyhydric alcohol composition of

the present invention is not limited to any particular value because it largely depends on the type of food material used or the specific formulation of the composition. It should however be noted that a preferable mixing ratio is such that the mixture can be readily formed into a film, and that the shaped food is easy to handle and does not reveal the mouth feel of the composition.

The aqueous solution of the composition of the present invention is viscous and its properties, in particular its strength, heat resistance and temperature for dissolution in water, can be altered by allowing it to stand at ordinary temperatures, freezing, refrigerating or heating the same. Therefore, the aqueous solution, after being shaped into a gelled block of an appropriate hardness, may be mixed with a non-alcoholic beverage such as juice or yogurt or foods, and the resulting mixture can be safely heated without melting to thereby provide a composite dietary product that shows a desirable combination having the sort of mouth feed that is possessed by dissimilar components. There is no particular limitation on the size of the gel block and its hardness varies with the type of base used: if the base is a liquid material such as juice, the moisture content of the block is preferably increased to provide a soft texture, whereas if the base is jelly or any other material that has a certain amount of self-retaining property, its moisture content is decreased to provide a hardness slightly lower than that of the jelly. In either case, the resulting product is composed to two dissimilar materials and yet displays good palatability.

Glucomannan has a complex structure containing various side chains and reactive groups and, because of the presence of many hydroxyl groups at high concentrations, glucomannan enters into reaction to form a complex matrix even under a substantially water-free condition. The matrix forming reaction will be enhanced by the presence of an alkali and an even more complex compound will form. In the presence of both an alkali and water, the development of a three-dimensional network is further promoted to form an irreversibly solidified product, which can be processed to provide a characteristic gel-like base or a coating.

The present invention is hereinafter described in greater detail with reference to the following examples to which the scope of the invention is by no means limited and wherein all parts are on a weight basis.

EXAMPLE 1

Eight parts of glucomannan was mixed with 2 parts of glycerin for 15 minuites an 70 °C to form a sample of the composition of the present invention which was a somewhat moist powder. Two parts and a half of this composition were mixed with 97.5 parts of water to form a viscous aqueous solution. This solution was coated onto the peel of orange and dried at 50 °C for 1 hour to provide orange having an edible film coating on its peel. This orange and uncoated orange were stored at 25 °C for 10 days. Thereafter, the appearance of the two oranges and the mouth feel of their pulp were compared. Compared with the uncoated orange, the one having an edible film coat had undergone a smaller degree of water evaporation and oxidation, retained more luster and experienced less surface discoloration. The pulp of the coated orange was fresher and more palatable.

EXAMPLE 2

Three parts of the composition prepared in Example 1 was mixed with 0.04 parts of a vitamin E powder (70% natural vitamin E and 30 % emulsifier) and 97 parts of water to form an aqueous solution. An orange whose peel was coated with the resulting aqueous solution as in Example 1 was stored at 25 °C for 15 days together with an uncoated orange. The results of comparison of the two oranges were the same as in Example 1.

EXAMPLES 3 - 10

The components listed in Table 1 were mixed for 10 minutes at 80 °C in the amounts also shown in Table 1, so as to prepare eight additional samples of the composition of the present invention. Three parts of each of the samples was mixed with 97 parts of water and the resulting aqueous solutions were cast by the wet process to form translucent edible films having thicknesses ranging from 10 to 20 μm. The films prepared in Examples 3 to 6 were water-resistant and stable in the following solutions: aqueous solutions with NaCl concentrations of 5% or more ; acidic aqueous solutions with pH of 2.5 - 4.5; alkaline aqueous sloutions with pH of 9.0 - 12.0 ; aqueous solutions with ethanol concentrations of 10 % or more. The films prepared in Examples 7 - 10 were not only water-resistant; they were resistant to hot water and stable in aqueous solutions heated to 80 - 100 °C.

Table 1

(unit in parts by weight)

Example No.		3	4	5	6	7	8	9	10
natural polysaccharide	glucomannan	5	5	5	5	5	5	5	5
	carrageenan	3			2		4		3
	agar		2					1	
	locust bean gum			2					1
	xanthan gum				1		0.5		
alkali	calcium carbonate							0.3	0.1
	calcium hydroxide					0.05			
	sodium bicarbonate						0.5		0.3
glycerin			1.5		1.5	1		1	
sorbitol (70% aq.sol.)		1.5					1		
saccharose (80% aq. sol.)				1.5					1

EXAMPLE 11

An edible package film 15 μm thick was formed from a composition having the same formulation as used in Example 3. Stripped lobster (150g) was wrapped with this film and stored at-25°C for 3 months. The frozen lobster as wrapped in the film was thawed in a microwave oven and cooked. The cooked lobster had the edible film on it but one did not sense any peculiar feel as a result of the presence of the film.

EXAMPLE 12

An edible film 15μm thick was formed from a composition having the same formulation as used in Example 8. Vegitable salad with dressing was sandwiched between two slices of bread. During subsequent storage, the dressing did not permeate into the bread at all. After the strage, the bread was eaten ; it tasted good and the taste of the edible film was not sensed.

EXAMPLE 13

Components	Amount (in parts)
Glucomannan	5
Sodium bicarbonate	0.1
Calcium Carbonate	0.02
Glycerin	1

These components were mixed at 75 °C for 20 minutes. Three parts of the resulting composition were dissolved in 97 parts of water. The aqueous solution was applied continuously to form a uniform coating on the inner surface a fluoroethylen resin-coated cylindrical pipe having a diameter of 120 mm. The applied coat was dried to form a tubular casing.

Processed meat was packed into the casing at a pressure of up to 2 kg/cm^2 without causing its disruption. The packed meat was smoked and sterilized by heating in hot water (80 °C) for 2 hours to produce a satisfactory ham.

EXAMPLE 14

Components	Amount (in parts)
Glucomannan	5
Agar	0.5
Calcium carbonate	0.5
Sodium citrate	0.3
Sorbitol (70% aq. sol.)	1

These components were mixed at 80 °C for 10 minuites. Three parts and a half of the resulting composition were dissolved in 96.5 parts of water to form a viscous aqueous solution. A sheet of porous paper having a thickness of 100 μm was prepared, with wood pulp and cotton linter being used as chief components. The two side edges of the sheet were adhered together to form a tubular base. The wall of this base was impregnated with the previously prepared viscous aqueous solution and dried to form a casing that was formed of a sample of the film of the present invention that had a thickness of 120 -130 μm and which was reinforced with a fibrous product.

Processed meat was packed into the casing at a pressure of up to 6 kg/cm^2 without causing its disruption. The packed meat was smoked and sterilized by heating in hot water (80 °C) for 2 hours to produce a satisfactory sausage.

EXAMPLE 16

A mixture of gelatin (100 parts) and glycerin (30 parts) was dissolved in 60 parts of water at 75 °C with stirring and defoamed with a vacuum pump. The solution was shaped into a 450 μm thick film on an automatic rotary continuous soft capsule filling machine. A film 25 μm thick that was prepared asin Example 6 was stacked on the inside surface of the 450 μm thick film to form a double-layered film. Two units of this double-layered film were passed between a pair of die rolls to be adhered to each other and an aqueous solution of 30% L-ascorbic acid was forced in with a filling pump to form capsules each containing 500 mg of the fill. The capsules were dried to produce soft capsules.

EXAMPLE 16

Components	Amount (in parts)
Glucomannan	5
Carrageenan	0.5
Calcium carbonate	0.12
Glycerin	1

These components were mixed at 70 °C for 30 minutes. Three parts of the resulting composition was dissolved in 97 parts of water to form a viscous aqueous solution. the solution was formed into an edible film 15 μm thick by the wet casting method. As in Example 15, a dual-layered capsule shell was formed by staking this film over a gelatin film. Using this shell, soft capsules each containing 5 g of seasonings for instant chicken soup were produced. On of these capsules was mixed well with 150 ml of hot water (90 °C) under agitation ; the capsule was disintegrated in the water to provide chicken soup.

EXAMPLE 17

A mixture of gelain (100 parts) and glycerin (30 parts) was dissolved in 10 parts of water at 75 °C with stirring. Thesolution was defoamed with a vacuum pump and designated A. In a separate step, 5 parts of glucomannan, 3.5 parts of carrageenan and 1.5 parts of glycerin were mixed at 70 °C to form a sample of the composition of the presnet invention ; 3 parts of the composition was dissolved in 97 parts of water to form an aqueous solution which was designated B. An intimate blend of solution A (60 parts) and solution B (40 parts) was fed into an automatic rotary continuous soft capsule filling machine to form soft No. 5 oval capsules by the known rotary die method, with each capsule having confined therein 290 mg of an astringent lotion. Just prior to use, each soft capsule was punctured with a needle to recover to lotion in an amount sufficient for single use.

EXAMPLE 18

Components	Amount (in parts)
Glucomannan	5
Carrageenan	3
Cellulose	1
Glycerin	2

These components were mixed at 80 °C for 10 minutes and 2.5 parts of the resulting composition was dissolved in 97 parts of water. The solution was formed into a circular film (thickness, 15 μm ; diameter, 29 mm) by the wet casting method. The film was set in a filtration vessel which was filled with 450 ml of tap water in its lower compartment and with 150 ml of soy sauce (18% NaCl) in its upper compartment. The vessel was left to stand at 20 °C for a given period and the contents of NaCl and amino acid nitrogen in the soy sauce were measured at predetermined intervals. The results are shown in Table 2.

Table 2

(effective surface area of film: 960.6 mm²)

Time (min)	NaCl (%)	Amino acid N_2	Increase in water content (%)
0	16.4	0.91	0
30	15.7	0.86	0.7
60	16.5	0.82	1.6
90	15.0	0.86	2.7
120	14.1	0.79	4.1
150	13.3	0.78	5.7

As Table 2 shows, the NaCl content of the soy sauce decreased with time and this was accompanied by gradual depletion of amino acids and increase in the moisture content. However, most of the amino acids that flowed out were those having low molecular weights such as glycin and alanine and their depletion did not cause any substantial deterioration of the taste of the soy sauce. The soy sauce prepared in accordance with the present invention had a generally mellow taste and its sodium chloride content was low.

EXAMPLE 19

An aqueous solution of the composition used in Example 18 was heated to 70 °C with stirring and applied to a thin sheet of paper (basis weight: 16g / m^2) to form a film having a thickness of 35μm. This fiber-reinforced film was tested as in Example 18. The results were substantially the same as those obtained in Example 18. The film prepared in this example was superior to that prepared in Example 18 in terms of self-retaining property and tensile strength.

EXAMPLE 20

Components	Amount (in parts)
Glucomannan	5
Xanthan gum	0.5
Calcium hydroxide	0.06
Glycerin	1

These components were mixed at 60 °C for 20 minuites to obtain a sample of the composition of the present invention. Three parts of this composition were dissolved in 97 parts of water and a thin layer of the solution was spread onto a fluoroethylen resin-coated sheet. The coating was freeze-dried by a conventional method to prepared a wound dressing in a film form having a thickness of 12 μm. The film was sterilized, coated with a drug layer and attached to the surface of a wound produced by a third-degree burn. The treatment that ensured consisted of delivering the drug daily onto the surface of the film. Formation of granulations continued steadily without suppuration and in 10 days normal skin tissue was restored,

whereupon the film separated from the skin spontaneously.

EXAMPLE 21

An aqueous solution of the composition used in Example 20 was coated onto a nonwoven polyester fabric (basis weight : 10g / m^2) and freeze-dried by a known method so as to make a film having a thickness of 30μm. This film was used as a wound dressing to cure a burn in accordance with the same regimen as employed Example 20. The results were substantially the same as those obtained in Example 20.

EXAMPLE 22

Components	Amount (in parts)
Glucomannan	5
Alginic acid	1
Guar gum	0.5
Glycerin	1

These components were mixed at 65°C for 20 minutes to form a sample of the composition of the present invention. Three partsof this composition were dissolved in 97 parts of water. Seventyfive parts of the solution were mixed with 25 parts of a beef fillet and the blend was shaped into an edible film (thickness : 25μm) by the wet casting method. The film was laid down on a slice of bread ; the product had a characteristic flavor originating from the blending of the taste of beef with the bread.

EXAMPLE 23

Components	Amount (in parts)
Glucomannan	5
Tamarind seed polysaccharide	1
Gelatin	1
Glucose (80% aq. sol.)	1

These components were mixed at 60°C for 40 minuites to form a sample of the composition of the present invention. Three parts of this composition were dissolved in 97 parts of water to form a viscous aqueous solution. Eighty parts of this solution were blended with 20 parts of a dried spinach powder (particle size : 100-Tylermesh pass) and the blend was shaped into an edible film (15μm thick) by a known freeze-drying technique. This film was rolled around a bar of cooked rice so as to provide a low-calorie dietary product.

EXAMPLE 24

Components	Amount (in parts)
Glucomannan	5
Carrageenan	5
Calcium carbonate	0.2
Glycerin	1.5

These components were mixed at 70 °C for 30 minutes to form a sample of the composition of the present invention. Five parts of this composition were mixed and kneaded with 95 parts of cocoa paste and the necessary seasonings to make a chocolate mass, which was refined and molded into a sheet. Although conventional chocolate products are soften at 35 °C or higher, the chocolate sheet of the Example 24 did not soften until it was heated to 50 °C.

Claims

1. A glucomannan/polyhydric alcohol composition prepared by uniformly mixing at 5 to 150 °C 1 part by weight of a glucomannan powder with 0,05 to 10 parts by weight of an aqueous solution of 30-100 wt.-% of at least one polyhydric alcohol selected from the group consisting of propylene glycol, glycerin, sugar alcohols, monosaccharides, disaccharides and oligosaccharides.

2. A composition according to claim 1, characterized in that the components are mixed in the presence of an alkali.

3. A composition according to claim 1 or 2 wherein part of the glucomannan is replaced by another natural polysaccharide.

4. A composition according to claim 3, wherein the other natural polysaccharide is carrageenan.

5. A film prepared by a process comprising the steps of: dissolving a glucomannan/polyhydric alcohol composition according to anyone of the claims 1 to 4 in water, forming the solution into a film by shaping it into a solidified form of a suitable thickness between 1 and 1000 µm by any of the known techniques, and drying the film.

6. A film according to claim 5, characterized in that it is edible.

7. A film according to claim 5 or 6 which is reinforced with a thin fibrous product.

8. The use of a film according to anyone of the claims 5 to 7 as a food packaging.

9. The use of a film according to anyone of the claims 5 to 7 as a casing in the manufacture of smoked food products.

10. The use of a film according to anyone of the claims 5 to 7 as a shell of a soft capsule.

11. The use of a film according to anyone of the claims 5 to 7 as a semipermeable membrane for separating a high-molecular weight substance from a low-molecular weight substance.

12. The use of a film according to anyone of the claims 5 to 7 as a wound dressing.

Patentansprüche

1. Glucomannan/mehrwertiger Alkohol-Zusammensetzung, erhalten durch gleichförmiges Vermischen bei

5 bis 150 °C von 1 Gew.-Teil eines Glucomannanpulvers mit 0,05 bis 10 Gew.-Teilen einer wäßrigen Lösung von 30 bis 100 Gew.-% mindestens eines mehrwertigen Alkohols, ausgewählt aus der aus Propylenglykol, Glycerin, Zuckeralkoholen, Monosacchariden, Disacchariden und Oligosacchariden bestehenden Gruppe.

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß die Komponenten in Gegenwart von Alkali vermischt werden.

3. Zusammensetzung nach Anspruch 1 oder 2, bei der ein Teil des Glucomannans durch ein anderes, natürliches Polysaccharid ersetzt ist.

4. Zusammensetzung nach Anspruch 3, bei der das andere natürliche Polysaccharid Carrageen ist.

5. Film bzw. Folie, erhalten durch ein Verfahren, das die Schritte umfaßt:
Auflösen einer Glucomannan/mehrwertiger Alkohol-Zusammensetzung gemäß einem beliebigen der Ansprüche 1 bis 4 in Wasser,
Überführung der Lösung in einen Film bzw. eine Folie durch Überführen derselben in eine verfestigte Form mit einer geeigneten Dicke zwischen 1 und 1000 µm durch eine beliebige, bekannte Arbeitsweise,
und
Trocknen des Films bzw. der Folie.

6. Film bzw. Folie nach Anspruch 5, dadurch gekennzeichnet, daß er bzw. sie eßbar ist.

7. Film bzw. Folie nach Anspruch 5 oder 6, der bzw. die mit einem dünnen, faserförmigen Produkt verstärkt ist.

8. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Verpackung für Lebensmittel.

9. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Umhüllung bei der Herstellung von geräucherten Lebensmitteln.

10. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Hülle einer Weichkapsel.

11. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als semipermeable Membran zur Abtrennung einer Substanz mit hohem Molekulargewicht von einer Substanz mit niedrigem Molekulargewicht.

12. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Wundverband bzw. Wundabdeckung.

Revendications

1. Composition à base de glucomannan et d'alcool polyhydrique, préparée en mélangeant uniformément à la température de 5 à 150 °C, une partie en poids de poudre de glucomannan avec 0,05 à 10 parties en poids d'une solution aqueuse de 30-100% en poids d'au moins un alcool polyhydrique, choisi parmi le groupe comportant propylène glycol, glycérine, alcools de sucres, monosaccharides, disaccharides et oligosaccharides.

2. Composition selon la revendication 1, caractérisée en ce que les composants sont mélangés en présence d'un alcali.

3. Composition selon la revendication 1 ou 2, dans laquelle une partie du glucomannan est remplacée par un autre polysaccharide naturel.

4. Composition selon la revendication 3, dans laquelle l'autre polysaccharide naturel est le carrageenan.

5. Film préparé par un procédé comprenant les étapes de :
dissoudre une composition à base de glucomannan et d'alcool polyhydrique selon l'une quelconque des revendications 1 à 4, dans l'eau, former avec solution un film en la traitant dans une forme solidifiée, d'une épaisseur convenable, entre 1 et 1000 µm par n'importe quelle technique connue, et sécher le film.

6. Film selon la revendication 5, caractérisé en ce qu'il est comestible.

7. Film selon la revendication 5 ou 6, qui est renforcé avec un produit fibreux mince.

8. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme emballage de nourriture.

9. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme emballage dans la fabrication des produits alimentaires fumés.

10. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme enveloppe d'une capsule molle.

11. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme membrane semiperméable pour séparer une substance de poids moléculaire élevé d'une substance de faible poids moléculaire.

12. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme pansement d'une plaie.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 381 194 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **31.08.94** (51) Int. Cl.5: **A61K 9/70**

(21) Application number: **90101920.8**

(22) Date of filing: **31.01.90**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **Drug preparation applicable to oral mucosa.**

(30) Priority: **31.01.89 JP 23305/89**

(43) Date of publication of application:
08.08.90 Bulletin 90/32

(45) Publication of the grant of the patent:
31.08.94 Bulletin 94/35

(84) Designated Contracting States:
CH DE FR GB IT LI SE

(56) References cited:
EP-A- 0 020 777
EP-A- 0 106 107
EP-A- 0 200 508
EP-A- 0 241 179
EP-A- 0 275 550

CHEMICAL ABSTRACTS, vol. 83, 1975, page 373, abstract no. 103302t, Columbus,Ohio, US; & JP-A-75 19 838 (TEIJIN LTD) 03-03-1975

CHEMICAL ABSTRACTS, vol. 99, no. 22, November 1983, page 349, abstract no.181420z, Columbus, Ohio, US; L. STANOEVA et al.: "Polymer film forming forlocal application. Experimental characteristics",&& MBI, MED. BIOL. INF. 1982, (2), 3-8

(73) Proprietor: **NITTO DENKO CORPORATION**
1-2, Shimohozumi 1-chome
Ibaraki-shi
Osaka (JP)

(72) Inventor: **Kuroya, Takamasa**
c/o Nitto Denko Corp.,
1-2, Shimohozumi 1-chome
Ibaraki-shi, Osaka (JP)
Inventor: **Inoue, Yuichi**
c/o Nitto Denko Corp.,
1-2, Shimohozumi 1-chome
Ibaraki-shi, Osaka (JP)

(74) Representative: **Patentanwälte Grünecker, Kinkeldey, Stockmair & Partner**
Maximilianstrasse 58
D-80538 München (DE)

Rank Xerox (UK) Business Services
(3.10/3.09/3.3.3)

EP 0 381 194 B1

Description

This invention relates to a drug preparation applicable to the oral mucosa to maintain a long-term administration of a systemic drug.

Known dosage forms for intraoral administration of drugs include solutions, ointments, troches, buccal tablets, and sublingual tablets. Recently, slow-releasing intraoral tablets of the track-field type which are less causative of a feeling of foreign matter (as described in JP-A-55-59109, JP-A-58-154547, and JP-A-58-154548, the term "JP-A" as used herein means an "unexamined published Japanese patent application") and slow-releasing Nifedipine tablets of the track-field type applied to the oral mucosa (as described in JP-A-61-15829 and JP-A-61-17510) have been proposed. For the purpose of further reducing an adverse feeling in the oral cavity, a medical bandage using, as a base, a water-soluble high polymer which exhibits adhesion when dissolved or gelled with water (as described in JP-A-60-142927), preparations applicable to the oral mucosa comprising a water-soluble film having incorporated thereinto a steroid or non-steroid agent (as described in JP-A-61-280423), and sheet preparations comprising a support sheet having thereon a drug, gelatin, agar, gluten, a carboxyvinyl polymer, a polyhydric alcohol, a gum, and a wax as essential components (as described in JP-A-61-85315) have also been proposed.

More recently, there have been proposed bases for application to the oral mucosa which comprise a mixture of a water-soluble substance and a water-insoluble substance; for example, an intraoral bandage composed by a soft film in which at least one of a polycarboxylic acid and a polycarboxylic acid anhydride, and a vinyl acetate polymer are mixed in a compatible state as disclosed in JP-A-61-249472 and JP-A-61-249473; a base comprising a water-insoluble or sparingly water-soluble support having thereon an adhesive layer containing an acrylic acid polymer which exhibits adhesion when dissolved in or swollen with water and a water-insoluble cellulose derivative as disclosed in JP-A-63-160649; a composite for application to the oral mucosa comprising a surface layer containing ethyl cellulose and a vinylpyrrolidone polymer or copolymer having thereon an adhesive layer as disclosed in JP-A-63-171564 and JP-A-63-171565; and an adhesive composition containing a vinylpyrrolidone polymer or copolymer, at least one of hydroxyethyl cellulose and hydroxypropyl cellulose, and a water-retaining softener as disclosed in JP-A-63-174660.

However, none of these known intraoral preparations or bases satisfies both duration of adhesion and freedom from an adverse feeling in the oral cavity on use. For example, since solutions, ointments or the like preparations easily run away with saliva or water , it is difficult to maintain efficacy for a long time with these preparations. Troches, which are large tablets prepared by punching a mixture of a drug and a base, e.g., sacchardides, cause a considerable adverse feeling. Buccal tablets and sublingual tablets are generally designed for rapid mucosal absorption of drugs and are, therefore, of short duration. The track-field type tablets, though slowly releasing a drug, have a thickness as large as 1.3 to 3 mm and lack softness, still involving the problem of an adverse feeling on use. The preparations for application to the oral mucosa comprise a water-soluble film containing a drug have softness and thereby cause a reduced adverse feeling in the oral cavity. However, since the film base is water-soluble, it is easily dissolved in saliva or water in the oral cavity and is, therefore, poor in duration of efficacy. The bases comprising a mixture of a water-soluble substance and a water-insoluble substance are soft and less causative of an adverse feeling upon use. Also, they take time to disappear in the oral cavity and are thus expected to have a longer duration of pharmaceutical effects as compared with bases comprising a water-soluble substance alone. These bases nevertheless exhibit adhesion only for 2 to 10 hours at the longest.

Hence, an intraoral preparation satisfying all three requirements, i.e., freedom from a feeling of foreign matter on use, excellent shape retention on water absorption, and long-term adhesion to the wet oral mucosa, has not yet been developed.

EP-A-0106107 discloses a drug preparation applicable to the oral mucosa comprising an adhesive sheet containing prostaglandin, said sheet comprising a homogeneous mixture comprising one or more high molecular weight compounds. The high molecular Weight compounds may be, for example, a vinyl acetate resin, polyacrylic acid salts and cellulose derivatives.

EP-A-0241179 discloses a pharmaceutical composition comprising a mixture of an active ingredient and a polymer capable of dissolving in an aqueous medium of pH 4.0 or higher.

SUMMARY OF THE INVENTION

It is the object of this invention to provide a drug preparation applicable to the oral mucosa for administering a systemic drug, which is less causative of an adverse feeling in the oral cavity on use, excellent in shape retention on water absorption, and adhesive to the oral mucosa for an extended time.

Said object is achieved by a drug preparation applicable to the oral mucosa comprising a soft

adhesive film containing a systemic drug, the adhesive film comprising a homogeneous mixture comprising a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative capable of being dissolved in or swollen with water and a lower alcohol, wherein said mixture contains maximum 0.2 equivalent based on said acrylic acid polymer, of a salt or base.

Figure 1 illustrates the relationship of the rate of Propranolol Hydrochloride release to the time.

Figure 2 illustrates the relationship of the rate of Sodium Indometacin release to the time.

When the drug preparation applicable to the oral mucosa according to the present invention is applied to, for example, the fore gingiva of the upper jaw, the adhesive film base absorbs saliva and water in the oral cavity to exhibit adhesion to the oral mucosa. The adhesiveness in retained for a long period of time because of the excellent shape retention. Since the film base is homogeneous and soft, it is tightly adhered to the oral mucosa without causing an adverse feeling during application. The terminology "homogeneous" as used herein means that the vinyl acetate homopolymer, acrylic acid polymer and cellulose derivative in the mixture are homogeneously mixed under optical microscopic observation and that each of these components does not exist solely in parts.

The adhesive film of the drug preparation according to the present invention is obtained using a homogeneous mixture of a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative. A two-component mixture comprising only the vinyl acetate homopolymer and the acrylic acid polymer forms a homogenous and soft film but is swollen with saliva or water in the oral cavity and is inferior in shape retention on application to the oral mucosa. Further, a two-component mixture comprising only the acrylic acid polymer and the cellulose derivative forms a homogeneous and soft film but does not withstand long-term use in the oral cavity because of water-solubility of these components. Furthermore, a two-component mixture comprising only the vinyl acetate homopolymer and the cellulose derivative hardly forms a homogeneous and soft film.

The vinyl acetate homopolymer which can be used in the present invention is not particularly limited, and any known vinyl acetate homopolymer (as disclosed, e.g., in S.Imoto, Plastic Zairyo Koza - (Lectures on Plastic Materials) vol.14 Vinyl Acetate Resins, published by Nikkan Kogyo Press, Japan, on May 15, 1970) can be used as such either alone or in combination thereof. The weight average molecular weight of the vinyl acetate homopolymer is preferably from 40,000 to 200,000.

Examples of the acrylic acid polymer which can be used in the present invention includes an acrylic acid homopolymer; copolymers of acrylic acid and vinyl monomers, such as acrylic esters (e.g., butyl acrylate and 2-ethylhexyl acrylate), methacrylic esters (e.g., methyl methacrylate), and vinyl acetate; and other polymers, e.g., a carboxyvinyl polymer. Among these, an acrylic acid polymer having a carboxyl group content of 20% by weight or more is preferred. These polymers may be used either alone or in combinations thereof.

The cellulose derivative which can be used in the present invention must be capable of being dissolved in or swollen with water and a lower alcohol. Examples of the cellulose derivatives include methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose. The degree of substitution of the cellulose derivative is preferably from 0.1 to 4.5, and more preferably from 1.0 to 2.5. Hydroxypropyl cellulose having a degree of substitution of from 1.3 to 2.0 is most preferred. These cellulose derivatives may be used either alone or as a mixture of two or more thereof.

The weight ratio of acrylic acid polymer (B) to cellulose derivative (C) (B/C) preferably ranges from 1/9 to 9/1. To ensure long-term adhesion to the oral mucosa, the weight ratio B/C suitably ranges from 3/7 to 6/4. The weight ratio of vinyl acetate homopolymer (A) to the sum of acrylic acid polymer (B) and cellulose derivative (C) (A/(B + C)) preferably ranges from 2/8 to 8/2. To further ensure long-term adhesion to the oral mucosa, the weight ratio B/C more preferably ranges from 4/6 to 6/4.

Thus, the working time of the preparation in the oral cavity, which partly depends on the duration of adhesion, can be appropriately controlled by varying the ratio of vinyl acetate homopolymer (A), acrylic acid polymer (B), and cellulose derivative (C).

If desired, the drug preparation of the present invention may further contain a salt or a base. Since the drug preparation comprising only the above-described components assumes acidicity attributed to the acrylic acid polymer, it sometimes give a slight irritation to excitable parts, such as an injured part. Where such an irritation due to acidicity gives rise to troubles, incorporation of a salt or base having a neutralizing effect substantially removes the irritation to the injured part.

Examples of suitable salts and bases are salts of metals and weak acids, e.g., a salt of an alkali metal (e.g., sodium and potassium) and a carboxylic acid (e.g., acetic acid, lactic acid, and citric acid); metal hydroxides, e.g., sodium hydroxide and potassium hydroxide; amines, e.g., triethanolamine and diisopropanol amine; and mixtures thereof. A salt of an alkali metal (e.g., sodium and potassium) and a carboxylic acid (e.g., acetic acid, lactic' acid, and citric acid) is preferably used.

The amount of the salt or base to be incorporated is maximum 0.2 equivalent based on the acrylic acid polymer. For example, a monovalent metal salt is preferably used in an amount of from 0.03 to 0.2 equivalent based on the acrylic acid polymer. Amounts less than 0.03 equivalent produce insufficient effects to reduce the irritation of an injured part. If the amount exceeds 0.2 equivalent, water resistance of the adhesive film is reduced, failing to attain sufficient adhesion to the oral mucosa.

The drug preparation applicable to the oral mucosa according to the present invention can be obtained as follows. A vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative are dissolved in a solvent commonly compatible to them, and a systemic drug is added to the solution to form a film-forming composition. The systemic drug in the composition may be either in a dissolved state or in a dispersed state so that the mode of addition is arbitrarily chosen. The film-forming composition is cast on a releasable liner and dried to form a film.

Examples of the solvent commonly compatible to the film-forming components include an alcohol and a water-alcohol mixed solvent. Taking the solubility of the cellulose derivative into consideration, lower alcohols, e.g., methanol and ethanol are exemplified as the alcohol. The water content in the mixed solvent is preferably not more than 30% by weight. If it exceeds 30% by weight, the vinyl acetate homopolymer tends to be hardly dissolved.

Examples of the releasable liner on which the film-forming composition is cast include a release-treated polyethylene laminated paper, a polyethylene film, and a silicon-treated polyethylene terephthalate film.

Drying of the cast film is carried out in a high-temperature air bath using a drying oven or a drying tower, and a vacuum drier.

The thickness of the drug preparation of the present invention can be adjusted by controlling the amount of the composition cast and is preferably in the range of from 5 to 500 μm. From the standpoint of film strength and feeling on use, a thickness of from 10 to 100 μm is more preferred.

The drug preparation applicable to the oral mucosa according to the present invention basically comprises a homogeneous and soft adhesive film which is obtained from a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative as described above. If desired, a water-insoluble support may be provided on the adhesive film to endew the preparation with improved shape retention on water absorption.

Examples of the water-insoluble support includes a film of a synthetic resin, e.g., polyethylene, a vinyl acetate homopolymer, an ethylene-vinyl acetate copolymer, polyvinyl chloride, and polyurethane; a metal foil, e.g., an aluminum foil and a tin foil; and a laminate film comprising cloth or paper and a synthetic resin film. From the viewpoint of safety and feeling on use, it is preferable to use a film of a synthetic resin, e.g., polyethylene, a vinyl acetate homopolymer, and an ethylene-vinyl acetate copolymer as a support. In order to assure ease in handling and to avoid to give an adverse feeling on use, the water-insoluble support preferably has a thickness of from 10 to 100 μm.

The above-described drug preparation of a laminate type can be prepared by, for example, hot pressing the adhesive film and the water-insoluble support film. Alternatively, the laminate type drug preparation can be obtained by casting the film-forming composition on the water-insoluble support followed by drying.

The thus obtained drug preparation according to the present invention, when applied to the wet oral mucosa, absorbs water and is swollen with the water to exhibit excellent adhesion and shape retention for an extended time without causing an adverse feeling, thereby liberating a systemic drug present in the preparation for a prolonged time while protecting the site. During the application, the drug can be prevented from running off due to saliva, etc., and the administration of the drug can be maintained in a stable manner.

The drug preparation of the present invention contains a systemic drug and administers it through the oral mucosa. Some drugs, when orally administered, are difficult in manifestation of efficacy commensurate with dosages because they undergo primary metabolism in the liver. Moreover, some drugs produce undesired side effects to organs, such as stomach. In order to eliminate these disadvantages associated with oral administration of drugs, preparations applicable to the skin which deliver the active ingredient by cutaneous absorption have recently called attention. However, the skin essentially functions to prevent entrance of a foreign substance into the body and does not easily absorb drugs. This is the reason why studies have been directed to the administration route through the oral mucosa which is considered to have a higher absorption of a drug than the skin. By the route through the oral mucosa, the drug preparation according to the present invention makes it possible to effectively deliver a systemic drug present in the preparation into the body.

The systemic drug which can be incorporated into the drug preparation of the invention may be either solid or liquid at room temperature, and any systemic drug which can be dissolved or dispersed in the soft adhesive film can be employed. The method for dissolving or dispersing the systemic drug in the soft adhesive film is not particularly

limited. For example, the vinyl acetate homopolymer, the acrylic acid polyer and the cellulose derivative are dissolved in a solvent which is compatible With these components, and the systemic drug is separately dissolved or dispersed in the same solvent. The resulting solutions (or solution and dispersion) are mixed with each other to form a film-forming composition, and the film-forming composition is then cast on a releasable liner followed by drying so as to form the preparation.

Examples of the systemic drugs include general anesthetic agents, hypnotics, sedatives, antiepileptics, analeptics, awakening agents, anti-dizziness agents, psychoneurotropic agents, neuromuscular blocking agents, autonomic neutrotropic agents, antispasmodics, anti-Perkinson's disease, antihistaminics, stimulation therapeutics, antiallergic agents, cardiotonics, antiarrhythmics, diuretics, hypotensives, vasopressors, coronary vasopressors, peripheral vasopressors, anti-arteriosclerotic agents, agents for other circulatory organs, respiration accelerating agents, antitussive expectorants, treating agents of peptic ulcers, pituitary hormone, thyroid hormone, parathormone, androkinin, female sex hormone (i.e., vesicular ovarian follicle hormone and corpus luteum hormone), other hormones, oxytocics, agents for the urogenital system, oxygen preparations, anti-diabetic agents, other metabolic drugs, anti-tumor agents, antibiotics, chemotherapeutics, and narcotics.

The amount of the systemic drug to be incorporated into the drug preparation depends on the kind of the drug and is usually selected from 0.001 to 40% by weight, preferably from 0.002 to 20% by weight, based on the adhesive film in view of the pharmacological effects and adhesion to the oral mucosa.

The drug preparation applicable to the oral mucosa according to the present invention is less causative of an adverse feeling on use, excellent in shape retention on water absorption, and adhesive to the oral mucosa for an extended period of time. Accordingly, the present invention makes it possible to maintain a stable administration of a systemic drug.

As described above, the drug preparation applicable to the oral mucosa of the present invention which comprises a soft adhesive film prepared from a homogeneous mixture of a vinyl acetate homopolymer, an acrylic acid polymer, and a specific cellulose derivative is soft, less causative of an adverse feeling in the oral cavity on use and excellent in shape retention on water absorption. Further, since the drug preparation can be adhered to the oral mucosa for a long period of time, a systemic drug present in the preparation can be stably administered for a long time. Furthermore, because of the homogeneity and softness of the film base, the drug preparation can be deformed in perfect accordance with the shape of the oral mucosa simply by lightly pressing and adhered close to the mucosa.

The present invention is now illustrated in greater detail by way of the following examples. In these examples, all parts, percents and ratios are by weight unless otherwise specified.

Prior to conducting the examples, an agar gel as a substitution for the oral mucosa was prepared as follows.

Preparation of Agar Gel:

Distilled water was added to 2 g of an agar powder (Japanese Pharmacopeia) to make 100 g, and the mixture was boiled to completely dissolve the agar. The solution was poured into a dish and allowed to cool to prepare an agar gel.

EXAMPLE 1

Five parts of a vinyl acetate homopolymer (weight average molecular weight: 129,000), 2 parts of a carboxyvinyl polymer (carboxyl group content: 58-63% by weight) (as the acrylic acid polymer), 3 parts of hydroxypropylmethyl cellulose (degree of substitution: 1.86-1.90) (as the cellulose derivative), 0.2 part of diisopropanolamine (as the base for neutralizing the acrylic acid polymer), and 2 parts of Propranolol Hydrochloride (as the systemic drug) were added to 90 parts of a 2/8 water-methanol mixture as a common solvent to prepare a film-forming composition containing the systemic drug. The composition was cast on a silicon-release paper, dried, and stripped off to obtain a 30 μm thick adhesive film. A 20 μm thick soft alumina foil as a water-insoluble support was hot-pressed on the resulting adhesive film to obtain a drug preparation applicable to the oral mucosa.

EXAMPLE 2

Five parts of a vinyl acetate homopolymer (weight average molecular weight: 129,000), 2 parts of a carboxyvinyl polymer (carboxyl group content: 58-63% by weight) (as the acrylic acid polymer), 3 parts of hydroxypropylmethyl cellulose (degree of substitution: 1.86-1.90) (as the cellulose derivative), and 0.5 parts of Sodium Indometacin (as the systemic drug) were added to 90 parts of a 1/9 water-methanol mixture as a common solvent to prepare a film-forming composition. The composition was cast on a silicon-release paper, dried, and stripped off to obtain a 60 μm thick adhesive film. A 20 μm thick soft vinyl acetate film as a water-insoluble support was hot-pressed on the resulting adhesive film to obtain a preparation applicable to the oral

mucosa.

Evaluation:

Specimens having a size of 1 cm x 2 cm were cut out of each of the drug preparations obtained in Examples 1 and 2 and adhered to the surface of the above-prepared agar gel. After a prescribed period of time, the specimen was peeled off the agar gel and extracted from 50 mℓ of methanol. The drug in the extract was determined by high performance liquid chromatography. The resulting data of Examples 1 and 2 were plotted in Figs. 1 and 2, respectively, with rate of drug release as ordinate and time as abscissa.

It can be seen from Figs. 1 and 2 that the drug preparation according to the present invention keeps adhered to the agar gel, a substitution for the oral mucosa, for a long time so that the active ingredient in the preparation is stably and steadily released with time.

Further, the specimens were adhered to the oral mucosa of panel members to conduct organoleptic tests of the feeling. As a result, the specimens were judged to have little adverse feeling.

Claims

1. A drug preparation applicable to the oral mucosa comprising a soft adhesive film containing a systemic drug, said adhesive film comprising a homogeneous mixture comprising a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative capable of being dissolved in or swollen with water and a lower alcohol, wherein said mixture contains maximum 0,2 equivalent based on said acrylic acid polymer of a salt or base.

2. The drug preparation of claim 1, wherein said cellulose derivative is selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose.

3. The drug preparation of claim 1, wherein said acrylic acid polymer and cellulose derivative are present in a weight ratio of from 1/9 to 9/1.

4. The drug preparation of claim 3, wherein said acrylic acid polymer and cellulose derivative are present in a weight ratio of from 3/7 to 6/4.

5. The drug preparation of claim 1, wherein the weight ratio of said vinyl acetate homopolymer to the sum of said acrylic acid polymer and cellulose derivative is from 2/8 to 8/2.

6. The drug preparation of claim 5, wherein said acrylic acid polymer and cellulose derivative are present in a weight ratio of from 4/6 to 6/4.

7. The drug preparation of claim 1, wherein said adhesive film has a thickness of from 5 to 500 μm.

8. The drug preparation of claim 1, wherein said preparation further comprises a water-insoluble soft film support laminated on said adhesive film.

9. The drug preparation of claim 8, wherein said support has a thickness of from 10 to 100 μm.

10. The drug preparation of claim 8, wherein said support is a polyethylene film, a vinyl acetate homopolymer film or an ethylene-vinyl acetate copolymer film.

Patentansprüche

1. Auf die Mundschleimhaut aufbringbare Arzneimittelzubereitung umfassend einen weichen Klebefilm, der ein systemisches Arzneimittel enthält, wobei der Klebefilm ein homogenes Gemisch, umfassend ein Vinylacetathomopolymer, ein Acrylsäurepolymer und ein Cellulosederivat, das in Wasser und einem niederen Alkohol aufgelöst oder damit gequollen werden kann, umfaßt, worin das Gemisch maximal 0,2 Äquivalente, bezogen auf das Acrylsäurepolymer, eines Salzes oder einer Base enthält.

2. Arzneimittelzubereitung nach Anspruch 1, worin das Cellulosederivat ausgewählt ist aus der Gruppe bestehend aus Methylcellulose, Ethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose und Hydroxypropylmethylcellulose.

3. Arzneimittelzubereitung nach Anspruch 1, worin das Acrylsäurepolymer und das Cellulosederivat in einem Gewichtsverhältnis von 1/9 bis 9/1 vorhanden sind.

4. Arzneimittelzubereitung nach Anspruch 3, worin das Acrylsäurepolymer und das Cellulosederivat in einem Gewichtsverhältnis von 3/7 bis 6/4 vorhanden sind.

5. Arzneimittelzubereitung nach Anspruch 1, worin das Gewichtsverhältnis des Vinylacetathomopolymers zu der Summe des Acrylsäurepolymers und des Cellulosederivats 2/8 bis 8/2 beträgt.

6. Arzneimittelzubereitung nach Anspruch 5, worin das Acrylsäurepolymer und das Cellulosederivat in einem Gewichtsverhältnis von 4/6 bis 6/4 vorhanden sind.

7. Arzneimittelzubereitung nach Anspruch 1, worin der Klebefilm eine Dicke von 5 bis 500 µm hat.

8. Arzneimittelzubereitung nach Anspruch 1, worin die Zubereitung ferner einen wasserunlöslichen weichen Filmträger auf dem Klebefilm laminiert umfaßt.

9. Arzneimittelzubereitung nach Anspruch 8, worin der Träger eine Dicke von 10 bis 100 µm hat.

10. Arzneimittelzubereitung nach Anspruch 8, worin der Träger ein Polyethylenfilm, ein Vinylacetathomopolymerfilm oder ein Ethylen-Vinylacetat-Copolymerfilm ist.

Revendications

1. Préparation pharmaceutique applicable sur la muqueuse buccale, comprenant un film adhésif souple contenant un médicament systémique, ledit film adhésif comprenant un mélange homogène qui comprend un homopolymère d'acétate de vinyle, un polymère d'acide acrylique et un dérivé de cellulose capable de se dissoudre ou de gonfler dans l'eau et un alcool inférieur, ledit mélange contenant au maximum 0,2 équivalent, par rapport audit polymère d'acide acrylique, d'un sel ou d'une base.

2. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit dérivé de cellulose est choisi dans le groupe constitué par la méthylcellulose, l'éthylcellulose, l'hydroxyéthylcellulose, l'hydroxypropylcellulose et l'hydroxypropylméthylcellulose.

3. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit polymère d'acide acrylique et ledit dérivé de cellulose sont présents en un rapport en masse compris entre 1/9 et 9/1.

4. Préparation pharmaceutique selon la revendication 3, dans laquelle ledit polymère d'acide acrylique et ledit dérivé de cellulose sont présents en un rapport en masse compris entre 3/7 et 6/4.

5. Préparation pharmaceutique selon la revendication 1, dans laquelle le rapport en masse dudit homopolymère d'acétate de vinyle à la somme dudit polymère d'acide acrylique et dudit dérivé de cellulose est compris entre 2/8 et 8/2.

6. Préparation pharmaceutique selon la revendication 5, dans laquelle ledit polymère d'acide acrylique et ledit dérivé de cellulose sont présents en un rapport en masse compris entre 4/6 et 6/4.

7. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit film adhésif a une épaisseur de 5 à 500 µm.

8. Préparation pharmaceutique selon la revendication 1, dans laquelle ladite préparation comprend en outre un support formé d'un film souple insoluble dans l'eau laminé sur ledit film adhésif.

9. Préparation pharmaceutique selon la revendication 8, dans laquelle ledit support a une épaisseur de 10 à 100 µm.

10. Préparation pharmaceutique selon la revendication 8, dans laquelle ledit support est un film de polyéthylène, un film d'un homopolymère d'acétate de vinyle ou un film de copolymère éthylène-acétate de vinyle.

Figure 1

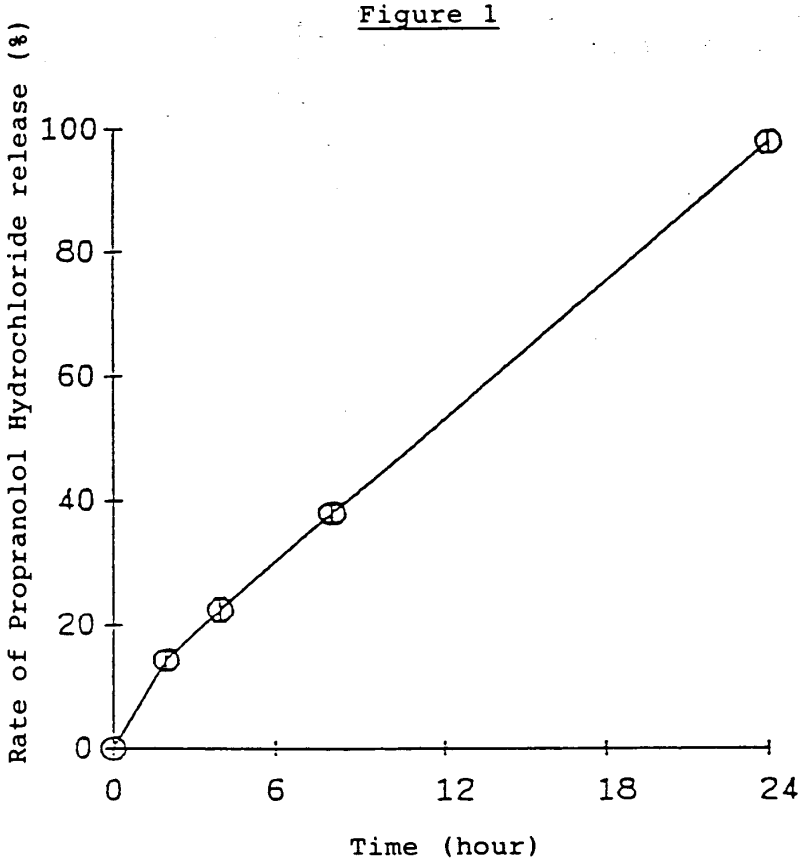
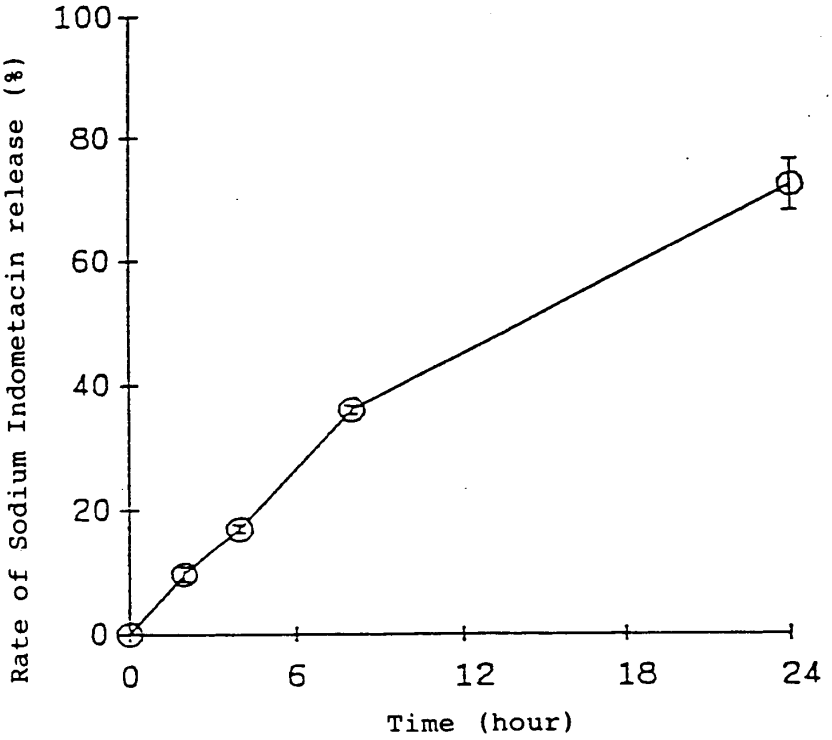


Figure 2



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Veröffentlichungsnummer : **0 452 446 B1**

(12) # EUROPÄISCHE PATENTSCHRIFT

(45) Veröffentlichungstag der Patentschrift : **29.12.93 Patentblatt 93/52**

(51) Int. Cl.[5] : **A61K 7/16**

(21) Anmeldenummer : **90915758.8**

(22) Anmeldetag : **15.10.90**

(86) Internationale Anmeldenummer : **PCT/EP90/01936**

(87) Internationale Veröffentlichungsnummer : **WO 91/05540 02.05.91 Gazette 91/10**

(54) **MUND- UND ZAHNPFLEGEMITTEL.**

(30) Priorität : **14.10.89 DE 3934416**

(43) Veröffentlichungstag der Anmeldung : **23.10.91 Patentblatt 91/43**

(45) Bekanntmachung des Hinweises auf die Patenterteilung : **29.12.93 Patentblatt 93/52**

(84) Benannte Vertragsstaaten : **AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

(56) Entgegenhaltungen :
EP-A- 0 219 762
EP-A- 0 259 749
GB-A- 1 476 057
GB-A- 2 163 348
GB-A- 2 186 190

(73) Patentinhaber : **Desitin Arzneimittel GmbH**
Weg beim Jäger 214
D-22335 Hamburg (DE)

(72) Erfinder : **SCHMIDT, Wolfgang**
Reembroden 44
D-2000 Hamburg 63 (DE)

(74) Vertreter : **UEXKÜLL & STOLBERG**
Patentanwälte
Beselerstrasse 4
D-22607 Hamburg (DE)

EP 0 452 446 B1

Beschreibung

Zahnpflegemittel werden seit vielen Jahren als Pasten, sogenannte Zahnpasten hergestellt. Dabei ist der wesentliche Ausgangsstoff eine Schlämmkreide, die mit Wasser, Glycerin, waschaktiven Stoffen und Verdickungsmitteln zu einer Paste verarbeitet und in Tuben oder Spendern abgefüllt wird. Die Zahnpasta hat den Markt erobert, während andere Zahnpflegemittel wie Tropfen, Zahnseifen und - pulver oder Granulate kaum noch eine Rolle spielen. Mit den Mitteln soll der bakterielle Zahnbelag entfernt, Kariesprophylaxe betrieben sowie die Reinigung der Zähne schonend und durch die Bürstenbehandlung wesentlich unterstützt durchgeführt und der Mundraum gründlich gereinigt und angenehm erfrischt werden.

In neuerer Zeit hat sich das Bild der Zahnpasten nicht wesentlich verändert, obwohl die Rezepturen in vielerlei Hinsicht abgewandelt wurden. Die Verwendung einer recht groben Kreideform zum mechanischen Reinigen der Zähne wich mehr und mehr modernen, feineren Poliermitteln auf Basis von Aluminiumoxid oder Siliciumdioxid (Kieselgele). Neben Tensiden finden strukturbildende Komponenten und ausgefeilte Geschmackskorrigentien Verwendung. Oft werden Wirkstoffe wie insbesondere verschiedene Fluorderivate oder Mineralsalze zugefügt. Das Volumen konnte teilweise reduziert werden; sicherlich hat die Einführung und allgemeine Verwendung elektrischer Zahnbürsten hierbei einen starken Einfluß gehabt.

Die Handhabung von Zahnpasten ist jedoch mit einer Reihe von Nachteilen verbunden. Weil die Dosierung aus einfachen Tuben Schwierigkeiten bereitet, hat man in neuerer Zeit Zahnpastaspender entwickelt, welche jeweils eine vorbestimmte Menge Zahnpasta abgeben. Diese Spender sind jedoch verhältnismäßig groß und daher keinesfalls zur Mitnahme auf Reisen geeignet. Tuben sind druckempfindlich und daher auf Reisen ebenfalls nicht ideal. Sowohl in Spendern als auch in Tuben kann Zahnpasta austrocknen, so daß die angebrauchten Behälter dann weggeworfen werden müssen. Ferner lassen sich sowohl Tuben als auch Spender nicht vollständig entleeren. Nach Verbrauch bleiben die aus Metall oder Plastik hergestellten Behälter zurück und verursachen Umweltprobleme.

Aus der GB-A-21 63 348 sind Zahnreinigungstabletten bekannt, welche durch Zerbeißen und längeres Kauen im Munde eine pastenartige Konsistenz annehmen und dann zur Zahnreinigung dienen können. Eine Anwendung in der üblichen Weise durch Aufbringung auf eine Zahnbürste und anschließendes Einführen in den Mund ist nicht möglich. Verbrauchern mit schadhaften Zähnen oder Zahnersatz ist ein Zerbeißen spröder, harter Tabletten nicht möglich. Ferner können Kautabletten dieser Art auch nicht zur Reinigung künstlicher Zähne bzw. Gebisse verwendet werden.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine neue Verabreichungs- und Dosierungsform für Mund- und Zahnpflegemittel zu entwickeln, welche die vorstehend genannten Nachteile nicht aufweist, sich jedoch ähnlich wie Zahnpasta mit Hilfe einer Zahnbürste anwenden läßt.

Insbesondere soll eine genaue Dosierung für eine Zahnreinigung ermöglicht und sichergestellt werden, daß das Mittel vollständig aufgebraucht werden kann, ohne daß Reste in der Packung zurückbleiben.

Das erfindungsgemäße Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusätzen ist dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittelmischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildnern bestehen, wobei die gebildete Folie in Dosiseinheiten vorzerteilt ist.

Als Bestandteile des Mund- und Zahnpflegemittels kommen die Komponenten in Frage, welche üblicherweise zur Herstellung von Zahnpasten Verwendung finden, wobei natürliche Rohstoffe besonders bevorzugt sind. Wichtig ist darüber hinaus, daß alle Bestandteile völlig ungiftig und physiologisch unbedenklich sind, was selbstverständlich auch für die verwendeten Folienbildner gilt. Als wesentliche Bestandteile von Zahnpflegemitteln sind zu nennen:

- Schleifmittel wie Kreide (Calciumcarbonat), Calcium- und Natriumphosphate, Aluminiumoxid oder Siliciumdioxid, insbesondere Kieselgele
- Tenside (Schaummittel) wie Natriumlaurylsulfat, Natriumlaurylsulfoacetat, Sarcoside, Monoglyceridsulfate und andere
- Aromastoffe wie Pfefferminzöl, Krauseminzöl, Anisöl, Zimtöl, Nelkenöl, Menthol und ähnliche
- Süßstoffe wie Saccharin, Cyclamat, Aspartam und ähnliche.

Die in Zahnpasten üblicherweise enthaltenen flüssigen Komponenten wie Glycerin, Propylenglykol oder Sorbitsirup müssen den erfindungsgemäßen Mitteln in Folienform nicht in den üblichen Mengen zugesetzt werden, da hier die für Tuben oder Spender erforderliche Plastizität keine Rolle spielt. Weitere übliche Zusätze wie Fluorverbindungen, Mittel gegen Zahnsteinbildung, antibakterielle Wirkstoffe und ähnliche, wie sie in Mund- und Zahnpflegemitteln üblicherweise Verwendung finden, können auch erfindungsgemäß eingesetzt werden.

Als wasserlösliche bzw. -quellbare Folienbildner eignen sich vor allem Stärken, Gelatinen, Glycerin und/oder Sorbit sowie ferner natürliche oder synthetische Harze und Gumme. Folgende Rahmenrezeptur hat sich

bewährt:

Gelatine	8 - 10 g
Stärke	3 - 8 g
Glycerin	1 - 2 g
Wasser	30 - 50 g.

In dieser Grundmasse werden die Bestandteile des Mund- und Zahnpflegemittels gelöst bzw. dispergiert, um eine gleichmäßige Verteilung der Stoffe zu erreichen. Die so erhaltene Mischung kann erfindungsgemäß in verschiedener Weise zu einem folienförmigen Mund- und Zahnpflegemittel verarbeitet werden:

a) Es ist einmal möglich, die Masse direkt zu einer Folie zu verarbeiten, welche im allgemeinen eine Dicke zwischen 0,1 und etwa 3 mm aufweist. Durch Sollbruchstellen mittels Stanzung oder Perforierung kann diese Folie in Dosiseinheiten vorzerteilt werden, wobei die Streifenbreite und -länge vorzugsweise etwa der Zahnbürstengröße, d.h. der von den freien Borstenenden gebildeten Fläche des Borstenblocks oder der Längsquerschnittfläche des Borstenblocks in der Borstenebene entsprechen sollte.

b) Alternativ kann die Masse auf eine Trägerfolie aufgebracht werden, deren Zusammensetzung derjenigen des Bindemittels der Masse entspricht, wie dies in der EP-A-219,762 im einzelnen offenbart ist. Auch die auf diese Weise erhaltenen Folien können wie oben angegeben vorzerteilt werden.

c) Es ist ferner möglich, die Masse auf eine Releasefolie oder ein Releasepapier aufzubringen, wie dies aus der EP-A-259 749 bekannt ist. In diesem Fall wird die Beschichtung in einzelne Abschnitte der oben angegebenen Größe vorzerteilt, welche sich ähnlich wie Haftetiketten von der Trägerfolie vor Gebrauch abziehen lassen.

In allen Fällen erhält man eine Darreichungs- und Dosierungsform, deren Anwendung besonders leicht ist, da die jeweils zu verwendende Menge gleichmäßig vorgegeben ist. Eine Dosis wird in Form eines Folienabschnittes abgetrennt bzw. abgezogen und auf die angefeuchtete Zahnbürste bzw. zwischen die Borsten gelegt, wo sie durch die Feuchtigkeitsberührung haftet und anquillt. Durch das Einführen in die Mundhöhle und in Verbindung mit dem Speichel und der intensiven Zahnbürstenbewegung wird der Streifen an- und aufgelöst, so daß die Inhaltsstoffe zur vollen Wirkung gelangen. Nach der Anwendung und der anschließenden Mundspülung mit Wasser verbleiben keinerlei Rückstände im Mund.

Gewünschtenfalls können die Folien in unterschiedlicher Weise bedruckt, geprägt oder gestanzt werden, wobei beispielsweise für Kinder auch bildliche Darstellungen möglich sind. Es entfällt das Öffnen und Schließen von Tubenverschlüssen, es wird keine Zahnpasta vergeudet und die erfindungsgemäße Darreichungsform läßt sich auch besondes gut auf Reisen einsetzen, da sie leicht ist, ein Auslaufen nicht befürchtet werden muß und sie äußerst wenig Platz beansprucht. Die Verpackung ist umweltfreundlich in Pappschachteln ohne Verwendung von Metallen oder Kunststoff möglich.

Die Mittel der Erfindung eignen sich nicht nur zur Zahnpflege im Mund, sondern bei geeigneter Zusammensetzung auch zur Reinigung und Pflege von künstlichen Zähnen und Gebissen. Für diesen letzteren Einsatzzweck ist eine Mehrfachbeschichtung besonders günstig, bei der sich in einer Schicht die reinigenden, desinfizierenden und sauren Komponenten befinden, während sich, ggf. getrennt durch eine ebenfalls wasserlösliche Sperrschicht, in einer zweiten Schicht die CO_2 bzw. O_2 abgebenden Substanzen enthalten sind.

Beispiel

Ein erfindungsgemäßes Zahnpflegemittel hat folgende Zusammensetzung:

Amylogum	57,0 g
Honig	25,0 g
Zitronensäure	2,0 g
Titandioxid	1,0 g
Aroma	1,0 g
Siliciumdioxid	3,0 g
Ca-Hydrog-phos.	10,0 g
Na-Laurylsulfat	1,0 g

Mit der erforderlichen Menge Wasser wird ein Brei hergestellt, der zu einer Folie verarbeitet wird, die ca. 0,5 mm dick ist. Durch Perforation wird die Folie in Abschnitte von 8 x 35 mm unterteilt.

Gegebenenfalls kann die Masse auch als Beschichtung auf ein Releasepapier als Träger aufgebracht und durch Stanzung in Abschnitte der angegebenen Größe vorzerteilt werden.

Patentansprüche

1. Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen, dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittel-Mischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildnern bestehen, und daß diese Mischung zu einer Folie verarbeitet ist, wobei die so gebildete Folie in Dosiseinheiten vorzerteilt ist.

2. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Stärken, Gelatinen, Glycerin und/oder Sorbitol oder natürliche und/oder synthetische Harze und Gumme enthält.

3. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Amylogum enthält.

4. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß es als Folienbildner eine Mischung aus 8 bis 10 Gewichtsteilen Gelatine, 4 bis 8 Gewichtsteilen Stärke und 1 bis 2 Gewichtsteilen Glycerin enthält.

5. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß es aus einer Trägerfolie aus dem Bindemittel oder der Bindemittel-Mischung besteht, auf welche eine Schicht aufgebracht ist, welche die Bestandteile des Pflegemittels zusammen mit Bindemittel oder der Bindemittel-Mischung enthält, wobei das Bindemittel oder die Bindemittel-Mischung in der Trägerfolie und in der Beschichtung im wesentlichen die gleiche qualitative Zusammensetzung aufweisen.

6. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß eine Beschichtung aus den Bestandteilen des Pflegemittels und dem Bindemittel oder der Bindemittel-Mischung auf eine Trägerfolie in Form eines Trennpapiers, eines Trennfilms oder einer Trennfolie aufgebracht ist, wobei die Beschichtung nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

Claims

1. Oral and dental hygiene preparation based on surfactants, polishing agents, flavours, and other conventional additives, characterised in that the active ingredients and additives are incorporated in a binder or a binder mixture comprising water-soluble or water-swellable, physiologically harmless film formers, and in that said mixture is processed to a film, the film thus formed being predivided into dose units.

2. Oral and dental hygiene preparation according to claim 1, characterised in that it contains as film formers starches, gelatins, glycerol and/or sorbitol or natural and/or synthetic resins and gums.

3. Oral and dental hygiene preparation according to claim 1, characterised in that it contains starch gum as film former.

4. Oral and dental hygiene preparation according to claims 1 to 3, characterised in that it contains as film former a mixture of 8 to 10 parts by weight of gelatin, 4 to 8 parts by weight of starch and 1 to 2 parts by weight of glycerol.

5. Oral and dental hygiene preparation according to claims 1 to 4, characterised in that it comprises a carrier film made of the binder or the binder mixture, onto which is deposited a layer which contains the constituents of the hygiene preparation together with binder or the binder mixture, whereby the binder or the binder mixture in the carrier film and in the coating have essentially the same qualitative composition.

6. Oral and dental hygiene preparation according to claims 1 to 4, characterised in that a coating consisting of the constituents of the hygiene preparation and the binder or the binder mixture is deposited on a carrier film in the form of a release paper, a release film or a release sheet, whereby the coating can be removed in doses from the carrier material after predivision into dose units.

Revendications

1. Préparation d'hygiène bucco-dentaire à base d'agents tensio-actifs, d'agents de polissage, de substances aromatiques ainsi que d'autres ingrédients habituels, caractérisée en ce que les principes actifs et les ingrédients additionnels sont incorporés à un agent liant ou à un mélange d'agents liants, qui sont constitués d'agents filmogènes solubles ou gonflables dans l'eau, physiologiquement sans danger, le film formé étant prédivisé en unités de dosage.

2. Préparation d'hygiène bucco-dentaire selon la revendication 1, caractérisée en ce qu'elle contient à titre d'agents filmogènes des amidons, des gélatines, de la glycérine et/ou du sorbitol ou des résines et des gommes naturelles et/ou synthétiques.

3. Préparation d'hygiène bucco-dentaire selon la revendication 1, caractérisée en ce qu'elle contient à titre d'agent filmogène de l'amylogum.

4. Préparation d'hygiène bucco-dentaire selon les revendications 1 à 3, caractérisée en ce qu'elle contient à titre d'agent filmogène un mélange de 8 à 10 parties en poids de gélatine, de 4 à 8 parties en poids d'amidon et de 1 à 2 parties en poids de glycérine.

5. Préparation d'hygiène bucco-dentaire selon les revendications 1 à 4, caractérisée en ce qu'elle est constituée d'une feuille de support formée de l'agent liant ou du mélange d'agents liants, feuille de support sur laquelle est appliquée une couche qui contient les composants de la préparation d'hygiène conjointement avec l'agent liant ou le mélange d'agents liants, l'agent liant ou le mélange d'agents liants de la feuille de support et du revêtement ayant essentiellement la même composition qualitative.

6. Préparation d'hygiène bucco-dentaire selon les revendications 1 à 4, caractérisée en ce que l'on applique un revêtement formé des composants de la préparation d'hygiène et de l'agent liant ou du mélange d'agents liants sur une feuille de support sous la forme d'un papier de séparation, d'un film de séparation ou d'une feuille de séparation, le revêtement pouvant être séparé de la matière de support par doses individuelles après prédivision en unités de dosage.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 514 691 A2**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **92107249.2**

(22) Date of filing: **29.04.92**

(51) Int. Cl.[5]: **C08J 5/18**, A61L 15/32, A61L 27/00, //C08L89:06

(30) Priority: **23.05.91 IT MI911423**

(43) Date of publication of application: **25.11.92 Bulletin 92/48**

(84) Designated Contracting States: **AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE**

(71) Applicant: **EURORESEARCH S.r.L.**
Via Mascheroni 23
I-20145 Milano(IT)

(72) Inventor: **Furlan, Diego**
Strada 8, N.N. 37, San Felice
I-20090 Segrate, (Milan)(IT)
Inventor: **Bonfanti, Giovanni**
Parco Diana
I-04023 Formia Santa Croce, (Latina)(IT)
Inventor: **Scappaticci, Giuseppe**
Via Pinchera, 1
I-03043 Cassino, (Frosinone)(IT)

(74) Representative: **Gervasi, Gemma, Dr. et al**
Studio Brevetti e Marchi NOTARBARTOLO & GERVASI 33, Viale Bianca Maria
I-20122 Milano(IT)

(54) Non-porous collagen sheet for therapeutic use, and the method and apparatus for preparing it.

(57) Type I collagen gel with an H_2O content not exceeding 20% by weight, in the form of a sheet of thickness between 0.02 and 2 mm, of compact transparent structure, with a capacity for absorbing aqueous biological liquids limited to a maximum of 15 times its weight, being free from native collagen degradation products, and suitable for the therapeutic treatment of wounds and burns.

EP 0 514 691 A2

Collagen is a scleroprotein widespread in nature. It represents about one third of the total proteins of the human body.

Medical practice has recently seen the introduction of the use of collagen as a stimulating agent in the cicatrization process involving an interaction effect with various growth factors, because of its capturing action on fibronectin, a glycoprotein which promotes cell attachment and the migration and replication of the resultant cells (see "Il collageno nella cicatrizzazione" by B. Palmieri, publ. Artestampa, January 1990, pp. 40-42) and other actions which are still not totally clear. The known collagen product, using a particular non-denaturing process, is prepared in stable form by a process of extraction from animal organs rich in this scleroprotein, purification and subsequent lyophilization.

The final product is in the form of mats of greater or lesser thickness, characterised by high absorbent power (exudates and liquids in general) because of its structure in the form of fibres which are spaced apart and branched in such a manner as to make a large specific surface available for absorption (up to 50 times its weight). The hydrophilic nature of collagen also greatly favours this absorbent power.

In addition to the aforesaid function, the role of collagen in cicatrization is characterised by collagen/platelet interaction and the formation of a bond between the collagen, the fibronectin and the growth factors, molecules which are known to be implicated in regulating the cicatrization process (see pages 45-46 of the aforesaid text).

There are however cases in which the absorbent formation of the collagen sponge and its hydrophilic nature lead to an excessive loss of physiological liquids. It is well known that an evaporation process normally occurs through the undamaged skin, and this increases considerably in the case of skin lesion, resulting in dehydration of the underlying layers. The phenomenon is accentuated for example in burn cases, when large skin portions are damaged traumatically. In this case the absorbent effect of lyophilized collagen further increases the process of evaporation, with consequent damage to the underlying structure.

The present invention provides a product which while maintaining the rapid cicatrization characteristics of collagen, at the same time prevents excessive evaporation, allows constant inspection of the bed of the wound without having to be removed (transparency), is simple and practical to use, adheres satisfactorily to the injured surface, does not require frequent replacement, can transpire to allow oxygenation of the bed of the wound while preventing its contamination by bacteria, is absorbable but not soluble in the biological liquids with which it comes into contact, unless by specific enzymatic action, and is structurally homogeneous.

Another important characteristic of the collagen according to the invention is that of being suitable as interposition material for preventing accretions in the internal surgery operations.

To obtain a product with these characteristics, type I collagen was used as defined in Table 1 on page 3 of the aforestated text, this having the characteristic of being insoluble in the various types of biological liquids. Type I collagen present in the skin represents about 80% of the total located in the deep dermis, 90-95% in the tendons and 100% in the bones. Type I collagen is therefore the most biologically similar to that present in the human skin.

Because of its insolubility, in order to obtain a product of homogeneous structure, use was made of the known method of dispersing fibrous collagen in a dilute acetic acid solution of about pH 2.5 and maintaining agitation until a good dispersion of the collagen fibres in the liquid is obtained. At this pH value the fibres swell to form a gel. The gel obtained, still comprising fibre fractions which have not completely gelled and possibly corpuscles of extraneous substances, is further diluted with an acetic acid solution of pH 2.5-3.5 until a sufficiently fluid mass is obtained, which is then filtered.

The filtering, which is done under vacuum, uses a special filter, indicative (but not limitative) characteristics of which are given hereinafter, and allows practically total elimination of the inevitable air bubbles which form during gelling and are difficult to eliminate given the viscosity of collagen gel.

By the effect of the vacuum, which has to be of the order of 30 mmHg residual pressure, these bubbles increase their volume, the passage through the mesh then breaks down and eliminates them. It has been found experimentally that the best filtration conditions to achieve the described phenomenon are a gel temperature of 10-30 °C, preferably 25-28 °C, and a residual vacuum of 20-60 mmHg, preferably about 30 mmHg.

These data are indicative and have been found experimentally to be the most effective, although not representing a limitation on the operating conditions of this process.

The filtered gel is collected in a closed vessel maintained under vacuum and constructed in such a manner that the filtered gel runs along vessel partition walls located below the filter mesh and structured to produce a continuous liquid film which does not allow further air absorption after filtration, following inclusion of air bubbles.

The filtered gel is further maintained under vacuum at 20-25 mmHg for a further hour to allow total elimination of any air bubbles which may still

be present in the gel.

FILTER APPARATUS

The filter required for filtering the collagen gel, which besides eliminating the solid particles, which are retained on the mesh, also eliminates the air bubbles contained in it, consists of an upper cylindrical stainless steel shell provided with a scraping stirrer to keep the collagen gel mixed and to remove solid particles from the mesh so that they do not clog it. The bottom of the cylindrical shell houses a stainless steel mesh with a mesh size of less than 0.1 mm (Taurail meshes have been found to be particularly effective).

The lower part (below the mesh) consists of a cylindrical shell in which vacuum can be generated by a suitable pump. The air bubbles contained in the gel which filters through the mesh increase considerably in volume because of the vacuum.

At about 3 mm below the filter mesh there is a device consisting of a series of stainless steel plates which are vertically or raking placed and parallel between them. The filtered gel descends along these plates in the form of a continuous liquid film and runs by gravity towards the bottom of the vessel.

Those air bubbles which do not break down by the effect of the reduced pressure remain mainly in the upper part of the device whereas the gel, now free or almost free of air, runs to the bottom of the vessel. Any very small bubbles still present in the filtered gel decrease considerably in volume when returned to atmospheric pressure, so that they become practically absent.

In this respect, during filtration because of the difference between the pressure of the gel environment before filtration and the residual pressure below the mesh (about 30 mmHg), the bubble volume increases more than 25 times. Likewise, on passing from vacuum to the environmental pressure the bubble volume decreases 25 times. Hence the air bubbles of diameter less than 0.100 mm (advisable mesh passage size) have a diameter of less than 0.034 mm when returned to atmospheric pressure, ie are practically invisible. During drying, these residual bubbles are eliminated without leaving appreciable craters in the structure of the obtained sheet.

This means that extremely uniform thicknesses can be obtained over the entire sheet surface, so avoiding any porosity which could represent a point of preferential attack by enzymatic action, which would annul the protective effect against invasion by micro-organisms.

DRYING

The filtered gel obtained as described, free from extraneous particles and air bubbles and perfectly clear and transparent, can then be used for preparing films of desired thickness and diameter.

For this, after analysis to exactly determine the concentration of the filtered gel, exactly measured quantities for obtaining films with the desired collagen thickness must be metered into suitable containers. This metering is generally effected by a suitable peristaltic pump which prevents incorporating air into the gel while at the same time preventing heating or friction which could damage the structure of the collagen protein. The containers are of tray shape and are formed of antiadherent material.

The described trays loaded with the gel in a controlled environment (relative humidity 60-80% temperature 20-22 °C, environment class 10,000 or less) are placed in a suitable controlled drying oven where they are left to stand for at least two hours to obtain perfect gel thickness uniformity. The oven is purged with a nitrogen stream for about 30 minutes to totally eliminate air and remove oxygen, in order to ensure constant operating conditions and prevent possible oxidation.

This operation has also been shown to practically totally block the growth of micro-organism colonies, which sometimes occurs if the procedure is carried out with air present in the environment.

Drying is effected in a nitrogen stream under closed cycle.

The drying, being the critical stage for obtaining films with the desired characteristics, is conducted under particular conditions in an appropriate oven shown schematically in Figure 1.

In this, the reference numeral 1 indicates the drying trays resting on perforated side walls, V indicates the fan for circulating nitrogen through the apparatus, N_2 indicates the nitrogen feed valve, GF indicates the refrigeration unit with coil, S represents a parallel plate device for separating condensate droplets, T_1 indicates a first thermometer, SC indicates the condensed water discharge, R indicates the heating device, T_2 indicates a second thermometer, I_1 indicates a first hygrometer, MO indicates an oxygen meter (analyzer), Sg indicates the gas discharge, Tr indicates an overpressure trap and I_2 indicates a second hygrometer.

The oven is arranged in this manner to satisfy the following requirements:

1) the facility for eliminating air by purging with nitrogen to a residual oxygen content of less than 2%;

2) the facility for varying the nitrogen cooling and heating temperature to a maximum of 30 °C, to control the relative humidity in the drying chamber and the water evaporation rate;

3) the facility for regulating the rate of nitrogen

circulation through the chamber so as not to create high flow points and hence maintain a uniform drying rate over the entire surface and prevent the formation of creases which, besides being undesirable from the appearance aspect, are an indication of different collagen concentrations and poor homogeneity of drying (localized drying).

The H_2O content of the product must not be higher than 20% by weight. It is preferable to achieve a higher level of drying (down to 2% or 3% of H_2O), in particular to ensure proper elimination of the acetic acid present in the initial gel. The dried product obtained easily reabsorbs moisture from the environment, while being maintained within the maximum limit of 20%.

EXAMPLE

The conditions found experimentally to be most appropriate for conducting a drying cycle are given below by way of non-limiting example.

1st stage:

Nitrogen purging until the oxygen content is less than 1%, standing for two hours to come to equilibrium, loaded gel level 10 mm, gel collagen concentration 0.5%.

2nd stage:

Starting of nitrogen circulation by fan.
Nitrogen temperature after cooling -5 °C (T_1).
Nitrogen temperature after heating 26-28 °C (T_2).
Time about 12 hours.
Relative humidity entry to drying region (point I_1) 12-14%.
Relative humidity exit of drying region (point I_2) 70-80%.

3rd stage:

Nitrogen temperature after cooling -15 °C (T_1).
Nitrogen temperature after heating 26-28 °C (T_2).
Time about 12 hours.
Relative humidity entry to drying region (point I_1) 6-7%.
Relative humidity exit of drying region (point I_2) 45-50%.

4th stage:

Final drying
Nitrogen temperature after cooling -40 °C (T_1).
Nitrogen temperature after heating 26-28 °C (T_2).
Time about 12 hours.

5th stage:

Product discharge, preparation of a new load. Complete removal of water from the cooling coil and purging the oven by nitrogen circulation at 70-80 °C for two hours, cooling to 20 °C and loading new product.

The nitrogen flow rate through the drier is adjusted on the basis of the required degree of drying.

A semi-transparent film with a thickness of about 200 micron is obtained. The thickness can vary in general between 0.02 and 2 mm.

This represents a non-specific item for the purposes of the therapeutic application as it determines only the product absorption time but not its specific characteristics. The degree of drying can also vary as stated.

The characteristics of the film obtained are:

- maintaining of the "native" structure of collagen fibre (the classical triple spiral structure of collagen has been demonstrated by the electron microscope)
- absence of degradation products such as monomers or dimers of collagen not organized into fibrils, or gelatin, an indication of potential allergenicity
- high protein nitrogen content (exceeding 90%)
- high hydroxyproline content (exceeding 12%)
- low absorbent power (about 10-15 times its weight against 50 times for the lyophilized product of the known art)
- high resistance to enzymatic attack
- good product transparency
- excellent plasticity after immersion in physiological solution.

The product obtained in this manner is sterilized by irradiation with gamma rays and used in the treatment of burns and generally all cases of skin removal or damage.

The result is excellent both in terms of tolerance (no case of allergenicity or hypersensitivity to the medicament has been recorded, the native characteristic of the product remaining unaltered during the process) and in terms of pain attenuation.

The cicatrization time is very rapid and product absorption considerably longer compared with equivalent treatment using lyophilized collagen (sponge) and consequently there is lesser need to replace it. Exudate loss is very low, and much lower than that when using lyophilized collagen.

The transparency of the product means that the progress of the injury can be viewed without the need to remove the collagen sheet (generally a painful procedure).

The product can be presented in the form of sheets of different dimensions (square, rectangular, round, elliptical or others) supported or not supported by adhesives (such as plasters) or by sheets of inert substances such as nylon, polyurethane, polyethylene etc., or associated during the drying process, or subsequently, with pharmacologically active substances.

Claims

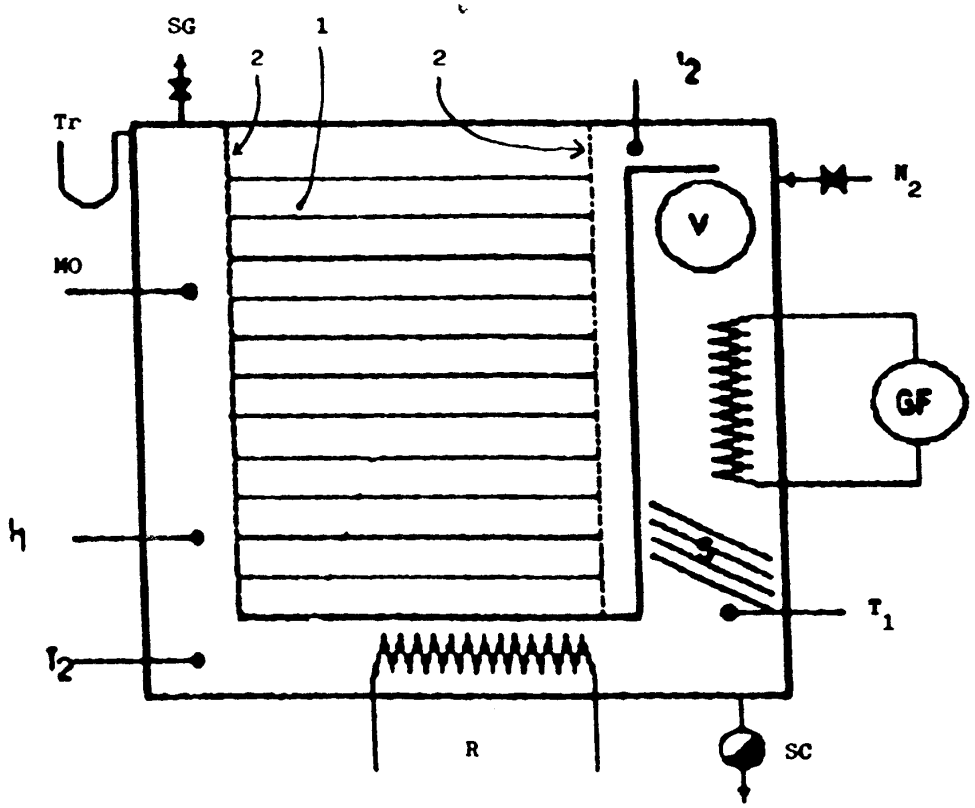
1. Type I collagen gel with an H_2O content not exceeding 20% by weight, in the form of a sheet of thickness between 0.02 and 2 mm, of compact transparent structure, with a capacity for absorbing aqueous biological liquids limited to a maximum of 15 times its weight, being free from native collagen degradation products, and suitable for the therapeutic treatment of wounds and burns.

2. A method for preparing collagen gel sheets claimed in claim 1 from aqueous diluted collagen gel of pH 2.5-3.5, comprising filtering the gel through a filter surface with a passage size of less than 0.1 mm, the filter being under a vacuum of 20-60 mmHg and provided with a device for preventing the incorporation of gas bubbles into the filtrate, then drying the liquid gel contained in trays with a nitrogen stream under controlled temperature and relative humidity conditions.

3. A device suitable for filtering the collagen gel in accordance with claim 2, consisting of a metal mesh with a mesh size of less than 0.1 mm and provided with a pack of parallel plates in the region below the filter mesh, for the purpose of conveying the filtrate as a continuous liquid film.

4. A device suitable for drying the collagen gel in accordance with claim 2, comprising a drying region for the liquid contained in trays, means for circulating a nitrogen stream in closed circuit through the drying region and through the cooling and heating regions, and means for controlling the cooling and heating temperature to obtain a gas stream of controlled relative humidity entering the drying region.

FIG. 1



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 110 546 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
27.06.2001 Bulletin 2001/26

(51) Int Cl.[7]: **A61K 9/70**, A61K 9/00

(21) Application number: **00311610.0**

(22) Date of filing: **22.12.2000**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **23.12.1999 US 172085**
12.01.2000 US 481178

(71) Applicant: **Johnson & Johnson Consumer Companies, Inc.**
Skillman, New Jersey 08558-9418 (US)

(72) Inventors:
- **Lin, Shun Y.**
  Plainsboro, New Jersey 08536 (US)
- **Patel, Kalpana J.**
  West Windsor, New Jersey 08550 (US)
- **Link, Martin**
  Sarasota, Florida 34241 (US)
- **Kang, Maria L.**
  Belle Mead, New Jersey 08502 (US)

(74) Representative: **Fisher, Adrian John**
CARPMAELS & RANSFORD
43 Bloomsbury Square
London WC1A 2RA (GB)

(54) Method of preparing a water soluble film

(57) The present invention provides a method of preparing a water soluble film. The method comprises (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. The film former is a polyacrylic acid, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. The water soluble film of the present invention may be incorporated into vaginal devices, such as tampons and applicators. This method produces a uniform and homogeneous film which is more flexible and drips less than prior water soluble films, especially those incorporated into vaginal dosage forms. As a result, the film is less irritating. Furthermore, unlike most prior art water soluble films, the film may be shaped to provide a larger contact area within a body cavity, such as the vagina, in order to increase drug delivery. The film is also non-messy.

EP 1 110 546 A1

Printed by Jouve, 75001 PARIS (FR)

Description

[0001] This application claims priority from U.S. Serial No. 60/172,085, filed December 23, 1999, which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to a method of preparing a water soluble film for use in dosage unit forms, such as tampons and applicators.

BACKGROUND OF THE INVENTION

[0003] Current vaginal dosage forms, except the sponge and film, are messy to use and readily drip out of the vagina. Furthermore, the sponge requires removal after use and is believed to cause infection. Films often cause irritation due to their rigidity and sharp edges.

[0004] U.S. Patent Nos. 5,393,528 and 5,529,782 disclose a device having a dissolvable element for administration of an agent material in an internal body area. The dissolvable element is a film made of polyvinyl alcohol, polyethylene oxide, and/or a complex carbohydrate material.

SUMMARY OF THE INVENTION

[0005] The present invention provides a method of preparing a water soluble film. The method comprises the steps of (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and a relative humidity of at least about 30%. The film former is a polyacrylic acid, cellulose derivative, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. The water soluble film of the present invention may be incorporated into vaginal devices, such as tampons and applicators. The formulation of the film may be optimized as known in the art to provide controlled release of the pharmaceutically active agent.

[0006] This method produces a uniform and homogeneous film which is more flexible and drips less than prior water soluble films, especially those incorporated into vaginal dosage forms. As a result, the film is less irritating. Furthermore, unlike most prior art water soluble films, the film may be shaped to provide a larger contact area within a body cavity, such as the vagina, in order to increase drug delivery. The film is also non-messy.

[0007] Another embodiment of the present invention is a dosage unit form, such as a tampon or applicator, comprising a water soluble film prepared by the aforementioned method.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The method of the present invention comprises the steps of (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. The inventors have discovered that curing the film under the aforementioned conditions produces a significantly more flexible film which drips less when administered into the vagina and other body cavities than the same film prepared without curing. The film is also non-messy, uniform, and homogeneous.

[0009] The solution may be prepared by mixing the ingredients, if the pharmaceutically active agent is water soluble.

[0010] Water insoluble pharmaceutically active agents may be dispersed, preferably uniformly, in the solvent by any method known in the art. The other ingredients may be added before or after dispersing the pharmaceutically active agent.

[0011] The film former is a polyacrylic acid, cellulose derivative, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. Suitable cellulose derivatives include, but are not limited to, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and any combination of any of the foregoing. The film former is preferably polyvinyl alcohol. More preferably, the film former is a partially hydrogenated polyvinyl alcohol, such as Elvanol™ grade 51-05, 52-22, and 50-42 available from DuPont Co. of Wilmington, DE, and Airvol™ grade 205S and 523S available from Air Products & Chemicals, Inc., of Allentown, PA. The viscosity of the polyvinyl alcohol generally ranges from about 3 to about 1000 cps and preferably ranges from about 3 to about 50 cps. The solution typically comprises from about 5 to about 40% by weight and preferably from about 15 to about 35% by

weight of film former, based upon 100% total weight of solution.

[0012] The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. Preferably, the boiling point of the plasticizer is greater than about 180° C. Suitable plasticizers include, but are not limited to, polyhydroxy compounds, such as propylene glycol, polyethylene glycol, glycerin, and any combination of any of the foregoing. Other suitable plasticizers include, but are not limited to, fatty acid derivatives having a melting point less than about 45 ° C, such as ehydrogenated vegetable oil available as Wecobee™ from Stepan Company of Northfield, IL, and hydrogenated coco-glycerides available as Witepsol H15™ from Hüls America of Somerset, N.J.; and fatty alcohol derivatives having a hydroxy value of greater than about 30. The solution typically comprises from about 0.1 to about 10% by weight and preferably from about 0.5 to about 5% by weight of water soluble plasticizer, based upon 100% total weight of solution.

[0013] The pharmaceutically active agent may be water-insoluble or water soluble. Suitable pharmaceutically active agents include, but are not limited to, imidazole antifungal agents, such as imidazole antifungal agents include, but are not limited to, miconazole, econazole, terconazole, ketoconazole, saperconazole, itraconazole, clotrimazole, tioconazole, and butaconazole; antibacterial agents, such as nystatin, neomycin, polymycin, tetracycline, clindamycin, and metronidazole; antiseptic agents, such as oxyquinoline benzoate and aminacrine; hormones, such as estrogens, testolactone, androgens, progestins, megestrol acetate, medroxyprogesterone acetate, esterified estrogens, conjugated estrogens, estradiol, polyestradiol, ethinyl estradiol, estropipate, diethylstilbestrol diphosphate, polyestradiol phosphate, and leuprolide acetate; anti-inflammatory agents, hydrocortisone, triamcinolone, betamethasone, flucinonide, and halcinonide; anesthetics, such as lidocaine and benzocaine; spermicides, such as nonoxynol-9 and octoxynol-9; and any combination of any of the foregoing. A preferred imidazole antifungal agent is miconazole nitrate. A preferred antibacterial agent is metronidazole. A preferred spermicide is nonoxynol-9.

[0014] Generally, the amount of pharmaceutically active agent in the solution is an amount effective to accomplish the purpose for which it is being used. The amount of pharmaceutically active agent is typically a pharmaceutically effective amount. However, the amount can be less than a pharmaceutically effective amount when the film is used in a dosage unit form, because the dosage unit form may contain a multiplicity of films or may contain a divided pharmaceutically effective amount. The total effective amount can then be determined in cumulative units containing, in total, a pharmaceutically effective amount of pharmaceutically active agent. The total amount of pharmaceutically active agent may be determined by those skilled in the art. Generally, the solution comprises from about 1 to about 30% by weight and preferably from about 5 to about 20% by weight of pharmaceutically active agent, based upon 100% total weight of solution.

[0015] The solvent may be water, ethanol, glycerin, ethylene glycol, amides, amines, or any combination of any of the foregoing. The solvent is preferably water or a mixture of water and ethanol. Preferably, the mixture comprises less than about 30% by weight of ethanol, based upon 100% total weight of mixture. The solution typically comprises from about 20 to about 90% by weight and preferably from about 40 to about 80% by weight of solvent, based upon 100% total weight of solution.

[0016] According to a preferred embodiment of the present invention, the solution comprises about 26.4% by weight of polyvinyl alcohol, about 2.4% by weight of glycerin, about 11.2% by weight of nonoxynol 9, and about 60% by weight of water, based upon 100% total weight of solution.

[0017] The solution may include other adjuvants, such as surfactants, preservatives, viscosity enhancers, colorants, fragrances, flavorants, lubricants, fillers, binders, wetting agents, penetration agents, pH adjusters, disintegrants, excipients, or any combination of any of the foregoing. Suitable surfactants include, but are not limited to, polyethylene glycol ether of cetearyl alcohol, such as ceteareth-20; hydrogenated coco-glycerides; and any combination of any of the foregoing.

[0018] The solution typically has a viscosity of from about 15,000 to about 30,000 cps at room temperature prior to drying. Generally, the water soluble film prepared by the method of the present invention has a thickness of from about 0.03 to about 0.50 mm. Preferably, the thickness of the film is from about 0.05 to about 0.10 mm.

[0019] The drying step is generally performed at a temperature of from about 50 to about 100° C. Preferably, the drying step is performed in two stages. In the first stage, the solution is heated to from about 50 to about 70° C. The solution in the first stage is typically heated for less than about 5 minutes. The solution is then heated to from about 70 to about 100° C during the second stage. The solution in the second stage is typically heated for less than about 25 minutes.

[0020] The curing step is preferably performed immediately after the drying step. Curing is generally performed at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. Preferably, the curing step is performed at a temperature of from about 25 to about 60° C. The curing step is preferably performed at a relative humidity of at least about 50% and more preferably at a relative humidity of from about 60 to about 90%. The solution may be dried and cured with a drying tunnel having multiple zones or chambers, such as a 5, 6, or 7 zone drying tunnel.

[0021] A preferred water soluble film prepared by the method of the present invention comprises about 66% by weight of polyvinyl alcohol, about 6% by weight of glycerin, and about 28% by weight of nonoxynol 9, based upon 100% total

weight of water soluble film.

[0022] The water soluble film may be coated or laminated onto a substrate, such as non-woven fiber or cotton, by pouring or casting the solution onto the substrate and then drying and curing the solution as described above. Casting may be performed by any method known in the art, such as with a weigh boat, stainless steel tray, teflon rod, cone shape rod, and reverse roller.

[0023] The water soluble film alone or coated or laminated on a substrate may be incorporated into a dosage unit form for administration into a body cavity, such as the vagina, rectum, and mouth. The dosage unit form may be a tampon or an applicator. For example, the film coated on a substrate may be utilized as a liner for a tampon. The dosage unit form is preferably flexible. The dosage unit form may be any shape, such as a flat sheet or thimble shape. Preferably, the film is contoured to maximize its contact area with the body cavity for which it is intended to be administered.

[0024] According to one embodiment, the outer wrap of the tampon is comprised of non-woven fiber laminiated with the water soluble film. According to another embodiment, the water soluble film is positioned between the inside material of a tampon, such as cotton, and an outer wrap, such as a non-woven fiber material.

[0025] A dosage unit form of the present invention containing an antifungal agent, such as miconazole, may be administered to treat yeast infections. It is possible to treat a yeast infection in 3 days, instead of the common 5 day period, with a dosage unit form of the present invention, since a film prepared by the present method has very little drip and may have controlled release of the antifungal agent.

[0026] The film may be formulated to be puncture resistant and tear resistant. Also, the film may be formulated to achieve desired release rates of the pharmaceutically active agent as known in the art.

[0027] The following examples are intended to describe the present invention without limitation.

Examples 1-32

[0028] Water soluble films having the formulations of Table 1 were prepared as follows. Water was heated to 50-80° C. The film former, *i.e.,* polyvinyl alcohol, is added to the water with constant mixing. The active ingredient, *i.e.,* nonoxynol-9, was added to the solution with constant mixing. The solution was mixed, deaerated, and cooled to room temperature. The solution was coated onto a substrate in the casting device indicated in Table 1 below. The substrate for Examples 1-8 was polypropylene. The substrate for Examples 9-18 and 32 was stainless steel. The substrate for Examples 19-25 was polyester. The substrate for Examples 26-28 was teflon. The substrate for Example 29 was a polyester liner. The substrate for Example 30 was aclar with foil liner. The substrate for Example 31 was a polyethylene and paper liner.

[0029] The solution was dried in a multi-zone drying tunnel to form a film. In Examples 1-28 and 31, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. In Examples 29 and 30, the solution was first dried at a temperature of about 60-75° C for less than about 8 minutes and then dried at a temperature of about 75-90° C for less than about 15 minutes. In Example 32, the solution was first dried at a temperature of about 60-80° C for less than about 5 minutes and then dried at a temperature of about 70-90° C for less than about 25 minutes.

[0030] After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature. For examples 29 and 32, the film was cured with moisture at a relative humidity of about 60-90% and at a temperature of about 40-60° C.

[0031] The thickness of the film was measured. The results are shown in Table 1 below.

Table 1

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
1	Weigh Boat	33.33	33.33	-	-	33.33% PG	0.3
2	Weigh Boat	33.33	33.33	-	-	33.33% PEG 300	0.3
3	Weigh Boat	33.33	50.00	-	-	16.67% PEG 300	0.45
4	Weigh Boat	33.33	58.33	-	-	8.33% Glycerin	0.3
5	Weigh Boat	33.33	41.67	-	-	25.00% Glycerin	0.1
6	Weigh Boat	33.33	50.00	-	-	16.67% Glycerin	0.1
7	Weigh Boat	33.33	50.00	-	-	16.67% PG	0.2
8	Weigh Boat	33.33	41.67	-	-	25.00% PG	0.1
9	Stainless Steel Tray	33.00	58.67	-	-	8.33% Glycerin	0.07
10	Stainless Steel Tray	33.33	63.33	-	-	3.33% Glycerin	0.05

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
11	Stainless Steel Tray	33.33	58.33	-	-	8.33% PEG 300	-
12	Stainless Steel Tray	33.33	58.67	-	-	8.33% PG	0.06
13	Stainless Steel Tray	27.78	69.44	-	-	2.78% Glycerin	-
14	Stainless Steel Tray	33.33	-	-	58.33	8.33% Glycerin	0.06
15	Stainless Steel Tray	32.79	-	-	49.18	18.03% Glycerin	0.07
16	Stainless Steel Tray	33.33	-	-	41.67	25.00% Glycerin	-
17	Stainless Steel Tray	33.33	-	-	63.33	3.33% Glycerin	0.07

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
18	Stainless Steel Tray	28.33	-	-	68.00	3.67% Glycerin	-
19	Resource I®	33.33	-	58.33	-	8.33% Glycerin	-
20	Resource I®	33.11	-	62.913	-	3.97% Glycerin	-
21	Resource I®	33.33	-	49.50	-	17.16% Glycerin	-
22	Resource I®	33.33	-	-	63.35	3.33% Glycerin	-
23	Resource I®	33.33	50.00	-	-	16.33% PEG 300	-
24	Resource I®	33.33	58.33	-	-	8.33% PEG 300	-
25	Resource I®	33.33	63.33	-	-	3.33% PEG 300	-
26	Teflon Rod, Thimble	33.33	-	-	63.35	3.33% Glycerin	-
27	Cone Shape Rod, Thimble	31.58	-	-	60.00	3.16% Glycerin & 5.26% H-15	-

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
28	Cone Shape Rod, Thimble	30.51	-	-	57.97	3.05% Glycerin & 8.47% H-15	-
29	Reverse Roller, Scale-up Run, with Polyester Liner	33.33	-	-	63.33	3.33% Glycerin	-
30	Reverse Roller, Scale-up Run, with Aclar and Foil Liner	33.33	-	-	63.36	3.30% Glycerin	-

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
31	Knife Over Roller, Scale-up Run, with Polyethylene and Paper Liner	28.00	-	-	67.00	5.00% Glycerin	-
32	Extrusion, Scale-up Run, with Stainless Steel Surface Carrier	28.00	-	-	67.00	5.00% Glycerin	-

* - Resource I is a casting device for solutions available from Byk-Gardner Instruments of Silver Spring, MD.

The polyvinyl alcohol is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.

PG is propylene glycol.

PEG 300 is polyethylene glycol having an average of 300 ethylene oxide repeating units.

H-15 is Witepsol H-15, which is hydrogenated coco-glycerides and is available from Hüls America of Somerset, NJ.

[0032] The release rate of nonoxynol-9 from the films prepared and VCF® available from Apothecus Pharmaceutical Corp. of Oyster Bay, NY, in a citrate phosphate buffer having a pH of 4.0 was determined by the USP basket method

(United States Pharmacopeia Method Section <711>). The results are shown in Table 2 below. The time to plateau is the time after which there is no significant increase in the release rate.

Table 2

Formulation	Time to Plateau (minutes)	Release Rate (% by weight per minute)
VCF®[1]	15-20	5.45
Example 6	50-60	2.59
Example 7	50-60	3.76
Example 9	40-50	2.33
Example 10	40-50	2.97
Example 12	40-50	3.15
Example 14	10-15	6.08
Example 15	10-15	6.66
Example 17	10-15	6.01
Example 19	15-20	5.82
Example 20	30-40	4.33
Example 21	30-40	3.93
Example 22	10-15	6.10
Example 23	40-50	2.34
Example 24	30-40	2.72
Example 25	30-40	2.76
Example 26	10-15	7.23
Example 27	5-10	8.47
Example 28	5-10	8.89
Example 29	<15	>6.0
Example 30	<15	>6.0
Example 31	<15	>6.0
Example 32	<15	>16

Examples 33-42

[0033] Water soluble films having the formulations of Table 3 were prepared as described in Examples 1-32. In Examples 33-41, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. In Example 42, the solution was first dried at a temperature of about 60-75 ° C for less than about 8 minutes and then dried at a temperature of about 75-90° C for less than about 15 minutes. After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature.

[0034] The substrate for Examples 33-35 was polyester. The substrate for Examples 36-41 was polyester and non-woven fiber. The substrate for Example 42 was a fiber and polyester liner.

[0035] The release rate of miconazole nitrate from the films prepared in a citrate phosphate buffer having a pH of 4.0 was determined by the USP basket method for Examples 33-35 and by the following modified USP method for Examples 36-38, 40, and 41. A dialysis membrane with known molecular weight cut-off and diameter was used instead of a mesh basket for holding the test samples. The membrane limited the amount of dissolution medium which contacted the release layer or composition. This modified dissolution procedure was designed to mimic a vaginal environment where only limited amounts of a medium are typically in contact with the composition. Each release layer and composition was tested in an aqueous medium and in a buffered aqueous medium, which were maintained at a pH of about 4.

[0036] The results are shown in Table 3 below.

Table 3

Example	Casting Device	Polyvinyl alcohol (<30 cps) (% by weight)	Plasticizer (% by weight)	Miconazole Nitrate (% by weight)	Release Rate
33	Resource I	36.2	18.4% Glycerin & 9.2% EB2	36.2	3.3%/min
34	Resource I	40.0	19.9% Glycerin	40.1	4.7%/min
35	Resource I	38.0	19.0% Glycerin & 4.8% EB2	38.2	4.7%/min
36	Resource I & Fiber	36.2	18.4% Glycerin & 9.2% EB2	36.2	3.50%/hr
37	Resource I & Fiber	34.7	17.3% Glycerin & 13.2% EB2	34.8	3.13%/hr
38	Resource I & Fiber	38.0	19.0% Glycerin & 5.0% EB2	38.0	3.33%/hr
39	Resource I & Fiber	39.6	20.6% Glycerin	39.8	-
40	Resource I, Fiber, & OB Tampon	34.7	17.3% Glycerin & 13.2% EB2	34.8	0.81%/hr
41	Resource I, Fiber, & OB Tampon	38.0	19.0% Glycerin & 5.0% EB2	38.0	1.07%/hr
42	Reverse Roller, Scale-up Run, Fiber & Polyester Liner	38.1	19.1% Glycerin & 4.7% EB2	38.1	-
EB2 is Eumulgin B2, which is ceteareth-20 and is available from Henkel Corp. of Hoboken, NJ. The polyvinyl alcohol is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.					

Examples 43-46

[0037] Water soluble films having the formulations of Table 4 were prepared as described in Examples 1-32. In Examples 43-46, the solution was dried at a temperature of about 60-90 ° C for less than about 30 minutes. After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature. The substrate for Example 43-46 was polyester.

[0038] The time for the dissolution rate to plateau was determined as discussed above.

[0039] The results are shown in Table 4 below.

Table 4

Example	Casting Device	Polymer (% by weight)	Plasticizer (% by weight)	Metro-nidazole (% by weight)	Dissolution (Time to Plateau) (min)
43	Resource I	67.2% PVA 52-22	21.7% PEG 400	11.1	20-30
44	Resource I	58.22% PVA 52-22	18.9% PG & 15.7% EB2	7.2	20-30
45	Resource I	34.9% PVA 52-22 and 11.7% PVA 71-30	20.9% PG & 17.5% EB2	15.0	10-15

Table 4 (continued)

Example	Casting Device	Polymer (% by weight)	Plasticizer (% by weight)	Metro-nidazole (% by weight)	Dissolution (Time to Plateau) (min)
46	Resource I	46.6% HPMC E50LV	20.9% PG & 17.5% EB2	15.0	5-10
PG is propylene glycol PEG is polyethylene glycol. EB2 is Eumulgin B2, which is ceteareth-20 and is available from Henkel Corp. of Hoboken, NJ. PVA is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA. HPMC is hydroxypropyl methylcellulose.					

Example 47

[0040] A water soluble film having the formulation of Table 5 was prepared as follows. Glycerin and nonoxynol-9 were added into cold water and mixed until uniform. The solution was heated to about 60-80° C and the film former, *i. e.,* polyvinyl alcohol, was added under constant mixing. The solution was mixed, deaerated, and cooled to about room temperature. The solution was coated onto a stainless steel surface with a web thickness of 0.01 to 0.03 cm. The solution was dried in a multi-zone drying tunnel at a temperature of about 60-90° C for less than about 30 minutes to form a film. The film was then cured with moisture at a relative humidity of about 65-90% and at a temperature of about 40-60° C.

Table 5

Ingredient	% by weight
Polyvinyl Alcohol (5 cps)	66.0
Glycerin	6.0
Nonoxynol-9	28.0

[0041] All patents, publications, applications, and test methods mentioned above are hereby incorporated by reference. Many variations of the present matter will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the patented scope of the appended claims.

Claims

1. A method of preparing a water soluble film, the method comprising the steps of:

(a) preparing a solution comprising:

(i) a film former selected from the group consisting of polyacrylic acids, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, and any combination of any of the foregoing,

(ii) a water soluble plasticizer having at least one of a hydroxyl, amido, or amino group and a boiling point greater than about 150° C,

(iii) a pharmaceutically active agent, and

(iv) a solvent;

(b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and

(c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%.

2. The method of claim 1, wherein the solution has a viscosity of from about 15,000 to about 30,000 cps at room temperature prior to drying.

3. The method of claim 1, wherein the film former is polyvinyl alcohol.

4. The method of claim 1, wherein the film former is a partially hydrogenated polyvinyl alcohol.

5. The method of claim 1, wherein the plasticizer is a polyhydroxy compound.

6. The method of claim 5, wherein the plasticizer is selected from the group consisting of propylene glycol, polyethylene glycol, glycerin, and any combination of any of the foregoing.

7. The method of claim 1, wherein the pharmaceutically active agent is selected from imidazole antifungal agents, antibacterial agents, antiseptic agents, hormones, anti-inflammatory agents, anesthetics, spermicides, and any combination of any of the foregoing.

8. The method of claim 1, wherein the pharmaceutically active agent is nonoxynol-9.

9. The method of claim 1, wherein the pharmaceutically active agent is miconazole.

10. The method of claim 1, wherein the water soluble film further comprises

(i) a surfactant,
(ii) a preservative,
(iii) a viscosity enhancer,
(iv) a colorant,
(v) a fragrance,
(vi) a flavorant,
(vii) a lubricant,
(viii) a filler,
(ix) a binder,
(x) a wetting agent,
(xi) a penetration agent,
(xii) a pH adjuster,
(xiii) a disintegrant,
(xiv) an excipient, or
(xv) any combination of any of the foregoing.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 31 1610

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X Y	EP 0 466 092 A (LABORATOIRE LUCCHINI) 15 January 1992 (1992-01-15) * claims 1-3 * * page 3; example 1 *	1-3,5-8, 10 9	A61K9/70 A61K9/00
Y	WO 99 58110 A (POLYTHERAPEUTICS) 18 November 1999 (1999-11-18) * claims 1,2,6,11,12,14,15,19,20 *	9	
A	GB 1 108 837 A (ASTRA) * claims 1,3 * * page 4, line 8 - line 15 * * page 4, line 41 - line 53 * * page 6; example 13 * * page 6, line 114 - page 7, line 16 *	1-10	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	22 February 2001	Ventura Amat, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 31 1610

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

22-02-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 466092 A	15-01-1992	CH 680188 A	15-07-1992
		AT 110264 T	15-09-1994
		DE 59102616 D	29-09-1994
		IE 912392 A	15-01-1992
		PT 98256 A,B	30-04-1992
		US 5380529 A	10-01-1995
WO 9958110 A	18-11-1999	US 5942243 A	24-08-1999
GB 1108837 A		AT 279035 B	25-02-1970
		BE 690383 A	29-05-1967
		DE 1617282 A	06-02-1975
		DK 118841 B	12-10-1970
		ES 333933 A	16-03-1968
		FR 6733 M	24-02-1969
		LU 52460 A	25-06-1968
		NL 6616878 A	31-05-1967

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [7] : **A61K 7/16**	**A2**	**(11) International Publication Number:** **WO 00/18365** **(43) International Publication Date:** 6 April 2000 (06.04.00)

(21) International Application Number: PCT/US99/22115

(22) International Filing Date: 23 September 1999 (23.09.99)

(30) Priority Data:
60/101,798 25 September 1998 (25.09.98) US

(71) Applicant: WARNER–LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors: LEUNG, Sau–Hung, Spence; 249 Camden Place, Parsippany, NJ 07054 (US). LEONE, Robert, S.; 6 Byron Lane, Fanwood, NJ 07023 (US). KUMAR, Lori, Dee; 5 Alvamar Court, Skillman, NJ 08558 (US). KULKARNI, Neema; 16 Wilkeshire Boulevard, Randolph, NJ 07869 (US). SORG, Albert, F.; 56 Lime Kiln Road, Columbia, NJ 07832 (US).

(74) Agents: RYAN, M., Andrea; Warner–Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.

(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: FAST DISSOLVING ORALLY CONSUMABLE FILMS

(57) Abstract

Physiologically acceptable films, including edible films, are disclosed. The films include a water soluble film–forming polymer such as pullulan. Edible films are disclosed that include pullulan and antimicrobially effective amounts of the essential oils thymol, methyl salicylate, eucalyptol and menthol. The edible films are effective at killing the plaque–producing germs that cause dental plaque, gingivitis and bad breath. The film can also contain pharmaceutically acitve agents. Methods for producing the films are also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

FAST DISSOLVING ORALLY CONSUMABLE FILMS

SPECIFICATION

FIELD OF THE INVENTION

This invention relates to fast dissolving orally consumable films. The films are used to deliver breath deodorizing agents, antimicrobial agents and salivary stimulants to the oral cavity. The films can also be used to deliver pharmaceutically active agents.

BACKGROUND OF THE INVENTION

In a more perfect world, people would thoroughly cleanse their mouths after each meal as part of their routine oral hygienic practices. Unfortunately, several factors conspire to prevent widespread compliance with this basic requirement of a good oral cleaning regimen.

Oral cleansing can be difficult or inconvenient at times, depending on the nature of the cleansing and the situation in which the cleansing must occur. Brushing, flossing, cleaning your tongue and gargling using a variety of devices and compositions well-suited for the privacy of one's home are common oral care practices. However, the devices and compositions used in oral cleansing practices are less convenient to use away from home, where bathroom facilities might be scarce, unavailable or unsanitary.

As brushing, flossing, cleaning your tongue and gargling in public are not considered to be socially acceptable behaviors in many, if not all cultures, a variety of

less obtrusive oral cleansing products have been developed. These include breath-freshening gums and lozenges. Although gums and lozenges have been formulated to achieve a variety of beneficial effects, they are not always socially acceptable. For example, gum is expressly banned from certain institutions, such as schools as well as in certain countries, such as Singapore. Gums and mints are used over extended periods of time, and they require an amount of sucking or chewing action on the part of the consumer, which can be distracting, tedious and undesirable.

Another portable oral cleansing product is a mouthspray. Like a mouthwash, a mouthspray can provide the consumer with a quick burst of strong breath-freshening action, which might be overwhelming in an extended-consumption product like gum or lozenges. On the other hand, mouthsprays are obtrusive. Spraying a mouthspray typically generates a noise, which undesirably draws the attention of the public to the consumer. Moreover, mouthsprays are typically packaged in relatively expensive and complex metal canisters, which can clog in use and are not environmentally friendly. Furthermore, misdirecting the spray not only wastes the product, but can result in irritated eyes, a sticky face and/or stained clothing.

It has been proposed to use an edible film as a vehicle for unobtrusively delivering breath-freshening agents. See JP 5-236885. This Japanese patent application does not, however, teach the inclusion of antimicrobial agents in the film, using the film to decrease the amount of undesirable bacteria within the oral cavity, or stimulating saliva. Furthermore, this patent application does not disclose employing

its film for purposes other than breath freshening or within cavities other than the mouth.

U.S. Patent No. 5,518,902 to Ozaki et al. (Hayashibara) discloses high pullulan content products, such as edible films, dentifrices and pharmaceuticals (column 3, lines 44-56 and Example B-8). The products can include a variety of ingredients in addition to pullulan, such as other polysaccharides, polyhydric alcohols, antiseptics and flavor-imparting agents (column 4, line 58 to column 5, line 11). None of the essential oils, such as thymol, eucalyptol, methyl salicylate or menthol, are mentioned as suitable ingredients.

U.S. Patent No. 5,411,945 to Ozaki et al. (Hayashibara) discloses a pullulan binder and products produced therewith, including edible films (Example B-2). The products can include a variety of ingredients in addition to pullulan, such as other polysaccharides, antibacterial agents, flavor-imparting agents and pharmaceutically active substances (column 4, lines 5-15). None of the essential oils are mentioned as suitable ingredients.

U.S. Patent No. 4,851,394 to Kubodera discloses glucomannan/polyhydric alcohol edible films, which can comprise pullulan (column 3, line 59 to column 4, line 21). The films are contrasted with existing pullulan-based films, which are said to lack resistance to water (column 1, lines 40-44). None of the essential oils are mentioned as suitable ingredients.

U.S. Patent No. 3,784,390 Hijiya et al. discloses pullulan films and their use in

coating and packing materials for foods, pharmaceuticals and other oxygen sensitive materials. All of the examples in this patent teach mixing pullulan in hot water.

U.S. Patent No. 4,623,394 Nakamura et al. discloses a gradually disintegrable molded article that can be a film made with pullulan. The articles contain a particular heteromannan, which can be locust bean gum.

U.S. Patent No. 4,562,020 Hijiya et al. discloses a process for producing a self-supporting film of a glucan, which can be pullulan.

Japanese Patent Document JP5-1198 discloses films made of polyvinyl alcohol and at least one of carrageenan, water-soluble cellulose alpha-starch and water-soluble polysaccharides.

WO 99/17753 discloses rapidly dissolving films for delivery of drugs to be adsorbed in the digestive tract.

WO 98/26780 discloses a flat, foil, paper or wafer type presentation for the application and release of active substances in the buccal cavity. The specific active ingredient disclosed in WO 98/26780 is buprenorphine.

WO 98/20862 discloses a film for use in the oral cavity that can contain a cosmetic or pharmaceutical active substance.

WO 98/26763 discloses a flat, foil, paper or wafer like presentation for release of active substances into the buccal cavity. The particular active disclosed is apomorphine.

Despite the existence of rapidly dissolving orally consumable films in the prior

art, there is still room for improvement in such films, and in processes for making them.

All references cited herein are incorporated herein by reference in their entireties.

SUMMARY OF THE INVENTION

The invention provides a physiologically acceptable film, which is particularly well adapted to adhere to and rapidly dissolve in the mouth of a consumer. In a first embodiment of the invention, the film delivers at least one oral care agent, such as antimicrobial agents and salivary stimulants. The antimicrobial agents are effective against germs that cause halitosis, dental plaque, and gingivitis. The salivary stimulants are effective against the condition known as xerostomia or dry mouth. Additionally, the oral care films are a breath freshener effective against oral malodor. The film former used to make the films according to the present invention entraps the oral care agents in the oral cavity to provide extended efficacy.

In a second embodiment of the invention, the rapidly dissolvable film acts as a vehicle for administering a pharmaceutically active agent orally, through a mucous membrane or an open wound of a patient.

The invention is also directed to a method for producing a supple, non-self-adhering film especially suitable for oral delivery. The method comprises mixing a film forming agent and at least one stabilizing agent to provide a film-forming mixture; dissolving water-soluble ingredients in water to provide an aqueous solution;

combining the film-forming mixture and the aqueous solution to provide a hydrated polymer gel; mixing oils to form an oil mixture; adding the oil mixture to the hydrated polymer gel and mixing to provide a uniform emulsified gel; casting the uniform gel on a substrate; and drying the cast gel to provide a film.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a photograph of an agar plate spread with *Streptococcus mutans*, ATCC 25175, and exposed to a film according to the present invention that contains 0.391 mg of essential oils.

Fig. 2 is a photograph of an agar plate spread with *Streptococcus mutans*, ATCC 25175, and exposed to drops of an essential oil mixture containing 0.391 mg of essential oils per drop.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Description of Oral Care Film Compositions

The first embodiment of the invention is a physiologically acceptable film that is particularly well adapted to adhere to and dissolve in a mouth of a consumer to deliver an antimicrobial agent that kills germs that cause halitosis, dental plaque and gingivitis. Thus, the film can be an effective tool in the prevention and treatment of halitosis, dental plaque accumulation, dental tartar accumulation and gingivitis. This film preferably comprises pullulan, thymol, methyl salicylate, eucalyptol and menthol.

LISTERINE® brand mouthwash is, perhaps, the most well-known example of an antiseptic oral composition that has proven effective in killing microbes in the oral

cavity that are responsible for plaque, gingivitis and bad breath. LISTERINE® brand mouthwash achieves its antimicrobial effect through a combination of essential oils that penetrate and kill the microorganisms. These essential oils include precisely balanced amounts of thymol, methyl salicylate, menthol and eucalyptol (hereinafter "the essential oils") in a hydro alcoholic solution. Many bad breath bacteria live in pits or fissure on the surface of the tongue. Listerine® Antiseptic mouthwash reduces bad breath because of high concentrations of antimicrobial agents in a liquid medium that can easily penetrate into these pits and fissures. This would not be possible with a solid dosage form containing low amounts of these antimicrobial ingredients. However, the preferred consumable film of the invention captures a significant portion of the hygienic benefits and the consumer appeal of LISTERINE® brand mouthwash, in a more portable and unobtrusively consumed form.

It was a significant challenge to maintain the essential oil interaction and relatively high oil content of LISTERINE® brand mouthwash in a film. However, the inventors have overcome this challenge in providing the film of the invention.

A further aspect of this invention is that while the amounts of LISTERINE® essential oils are relatively high for incorporation in a film, the film according to the present invention still delivers a lower total amount of essential oils per unit dose when compared to that of LISTERINE® mouthwash. Yet the film suprisingly provides antimicrobial efficacy in the oral cavity. The inventors theorize that the preferred film forming ingredient, pullulan, forms a thin layer on the oral surfaces

entrapping the small amount of essential oils which are capable of penetrating into the pits and fissures of the oral cavity to provide sustained antimicrobial efficacy.

Although the inventors are presently unaware of any other breath-freshening consumable film that provides antimicrobial efficacy, they are aware of a consumable film disclosed in JP 5-236885, which is said to possess breath-freshening activity, but is not described as possessing any ingredients having significant antimicrobial activity. Moreover, JP 5-236885 teaches that its film should contain flavor and extract in amounts of 5 to 7 wt %, with the flavor being added as an oil (the essential oils are not disclosed), whereas the film of the invention preferably has an oil content of at least about 10 wt %, more preferably about 15 wt % to about 30 wt %, most preferably about 15 wt % to about 25 wt %. Except as otherwise noted in the examples, the amounts of oils and other ingredients in the film are wt% after the film formulation has been dried to create the film.

The amounts of the specific essential oils used in the film compositions can vary as long as they are in amounts sufficient to provide antimicrobial efficacy. Generally the amount of thymol, methyl salicylate and eucalyptol is from about 0.01 to about 4 wt % of the film composition, preferably about 0.50 to about 3.0 wt % and even more preferably from about 0.70 to about 2.0 wt % of the film. Menthol can be added from about 0.01 to about 15 wt % of the composition, preferably about 2.0 to about 10 wt % and even more preferably from about 3 to about 9 wt % of the film. The amounts added can be readily determined to those skilled in the art and can

exceed these amounts as long as the total oil content does not create sticking or other processing problems. In certain embodiments, the essential oils are combined in amounts synergistically effective to kill the plaque-producing germs that cause dental plaque, gingivitis and bad breath.

A major difficulty in formulating a film having such a relatively high oil content is that simply increasing the amount of oil in the film without determining the precise proportions of the many other ingredients typically results in a film that is too moist and therefore difficult to handle or process. The inventors have discovered how to provide a high oil content film that is moist enough so that it is not brittle, but is not so moist that it feels undesirably slimy or significantly adheres to adjacent films. Thus, a non-self-adhering film according to the invention can be stored in contact with another such film (e.g., in a stack), or can be wound about itself (e.g., around a spool), without having to place a non-stick agent (e.g., a plastic film, paper or other support) between adjacent portions of film.

The film-forming agent used in the films according to the present invention can be selected from the group consisting of pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan,

elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof. A preferred film former is pullulan, in amounts ranging from about 0.01 to about 99 wt %, preferably about 30 to about 80 wt %, more preferably from about 45 to about 70 wt % of the film and even more preferably from about 60 to about 65 wt % of the film.

The film of the invention preferably comprises pullulan as a film-forming agent and the essential oils as antimicrobial/flavoring agents, and can further comprise water, additional antimicrobial agents, additional film-forming agents, plasticizing agents, additional flavoring agents, sulfur precipitating agents, saliva stimulating agents, cooling agents, surfactants, stabilizing agents, emulsifying agents, thickening agents, binding agents, coloring agents, sweeteners, fragrances, and the like.

Due to the relatively high oil content in the oral care film, it is preferable to avoid substantial amounts of humectant in the film (and more preferable to have no humectant in the film), so as to avoid producing an overly moist, self-adhering film. In particular, it is preferred to formulate the film with a plasticizing agent other than glycerin, which is also a humectant, and with a sweetener other than sorbitol, which is a mild humectant.

Sulfur precipitating agents that reduce oral malodor can also be added to the oral care films according to the present invention. These agents bind with, and inactivate, the volatile sulfur compounds that cause a large percentage of oral malodor. Sulfur precipitating agents useful in the present invention include metal salts such as

copper salts and zinc salts. Preferred salts include copper gluconate, zinc citrate and zinc gluconate. The amount of sulfur precipitating agent is from about 0.01 to about 2 wt %, preferably about .15 wt % to about 1.5 wt %, even more preferably about .25 wt % to about 1.0 wt % of the film.

Saliva stimulating agents can also be added to the oral care films according to the present invention. Useful saliva stimulating agents are those disclosed in U.S. Patent No. 4,820,506, which is incorporated by reference herein in its entirety. Saliva stimulating agents include food acids such as citric, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acids. Preferred food acids are citric, malic and ascorbic acids. The amount of saliva stimulating agents in the film is from about 0.01 to about 12 wt %, preferably about 1 wt % to about 10 wt %, even more preferably about 2.5 wt % to about 6 wt %.

Preferred plasticizing agents include triacetin in amounts ranging from about 0 to about 20 wt %, preferably about 0 to about 2 wt %. Other suitable plasticizing agents include monoacetin and diacetin.

Preferred cooling agents include monomenthyl succinate, in amounts ranging from about 0.001 to about 2.0 wt %, preferably about 0.2 to about 0.4 wt %. A monomenthyl succinate containing cooling agent is available from Mane, Inc. Other suitable cooling agents include WS3, WS23, Ultracool II and the like.

Preferred surfactants include mono and diglycerides of fatty acids and polyoxyethylene sorbitol esters, such as, Atmos 300 and Polysorbate 80. The

surfactant can be added in amounts ranging from about 0.5 to about 15 wt %, preferably about 1 to about 5 wt % of the film. Other suitable surfactants include pluronic acid, sodium lauryl sulfate, and the like.

Preferred stabilizing agents include xanthan gum, locust bean gum and carrageenan, in amounts ranging from about 0 to about 10 wt %, preferably about 0.1 to about 2 wt % of the film. Other suitable stabilizing agents include guar gum and the like.

Preferred emulsifying agents include triethanolamine stearate, quaternary ammonium compounds, acacia, gelatin, lecithin, bentonite, veegum, and the like, in amounts ranging from about 0 to about 5 wt %, preferably about 0.01 to about 0.7 wt % of the film.

Preferred thickening agents include methylcellulose, carboxyl methylcellulose, and the like, in amounts ranging from about 0 to about 20 wt %, preferably about 0.01 to about 5 wt %.

Preferred binding agents include starch, in amounts ranging from about 0 to about 10 wt %, preferably about 0.01 to about 2 wt % of the film.

Suitable sweeteners that can be included are those well known in the art, including both natural and artificial sweeteners. Suitable sweeteners include, e.g.:

A. water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of

fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, and glycyrrhizin;

B. water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2, 2-dioxide, the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (acesulfame-K), the free acid form of saccharin, and the like;

C. dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame) and materials described in U.S. Pat. No. 3,492,131, L-alpha-aspartyl-N-(2,2,4,4--tetramethyl-3-thietanyl)-D-alaninamide hydrate, methyl esters of L-aspartyl-L-phenylglycerin and L-aspartyl-L-2,5,dihydrophenyl-glycine, L-aspartyl-2,5-dihydro- L-phenylalanine, L-aspartyl-L-(1-cyclohexyen)-alanine, and the like;

D. water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as a chlorinated derivative of ordinary sugar (sucrose), known, for example, under the product description of sucralose; and

E. protein based sweeteners such as thaumatoccous danielli (Thaumatin I and II).

In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with

the sweetener selected. This amount will normally be 0.01 % to about 10 % by weight of the composition when using an easily extractable sweetener. The water-soluble sweeteners described in category A above, are usually used in amounts of about 0.01 to about 10 wt %, and preferably in amounts of about 2 to about 5 wt %. Some of the sweeteners in category A (e.g., glycyrrhizin) can be used in amounts set forth for categories B-E below due to the sweeteners' known sweetening ability. In contrast, the sweeteners described in categories B-E are generally used in amounts of about 0.01 to about 10 wt %, with about 2 to about 8 wt % being preferred and about 3 to about 6 wt % being most preferred. These amounts may be used to achieve a desired level of sweetness independent from the flavor level achieved from any optional flavor oils used. Of course, sweeteners need not be added to films intended for non-oral administration.

The flavorings that can be used include those known to the skilled artisan, such as natural and artificial flavors. These flavorings may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Representative flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also useful are artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot

and so forth. These flavorings can be used individually or in admixture. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in admixture. Flavorings such as aldehydes and esters including cinnamyl acetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and so forth may also be used. Generally, any flavoring or food additive, such as those described in Chemicals Used in Food Processing, publication 1274 by the National Academy of Sciences, pages 63-258, may be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamic aldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral, i.e. beta citral (lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream); heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter, cheese); valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal (citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits); aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla); 2,6-dimethyl- 5-heptenal, i.e. melonal (melon); 2-6-dimethyloctanal (green fruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

The amount of flavoring employed is normally a matter of preference subject to such factors as flavor type, individual flavor, and strength desired. Thus, the amount

may be varied in order to obtain the result desired in the final product. Such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In general, amounts of about 0.1 to about 30 wt % are useable with amounts of about 2 to about 25 wt % being preferred and amounts from about 8 to about 10 wt % are more preferred.

The compositions of this invention can also contain coloring agents or colorants. The coloring agents are used in amounts effective to produce the desired color. The coloring agents useful in the present invention, include pigments such as titanium dioxide, which may be incorporated in amounts of up to about 5 wt %, and preferably less than about 1 wt %. Colorants can also include natural food colors and dyes suitable for food, drug and cosmetic applications. These colorants are known as FD&C dyes and lakes. The materials acceptable for the foregoing spectrum of use are preferably water-soluble, and include FD&C Blue No. 2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye known as Green No. 3 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-N-ethyl-p-sulfobenzylamino) diphenyl-methylene]-[1-N-ethyl-N-p-sulfonium benzyl)-2,5-cyclo-hexadienimine]. A full recitation of all FD&C and D&C dyes and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, Volume 5, Pages 857-884, which text is accordingly incorporated herein by reference.

Antimicrobial Efficacy of Oral Care Films

The preferred embodiment of the oral care film composition according to the

present invention contains the essential oils used in Listerine® mouthwash to provide antimicrobial efficacy. The films are shaped and sized to be placed in the oral cavity. The film adheres to a surface in the mouth, usually the roof of the mouth or the tongue, and quickly dissolves. The amount of essential oils in one individual film that is a preferred size for placing in the mouth is significantly lower than that in the recommended amount, 20ml, of Listerine® mouthwash.

In a preferred formula according to the present invention, the amount of thymol and eucalyptol in the film is about 70 times less than in the mouthwash. The amount of methyl salicylate in the film is about 46 times less than in the mouthwash. The amount of menthol in the film is about 2.8 times less than in the mouthwash. These figures are based on comparing a 20 ml dose of liquid mouthwash with a 0.0358 gram film.

The inventors have unexpectedly found that the film provides sustained antimicrobial efficacy at these low amounts of oils. The inventors believe that the efficacy of the essential oils is enhanced by the creation of a layer of pullulan in the oral cavity that holds the essential oils. This is unexpected because pullulan is water-soluble and the film dissolves very quickly.

The extended antimicrobial activity is shown in the following experiments.

The purpose of these experiments was to determine the antibacterial efficacy of an application of a breath film on tongue malodor microorganisms thirty, sixty or ninety minutes after use. The thirty minute study also tested the efficacy of using two

films. Subjects' baseline oral malodor microbial recoverable counts were determined by plating the microorganisms recovered from a tongue swab on a selective agar medium. The test product was dispensed and subjects dissolved one or two breath films on their tongue. Subjects remained on the premises and returned for a second tongue swab thirty, sixty or ninety minutes after placement of the test product on their tongue. After a forty-eight hour washout period, subjects returned for a no treatment control.

The thirty minute single film use group showed a reduction in mean log malodor microbial counts compared to the control group. The data was borderline statistically significant ($p=0.052$). The difference between the one film group and the no treatment control group represented a 42.7% reduction in malodor microbial colony counts.

Statistically significant malodor microbial reduction was also observed with the two film use group. A 79.6% reduction in malodor microbial colony counts was obtained ($p<0.001$).

Statistically significant malodor microbial reduction was observed sixty minutes after use of a single breath film. A 69.8% reduction in malodor microbial colony counts was obtained ($p=0.002$).

Significant malodor reduction was also observed ninety minutes after use of a single breath film. A 69.1% reduction in malodor microbial colony counts was obtained ($p=0.006$).

The data from these studies support the following conclusions: (1) Pullulan polymer-based breath film containing essential oils is an effective antibacterial composition against oral malodor causing bacteria and (2) significant *in vivo* bacterial reductions were achieved at thirty, sixty and ninety minutes post use.

Experimental Procedures

The procedures used in these antimicrobial studies were as follows. The subject were required to refrain from all oral hygiene procedures (e.g., toothbrushing, oral lavage) eating or drinking any food, beverage or confectionery products from midnight prior to the study and until the study was completed on each test day. Subjects refrained from smoking on mornings prior to the odor evaluations.

In vivo Germ Kill Assay

1. Materials

Test tubes containing 10 ml of sterile 0.01% peptone

Sterile Swabs

OOPS III Agar (B.-F. Turng, G.E. Minah, and W.A. Falkler. Development of an Agar Medium for Detection of Oral H_2S-producing Organisms. J Dent Res 76 IADR Abstracts 1997.):

Columbia Agar Base (Catalogue # DF0792-17-3)	44 grams
Distilled Water	1 liter
Lead Acetate[a] (Sigma L3396)	0.2 grams
Hemin Solution[b] (Sigma H-1652)	2 ml

Glutathione[c] (Sigma G4251) 1.2 grams

Forty-four grams of Columbia Blood Agar Base was suspended in 1 liter distilled water and boiled to dissolve completely. The media was sterilized at 121-124°C for 15 minutes.

[a] Dissolved 0.2 grams of lead acetate in 1 ml of distilled H_2O and filter sterilized. Added after autoclaving the base media.

[b] Dissolved 50 mg of hemin in 1 ml of 1N NaOH; qs'd to 100 ml with distilled H_2O. Filter sterilized. Added 2 ml per liter of OOPS III after autoclaving base media.

[c] Dissolved 1.2 grams of glutathione in 10 ml of distilled H_2O. Filter sterilized. Added after autoclaving base media.

2. Procedure

a. All media were prereduced in an anaerobic chamber overnight. Plates were loosely wrapped in plastic bags to prevent excessive drying.

b. Panelists refrained from oral hygiene, eating and drinking from midnight prior to the assay and until the assay was complete. Twelve panelists were used for the sixty and ninety minute experiments. Eighteen panelists were used for the thirty minute experiments.

c. Each panelist swabbed the right side of his tongue by placing the swab at the midpoint of the tongue and swiping forward to the tip. The swab was placed in a tube of peptone.

d. The panelist received a film treatment, either a single or double film. Panelists

placed the breath film on the left side of their tongue covering the tongue from the midpoint to the tip and allowed the film to dissolve with the mouth slightly open for thirty seconds to prevent the film from sticking to the palate.

e. After thirty or sixty minutes, panelists swabbed the left side of the tongue by placing the swab at the midpoint of the tongue and swiping forward to the tip. The swab was placed in a tube of peptone.

f. The tubes of peptone were vortexed vigorously for 10 seconds, and serial dilutions were made. The 10^{-4} dilution was plated in duplicate on OOPS III Agar using a Spiral Biotech Autoplate 4000 (Bethesda, MD). All plates were identified with the subject's initials, assay date, sampling time station, and replicate number.

g. The plates were incubated in an anaerobic chamber at 35-37°C for 7 days to permit full development of colonies without overgrowth.

h. After a 48 hour wash out period, panelists returned for the no treatment control. No film was applied, and steps (e) through (g) were followed as described above.

i. After a 48 hour wash out period, the sixty minute panelists returned for another single film application. Steps (a) through (h) were followed, with the exception that panelists returned after 90 min in step e.

j. The dark-pigmented colonies (H_2S-producing organisms) were counted as whole plate counts by hand under appropriate magnification or by Segment

counts using a Spiral Biotech counting template. The appropriate code was entered on the data sheet to permit interpretation of the counts. The CFU's counted were converted to CFU/ml by dividing by the appropriate exponential volume constant listed in Table A and multiplying by 1000. This value was then multiplied by the dilution factor of the plate (10^4).

Table A. Exponential Volume Constants for Segment Pairs

Last Counted Segment	Exponential Volume Constant
8	1.214
9	2.968
10	5.500
11	9.157
12	14.482
13	25.015
Total Plate	50.030

The film used in the *in vivo* germ kill tests was Example 19 as described in Table 2. The films used in the study were approximately 22mm x 32mm, between about 0.0013 and 0.0015 inches thick and weighed between about 35 to about 37 mg.

The enhanced activity of the essential oil containing pullulan film is also shown in Figures 1 and 2. Figure 1 is a photograph of an agar plate spread with *Streptococcus mutans*, ATCC # 25175, to which a piece of an essential oil pullulan

film according to the present invention was added. The piece of film delivered approximately .391 mg of essential oils using Example 15 listed below.

Figure 2 is a photograph of an agar plate spread with Streptococcus mutans, ATCC # 25175 to which drops of essential oils have been added. The drops were 148 ul in volume and contained 0.391 mg of essential oils. The percentages of each essential oil in the drop are 2.200% menthol, 0.186% eucalyptol, 0.186% methyl salicylate and 0.1300% thymol in a hydro alcohol solution.

The area or zone of inhibition around the film in Figure 1 is much larger than the dimensions of the film. This is due to the presence of pullulan because the oils in the pullulan film were spread by the pullulan, diffused outward and did not wash away after repeated rinses. In contrast, the essential oils in Figure 2 did not diffuse away from the droplet, remained as a circle and easily washed off after 1-2 rinses. This shows that the antimicrobial efficacy of the essential oils is enhanced by the presence of pullulan.

Methods For Preparing Essential Oil Containing Films

Methods for preparing films according to the invention are capable of encapsulating the oil ingredients within the film-forming matrix and maintaining the integrity of the film, even when the film contains oils in amounts of 10 wt % or more.

In certain methods for preparing films according to the invention, the film-forming ingredients are mixed and hydrated with water separately from the water-soluble ingredients, which are mixed in aqueous solution separately from the organic

ingredients and surfactants. In these methods, the final formulation is preferably produced by mixing the film-forming phase with the aqueous phase, then mixing in the organic phase, which includes surfactants, such as Polysorbate 80 and Atmos 300. This mass is mixed until emulsified. In other embodiments, the aqueous and film forming phases are combined into a single phase by dissolving the water soluble ingredients in the water and then adding the gums to hydrate. The organic phase is then added to this single aqueous phase.

The resulting formulation is cast on a suitable substrate and dried to form a film. The film is preferably air-dried or dried under warm air and cut to a desired dimension, packaged and stored. The film can contain from about 0.1% to about 10 wt % moisture, preferably from about 3 % to about 8 wt % moisture, even more preferably from about 4 to about 7 wt % moisture.

The film-forming phase can include pullulan and stabilizing agents such as xanthan gum, locust bean gum and carrageenan. These ingredients are mixed and then hydrated in water for about 30 to about 48 hours to form a gel. The water is preferably heated to a temperature of about 25 to about 45 °C to promote hydration. The amount of water is about 40 to 80 % of the gel. The resulting hydrated gel is then chilled to a temperature of about 20 to about 30 °C for about 1 to about 48 hours. The water is preferably deionized.

The aqueous phase can include ingredients such as coloring agent(s), copper gluconate and sweetener. The water is preferably deionized and the amount of water

used is about 5 to about 80 wt % of the final gel mixture.

If sodium saccharin and copper gluconate are both ingredients in the formulation, it is preferable to dissolve them separately in solution to avoid precipitation.

In a preferred method of producing essential oil containing films according to the invention, it is possible to hydrate the film-forming ingredients and combine all of the ingredients without heating. The preferred method of producing films comprises dissolving the water-soluble ingredients in water to form an aqueous mixture; mixing the film-forming ingredients in powder form to form a powder mixture; adding the powder mixture to the aqueous mixture to form a hydrated polymer gel; stirring the hydrated polymer at room temperature for about 30 minutes to about 48 hours; mixing the cooling agent, thymol and menthol in the flavor oil to form an oil mixture; adding methyl salicylate; eucalyptol and surfactants to the oil mixture; adding the oil mixture to the hydrated polymer gel and mixing until uniform; deaerating the film until air bubbles are removed, casting the uniform mixture on a suitable substrate; and drying the cast mixture to form a film.

The preferred method for making an essential oil containing film hydrates the film-forming ingredients without heating the water. Heating the ingredients increases energy costs in the manufacturing process. Moreover, heating results in undesirable losses of volatile ingredients to evaporation, which also affects the germ killing activity of the composition due to the loss of essential oils. Further, mixing the oils in

two steps minimizes the amount of flavor lost.

While not wishing to be bound by any theories, it is believed that the film-forming ingredients can be hydrated and mixed without heating due to an ionic effect known as the Donnan equilibrium. Hydrating the film-forming agents in the presence of electrolytes in solution effectively lowers the viscosity of the polymer gel being formed, thus increasing the efficiency of the hydrating process. The water-soluble ingredients of the formulation provide the electrolytes, which are dissolved in the hydration solution prior to addition of the film-forming ingredients. High-shear mixing also accelerates hydration, which delumps the powders, providing greater surface area for water contact. In addition, local heating effects, generated in the shear regions, provide energy for hydration without substantially raising the temperature of the mass.

It is preferable to avoid adding both copper gluconate and saccharin at the same time to the aqueous solution, as a precipitate will form. Thus, it is preferred to combine sweeteners other than saccharin with copper gluconate.

Description of Film Compositions That Deliver Pharmaceutical Agents

A second embodiment of the invention is a fast dissolving film that includes at least one physiologically acceptable, pharmaceutically active agent. The expression "physiologically acceptable" as used herein is intended to encompass compounds, which upon administration to a patient, are adequately tolerated without causing undue negative side effects. The expression encompasses edible compounds.

The expression "pharmaceutically active agents" as used herein is intended to encompass agents other than foods, which promote a structural and/or functional change in and/or on bodies to which they have been administered. These agents are not particularly limited; however, they should be physiologically acceptable and compatible with the film. Suitable pharmaceutically active agents include, but are not limited to:

A. antimicrobial agents, such as triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA, and the like,

B. non-steroidal anti-inflammatory drugs, such as aspirin, acetaminophen, ibuprofen, ketoprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and the like,

C. anti-tussives, such as benzonatate, caramiphen edisylate, menthol, dextromethorphan hydrobromide, chlophedianol hydrochloride, and the like,

D. decongestants, such as pseudoephedrine hydrochloride, phenylepherine, phenylpropanolamine, pseudoephedrine sulfate, and the like,

E. anti-histamines, such as brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenylpyraline hydrochloride, azatadine meleate, diphenhydramine citrate, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine

hydrochloride, acrivastine, loratadine, brompheniramine, dexbrompheniramine, and the like,

F. expectorants, such as guaifenesin, ipecac, potassium iodide, terpin hydrate, and the like,

G. anti-diarrheals, such a loperamide, and the like,

H. H_2–antagonists, such as famotidine, ranitidine, and the like; and

I. proton pump inhibitors, such as omeprazole, lansoprazole, and the like,

J. general nonselective CNS depressants, such as aliphatic alcohols, barbiturates and the like,

K. general nonselective CNS stimulants such as caffeine, nicotine, strychnine, picrotoxin, pentylenetetrazol and the like,

L. drugs that selectively modify CNS function such as phenyhydantoin, phenobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phensuximide, trimethadione, diazepam, benzodiazepines, phenacemide, pheneturide, acetazolamide, sulthiame, bromide, and the like,

M. antiparkinsonism drugs such as levodopa, amantadine and the like,

N. narcotic-analgesics such as morphine, heroin, hydromorphone, metopon, oxymorphone, levorphanol, codeine, hydrocodone, xycodone, nalorphine, naloxone, naltrexone and the like,

O. analgesic-antipyretics such as salycilates, phenylbutazone, indomethacin, phenacetin and the like,

P. psychopharmacological drugs such as chlorpromazine, methotrimeprazine, haloperidol, clozapine, reserpine, imipramine, tranylcypromine, phenelzine, lithium and the like.

The amount of medicament that can be used in the rapidly dissolving films, according to the present invention, is dependent upon the dose needed to provide an effective amount of the medicament. Examples of doses for specific medicaments that can be delivered per one strip of rapidly dissolving oral film are reviewed in Table 1.

TABLE 1

MEDICAMENT	DOSE
Chlorpheniramine Maleate	4 mg.
Brompheniramine Maleate	4 mg.
Dexchlorpheniramine	2 mg.
Dexbrompheniramine	2 mg.
Triprolidine Hydrochloride	2.5 mg.
Acrivastine	8 mg.
Azatadine Maleate	1 mg.
Loratidine	10 mg.
Phenylephrine Hydrochloride	10 mg.
Dextromethorphan Hydrochloride	10-20 mg.
Ketoprofen	12.5 mg.
Sumatriptan Succinate	35 - 70 mg.
Zolmitriptan	2.5 mg.
Loperamide	2 mg.
Famotidine	10 mg.
Nicotine	2 mg.
Diphenhydramine Hydrochloride	25 mg.
Pseudoephedrine Hydrochloride	30 mg.

The ingredients used to make the pharmaceutical containing films are similar to those used to make oral care films. Specifically, the plasticizing agents, cooling agents, surfactants, stabilizing agents, emulsifiers, thickening agents, binding agents, film formers, sweeteners, flavors and colors described above can also be used in all of the films according to the present invention.

The films that deliver a pharmaceutical agent can also include a triglyceride. Examples of triglycerides include vegetable oils such as corn oil, sunflower oil, peanut oil, olive oil, canola oil, soybean oil and mixtures thereof. A preferred triglyceride is olive oil. The triglyceride is added to the film in amounts from about 0.1 wt % to about 12 wt %, preferably in a range from about 0.5 wt % to about 9 wt %, of the film.

The films that contain pharmaceutical agents also can include a preservative. The preservative is added in amounts from about 0.001 wt % to about 5 wt %, preferably from about 0.01 wt % to about 1 wt % of the film. Preferred preservatives include sodium benzoate and potassium sorbate.

The pharmaceutical agent containing films can also include a polyethylene oxide compound. The molecular weight of the polyethylene oxide compound ranges from about 50,000 to about 6,000,000. A preferred polyethylene oxide compound is N-10 available from Union Carbide Corporation. The polyethylene oxide compound is added in amounts from about 0.1 wt % to about 5 wt %, preferably from about 0.2 wt % to about 4.0 wt % of the film.

The pharmaceutical agent containing films can also include propylene glycol.

The propylene glycol is added in amounts from about 1 wt % to about 20 wt %, preferably from about 5 wt % to about 15 wt % of the film.

The active ingredient used in the film can be coated to mask the taste of the active ingredient or to prevent the active ingredient from numbing the tongue or other surfaces in the oral cavity. The coatings that can be used are known to those skilled in the art. These include polymers such, as Eudragit® E, cellulosics, such as ethylcellulose, and the like.

An additional way to mask the taste of the active ingredient is by using an ion exchange resin such as Amberlite RP-69, available from Rohm and Haas, and Dow XYS-40010.00, available from the Dow Chemcial Co.

Examples

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

Preparation Method I

The following method was used to prepare the films of Examples 1-13.

A. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) other than Polysorbate 80 and Atmos 300 are mixed and hydrated in hot purified water to form a gel and stored in a refrigerator overnight at a temperature of approximately 4 °C to form preparation A.

B. The coloring agent(s), copper gluconate and sweetener are added to and

dissolved in purified water to form preparation B.

C. Preparation B is added to preparation A and mixed well to form preparation C.

D. The flavoring agent and the oils (e.g., cooling agent, thymol, methyl salicylate, eucalyptol and menthol) are mixed to form preparation D.

E. The polysorbate 80 and Atmos 300 are added to preparation D and mixed well to form preparation E.

F. Preparation E is added to preparation C and mixed well to form preparation F.

Preparation F is poured on a mold and cast to form a film of a desired thickness at room temperature. The film is dried under warm air and cut to a desired dimension, packaged and stored.

Preparation Method II

Examples 14-18 were prepared using a preferred method, which comprised the following steps:

A. dissolve copper gluconate, acesulfame K, aspartame, glycerin, sorbitol and dye in purified water to form an aqueous mixture;

B. mix pullulan, xanthan gum, locust bean gum and carrageenan together in powder form to form a powder mixture;

C. add the powder mixture from step B to the aqueous mixture from step A to form a hydrated polymer gel;

D. stir the hydrated polymer from step C at slow speed (about 50-100 RPM) overnight at room temperature;

E. mix and dissolve cooling agent, thymol and menthol in the flavor oil;

F. add methyl salicylate, eucalyptol, Polysorbate 80 and Atmos 300 to the oil mixture from step E;

G. add the oil mixture from step F to the hydrated polymer gel from step D and mix until uniform;

H. cast the uniform mixture from step G on a suitable backing; and

I. dry the cast mixture to form a film.

Example 1

Example 1 produced a film according to the invention having a blue-green tint, a mint odor and a refreshing mint taste.

Examples 2-4

Examples 2-4 contain sorbitol, glycerin or both. These examples yielded products that easily broke off pieces, or were too moist and/or self-adhering. However they did produce films that rapidly dissolved in the oral cavity with a refreshing mint taste.

Examples 5-6

Examples 5 and 6 removed glycerin and sorbitol. The resultant films did not stick together during processing and packaging and were more moisture stable over a

long time frame.

Examples 7-9

Examples 7-9 were produced to determine the effect of Avicel® on germ killing activity. While Examples 7-9 produced more acceptable films from a processing and handling perspective, they had diminished antimicrobial activity relative to films without Avicel®, such as Example 8.

Examples 10-15

Examples 10 - 15 varied the amounts of aspartame and menthol to alter the sweetness and coolness of the film.

Example 16

Example 16 was prepared by replacing the sorbitol replaced with maltitol, which has less humectant properties. The resultant film was less sticky during processing and long term storage.

Example 17

Example 17 is prepared in which pullulan is replaced with another film former, polyvinyl pyrrolidone, to produce films according to the invention.

Example 18

Example 18 is prepared in which pullulan is partially replaced with another film former, konjac gum, to produce films according to the invention.

Example 19

Example 19 represents a film containing a salivary stimulant, citric acid.

Example 20

Example 20 is the film composition used in the antimicrobial efficacy studies described above.

The formulas for examples 1 - 20 are summarized in Table 2. The amounts in these examples are presented as the actual weight (grams) or w/w %. These formulas create the solution/gel that is cast and dried into a film. The actual amount of each ingredient in the finished, dried film depends upon the amount of relative moisture removed during drying.

Table 2

Ingredient	Ex. 1 w/w%	2 wt (g)	3 wt (g)	4 wt (g)	5 wt (g)	6 wt (g)	7 wt (g)	8 wt (g)	9 wt (g)
Xanthan Gum, Food Grade	0.1070						11.60	12.60	11.60
Xanthan Gum (1% solution)		3.85	3.85	3.85	3.85	3.85			
Locust Bean Gum, Clarified	0.2150						23.40	25.40	23.40
Locust Bean Gum (1% solution)		7.70	7.70	7.70	7.70	7.70			
Polyvinyl Pyrrolidone									
Konjac Gum									
Carrageenan	1.0730						116.60	126.10	116.60
Carrageenan (5% solution)		7.70	7.70	7.70	7.70	7.70			
Avicel							500.00		500.00
Pullulan	51.5780						5604.00	6513.00	5949.00
Pullulan (25% sol)		74	74	74	74	74			
Thymol NF	0.4070	0.146			0.146	0.146	40.70	40.70	40.70
Methyl Salicylate NF	0.4210	0.151			0.151	0.151	58.50	58.50	58.50
Eucalyptol	0.5850	0.21			0.21	0.21	42.10	42.10	42.10
Menthol USP	5.8830	2.23			2.11	2.11	588.00	588.00	588.00
Mint flavor	8.3640	2			3.0	3.0	836.00	836.00	836.00
Citric Acid									
Copper gluconate	1.1150	0.275			0.41	0.14	112.00	112.00	112.00
Purified water, USP/EP	22.32	2	10.22	12.22	8.0	8.0	2230.00	2230.00	2230.00
Sod. saccharin USP granulate	6.6910	1.8	1.4	1.4	2.0	2.4			
Sodium saccharin							609.00	609.00	609.00
Acesulfame-K									
Aspartame									
Cooling agent		0.05			0.05	0.05	13.90	13.90	13.90
Maltitol									
Sorbitol (crystalline)							64.30	64.30	64.30
Sorbitol 70% sol.		4	4.0						
Glycerin		2		2.0			136.00	136.00	136.00
Polysorbate 80 NF/EP	0.5580	0.3	0.2	0.2	0.2	0.2	112.00	112.00	112.00
Atmos 300	0.5580						112.00	112.00	112.00
Atlas 3000		0.3	0.2	0.2	0.2	0.2			
Hi Set C Starch									77.0
FD&C Green # 3	0.0084	0.3	0.3	0.3	0.3	0.3	0.84	0.84	0.84
D&C Yellow #10									

Table 2 cont.

Ingredient	10 wt (g)	11 wt (g)	12 wt (g)	13 wt (g)	14 w/w%	15 w/w%	16 w/w%	17 w/w%	18 w/w%	19 w/w%	20 w/w%
Xanthan Gum, Food Grade	0.0385	0.0385	0.0385	0.0385	0.0342	0.0342	0.0342	0.04	0.04	0.34	0.0342
Xanthan Gum (1% solution)											
Locust Bean Gum, Clarified	0.077	0.077	0.077	0.077	0.0684	0.0684	0.0684	0.07	0.07	0.68	0.0684
Locust Bean Gum (1% solution)											
Polyvinyl Pyrrolidone								16.5			
Konjac Gum									5.0		
Carrageenan	0.385	0.385	0.385	0.385	0.342	0.342	0.342	0.34	0.34	.34	0.342
Carrageenan (5% solution)											
Avicel											
Pullulan	18.5	18.5	18.5	18.5	16.43	16.43	16.43		11.0	16.34	16.43
Pullulan (25% sol)											
Thymol NF	0.146	0.146	0.146	0.146	0.130	0.13	0.13	0.13	0.13	0.129	0.13
Methyl Salicylate NF	0.21	0.21	0.21	0.21	0.186	0.186	0.186	0.186	0.186	0.185	0.18
Eucalyptol	0.21	0.21	0.21	0.21	0.186	0.186	0.186	0.186	0.186	0.185	0.18
Menthol USP	2.11	1.95	2.36	2.36	2.096	2.520	2.096	2.096	2.096	2.084	2.096
Mint flavor	3.0	3.0	3.0	3.0	2.664	2.344	2.664	2.664	2.664	2.649	2.0
Citric Acid											2.5
Copper gluconate	0.4	0.4	0.4	0.4	0.355	0.355	0.355	0.35	0.35	0.353	0.355
Purified water, USP/EP	84.25	84.25	84.25	84.25	74.81	74.63	74.81	75	75	74.39	72.2168
Sod. saccharin USP granulate											
Sodium saccharin											
Acesulfame-K	0.5	0.5	0.5	0.5	0.444	0.444	0.444	0.45	0.45	.04420	0.444
Aspartame	1.30	1.60	1.30	1.60	1.421	1.421	1.421	1.4	1.4	1.413	1.421
Cooling agent	0.10	0.10	0.10	0.10	0.089	0.089	0.089	0.089	0.089	0.088	0.89
Maltitol							2.80				
Sorbitol (crystalline)											
Sorbitol 70% sol.										0.199	
Glycerin										0.418	
Polysorbate 80 NF/EP	0.4	0.4	0.4	0.4	0.355	0.355	0.355	0.355	0.355	0.353	0.355
Atmos 300					0.355	.0355	0.355	0.355	0.355	0.353	0.355
Atlas 3000	0.4	0.4	0.4	0.4							
Hi Set C Starch											
FD&C Green # 3	0.003	0.003	0.003	0.003	0.0026	0.0026	0.0026	0.0026	0.0026		
D&C Yellow #10											

The following examples are films according to the second embodiment of the present invention, in which the rapidly dissolving film contains a pharmaceutical agent. Examples 21A-21E, listed in Table 3, are medicament containing rapidly dissolvable oral film formulas. The amounts in Table 3 are in milligrams.

TABLE 3

Example Number	21A	21B	21C	21D	21E
Dextromethorphan HBr	7.500				
Phenylepherine HCI		10.0000	10.0000		
Chlorpheniramine Maleate			4.0000		
Loperamide HCI				2.0000	
Nicotine					2.0000
Xanthan Gum	0.0818	0.0818	0.0818	0.0818	0.0818
Locust Bean Gum	0.0954	0.0954	0.0954	0.0954	0.0954
Carrageenan	0.4088	0.4088	0.4088	0.4088	0.4088
Pullulan	21.8036	21.8036	21.8036	21.8036	21.8036
Sodium Benzoate	0.0954	0.0954	0.0954	0.0954	0.0954
Acesulfame Potassium Salt	0.6814	0.6814	0.6814	0.6814	0.6814
Aspartame NF	1.9078	1.9078	1.9078	1.9078	1.9078
Purified Water	*	*	*	*	*
Cooling agent	0.1363	0.1363	0.1363	0.1363	0.1363
Menthol	2.7255	2.7255	2.7255	2.7255	2.7255
Polysorbate 80 NF	0.4770	0.4770	0.4770	0.4770	0.4770
Atmos 300	0.4770	0.4770	0.4770	0.4770	0.4770
Propylene Glycol	4.0882	4.0882	4.0882	4.0882	4.0882
Olive Oil	0.6814	0.6814	0.6814	0.6814	0.6814
Titanium Dioxide	0.3407	0.3407	0.3407	0.3407	0.3407
Total Dose Weight	41.5000	44.0000	48.0000	36.0000	36.0000

*Calculated assuming complete evaporation of water from the films after drying

Table 4 summarizes additional films according to the present invention. The amounts in Table 4 are % w/w prior to drying.

Table 4

Examples	22A	22B	22C	22D	22E	22F	22G	22H	22I
Xanthan Gum	.03	.03	.06	.03	.03	.03	.06	.06	.06
Locust Bean Gum	.07	.07	.07	.07	.07	.07	.07	.07	.07
Carrageenan	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Pullulan	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0
Sodium Benzoate	0.1	0.1	0.1	.07	.07	.07	.07	.07	0.7
Acesulfame Potassium	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aspartame	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Water	qs100	qs100	qs100	Qs100	qs100	qs100	qs100	qs100	Qs100
Cooling agent	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Menthol	2.0	2.0	2.0	1.3	2.0	2.0	2.0	2.0	2.0
Polysorbate 80	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Atmos 300	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Propylene Glycol	1.0	1.0	1.0	1.0	1.0	1.0	3.0	3.0	3.0
Peg 1450	-	3.10	-	-	-	-	-	-	-
Olive Oil	-	-	-	1-2	2.0	2.0	.5-2	-	.5
Polyox N-10	-	-	-	-	-	-	-	-	1.0
Titanium Dioxide	-	0.25	0.25	0.25	0.25	-	0.25	-	0.25

Example 22A was used to make films containing a) 7.5 mg of dextromethorphan hydrobromide, b) 2.5 mg of tripolidine, c) 4.0 mg of chlorpheniramine maleate and d) 12.5 mg of diphenhydramine hydrochloride.

Example 22B was used to make a film containing 10 mg of dextrometorphan hydrobromide.

Example 22C was used to make a film containing 10 mg of dextromethorphan hydrobromide.

Example 22D was used to make a film containing a) 10 mg of phenylepherine hydrochloride, b) 10 mg of phenylepherine hydrochloride and 4 mg of chlorpheniramine maleate and c) 10 mg of dextromethorphan hydrobromide.

Example 22E was used to make a film containing 7.5 mg dextromethorphan hydrobromide.

Example 22F was used to make a film containing 20 mg of coated dextromethorphan hydrobromide to provide a 7.5 mg dose.

Example 22G was used to make a film containing a) 7.5 mg dextromethorphan hydrobromide, b) 10 mg phenylepherine hydrochloride and c) 10 mg phenylepherine hydrochloride and 4 mg chlorpheniramine maleate.

Example 22H was used to make a film containing 15 mg of dextromethorphan hydrobromide.

Example 22I was used to make a film containing 15 mg of dextromethorphan

hydrobromide.

Processes For Making Pharmecutical Containing Films

Example 22A was made using the following procedure.

1. Add the sodium benzoate and sweeteners to water.
2. Mix the locust bean gum, xanthan gum and carrageenan together.
3. Add the gum mixture to the mixture of step 1 and mix until dissolved.
4. Mix the active ingredient with either water or propylene glycol. Heat if needed.
5. Add the remaining ingredients to the mixture of step 4 or mix the remaining ingredients in a separate mixture.
6. Add the mixtures of step 4 and step 5 to the mixture of step 3. Cast and dry to make a film and cut to a size to achieve the desired dose.

Examples 22B-22E were made using the following procedure.

1. Add the sodium benzoate to water heated to 50 C. Mix to dissolve.
2. Separately, add the Peg 1450, titanium dioxide and active ingredient to the mixture of step 1, mixing with each addition.
3. Mix the locust bean gum, xanthan gum and carrageenan together.
4. Add the gums to the mixture of step 2 and mix until dissolve.
5. Add the remaining ingredients together with heat if needed.
6. Add the mixture of steps 4 and 5 together. Cast and dry to make a film and cut to a size to achieve the desired dose.

Examples 22F - 22I were made in the same manner as Examples 20B - 20E, except the active was dispersed right before the film was cast.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

CLAIMS

WHAT IS CLAIMED IS:

1. A consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein said film comprises at least one water soluble polymer and an antimicrobial effective amount of at least one essential oil selected from the group consisting of thymol, methyl salicylate, eucalyptol and menthol.

2. The consumable film according to claim 1, comprising at least two of said essential oils.

3. The consumable film according to claim 1, comprising at least three of said essential oils.

4. The consumable film according to according to claim 1, comprising thymol, methyl salicylate, eucalyptol and menthol.

5. The consumable film according to claim 4, further comprising a salt of gluconic acid.

6. The consumable film according to claim 4, further comprising copper gluconate.

7. The consumable film according to claim 1, wherein said water soluble polymer is selected from the group consisting of pullulan, hydroxyproplymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid,

methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof.

8. The consumable film according to claim 7, wherein said water soluble polymer is pullulan.

9. The consumable film of claim 8, comprising:

about 40 to about 80 wt % pullulan;

about 0.01 to about 4 wt % thymol;

about 0.01 to about 4 wt % methyl salicylate;

about 0.01 to about 4 wt % eucalyptol; and

about 0.01 to about 15 wt % menthol.

10. The consumable film according to claim 7, further comprising:

about 0.01 to about 5 wt % of at least one stabilizing agent;

about 0.001 to about 0.1 wt % of at least one of at least one coloring agent;

about 0.1 to about 8 wt % of water;

about 0.1 to about 15 wt % of at least one sweetening agent;

about 0.1 to about 15 wt % of at least one flavoring agent;

about 0.1 to about 4 wt % of at least one cooling agent; and

about 0.1 to about 5 wt % of at least one surfactant.

11. The consumable film according to according to claim 10, wherein said least one stabilizing agent is selected from the group consisting of xanthan gum, locust bean gum and carrageenan, and said at least one sweetening agent is selected from the group consisting of saccharin, aspartame and acesulfame K.

12. The consumable film according to claim 1, wherein said film does not substantially adhere to itself.

13. The consumable film according to claim 1, wherein said film is free of glycerin and sorbitol.

14. The consumable film according to claim 1, wherein said film is free of humectants.

15. The consumable film according to claim 1, wherein the essential oils comprises at least about 10 wt % of the film.

16. The consumable film according to claim 15, wherein the essential oils comprises at least about 15 wt % of the film.

17. The consumable film according to claim 1, further comprising water in an amount from about 3 wt % to about 8 wt %.

18. A method for preparing a physiologically compatible film, said method comprising:

mixing at least one water soluble film former and at least one stabilizing agent to provide a film-forming mixture;

dissolving water-soluble ingredients in water to provide an aqueous solution;

combining said film-forming mixture and said aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

adding said oil mixture to said hydrated polymer gel and mixing to provide a uniform gel;

casting the uniform gel on a substrate; and

drying the cast gel to provide said film.

19. The method according to claim 18, wherein at least one surfactant is mixed into said oil mixture.

20. The method according to claim 18, wherein the total amount of said oils in said oil mixture is at least about 5 wt % of the total weight of ingredients in said method.

21. The method according to claim 20, wherein said total amount of oils is at least about 15 wt %.

22. The method according to claim 18, wherein said drying is conducted until said film has a moisture content of about 3 wt % to about 8 wt %.

23. The method according to claim 18, wherein, prior to being combined with said aqueous solution, said film-forming mixture is hydrated with water at a temperature of about 25 to about 50°C and subsequently chilled to a temperature of about 4 to about 30°C for about 2 to 48 hours.

24. The method according to claim 18, wherein said film-forming mixture is

a powder, which is directly combined with said aqueous solution.

25. The method according to claim 24, wherein said hydrated polymer gel is formed without heating.

26. The method according to claim 25, wherein said hydrated polymer gel is stirred at room temperature for about 2 to about 48 hours.

27. The method according to claim 26, wherein said oil mixture is prepared by mixing thymol and menthol in a flavor oil, and subsequently adding methyl salicylate and eucalyptol.

28. A non-self-adhering film produced according to the method of claim 18.

29. The method according to claim 18, wherein the water soluble film former is selected from the group consisting of pullulan, hydroxyproplymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof.

30. The method according to claim 29, wherein said water soluble polymer is pullulan.

31. A consumable film adapted to dissolve in the mouth of a consumer,

wherein said film comprises a single layer including pullulan and at least one pharmaceutical agent.

32. The consumable film according to claim 31, wherein said pharmaceutical agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory agents, anti-tussives, decongestants, anti-histamines, expectorants, anti-diaherrals, H_2 –antagonists, proton pump inhibitors, central nervous system agents, analgesics. and mixtures thereof.

33. The consumable film according to claim 32, wherein the antimicrobial agent is selected from the group consisting of triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA and mixtures thereof.

34. The consumable film according to claim 32, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of aspirin, acetaminophen, ibuprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and mixtures thereof.

35. The consumable film according to claim 32, wherein the anti-tussive is selected from the group consisting of benzonatate, caramiphen edisylate, dextromethorphan hydrobromide, chlophedianol hydrochloride and mixtures thereof.

36. The consumable film according to claim 32, wherein the decongestant is selected from the group consisting of pseudoephedrine hydrochloride, phenylepherine, phenylpropanolamine and mixtures thereof.

37. The consumable film according to claim 32, wherein the anti-histamine is selected from the group consisting of brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenhydramine citrate, diphenylpyraline hydrochloride, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride and mixtures thereof.

38. The consumable film according to claim 32, wherein the expectorant is selected from the group consisting of guaifenesin, ipecac, potassium iodide, terpin hydrate and mixtures thereof.

39. The consumable film according to claim 32, wherein the anti-diarrheal is loperamide.

40. The consumable film according to claim 32, wherein the H_2 –antagonist is selected from the group consisting of famotidine, ranitidine and mixtures thereof.

41. The consumable film according to claim 32, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, and mixtures thereof.

42. A method for delivering and enhancing the retention of an effective amount of an antimicrobial agent to the oral cavity comprising introducing in the oral cavity a rapidly dissolving film comprising pullulan and an antimicrobial agent comprising menthol and at least one of methyl salicylate, eucalyptol and thymol, wherein said pullulan enhances the retention of the antimicrobial agent in the oral

cavity.

43. The method according to claim 42, wherein the antimicrobial agent comprises menthol, methyl salicylate, eucalyptol and thymol.

44. The method according to claim 42, wherein the amount of pullulan in the film is from about 40 wt% to about 80 wt %.

45. The method according to claim 42, wherein the amount of antimicrobial agent in the film is from about 5 wt% to about 12 wt%.

46. The method according to claim 43, wherein the amount of antimicrobial agent in the film is from about 5 wt % to about 12 wt%.

47. A method for delivering and enhancing the retention of an effective amount of an antimicrobial agent to the oral cavity comprising introducing in the oral cavity the consumable film according to claim 9.

FIG-1

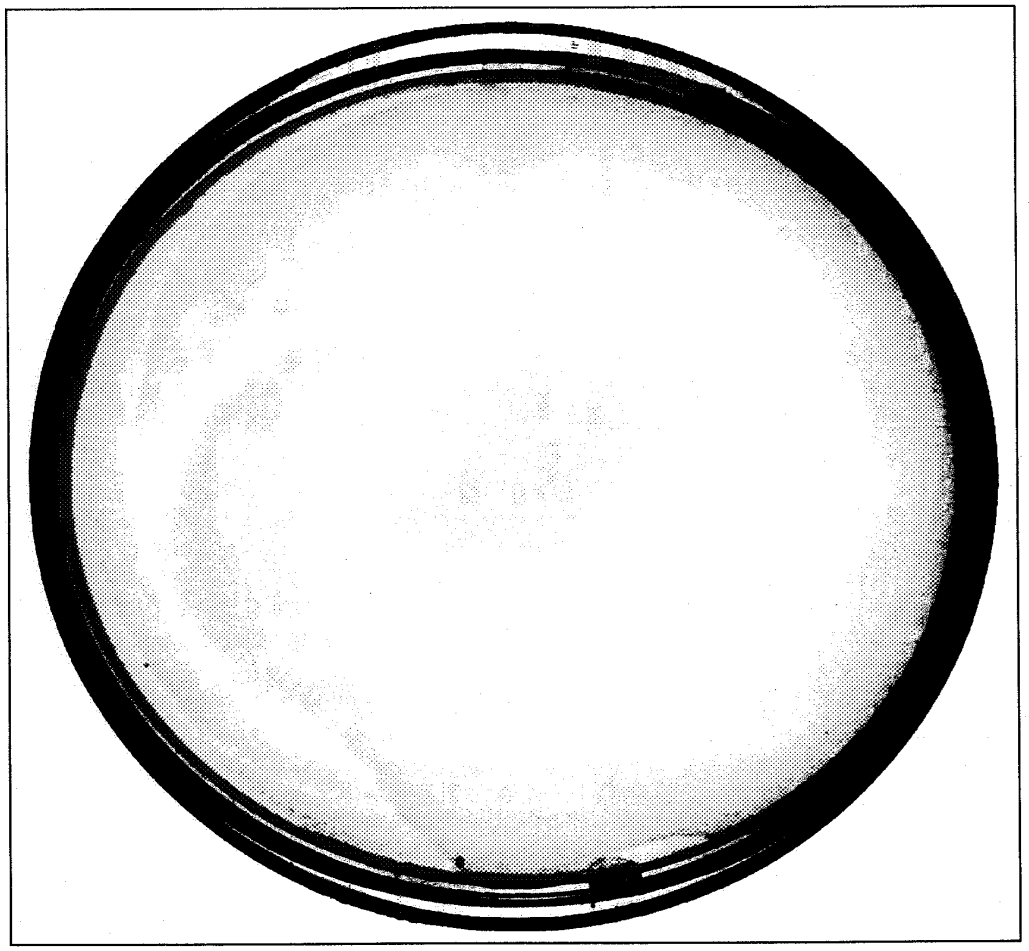
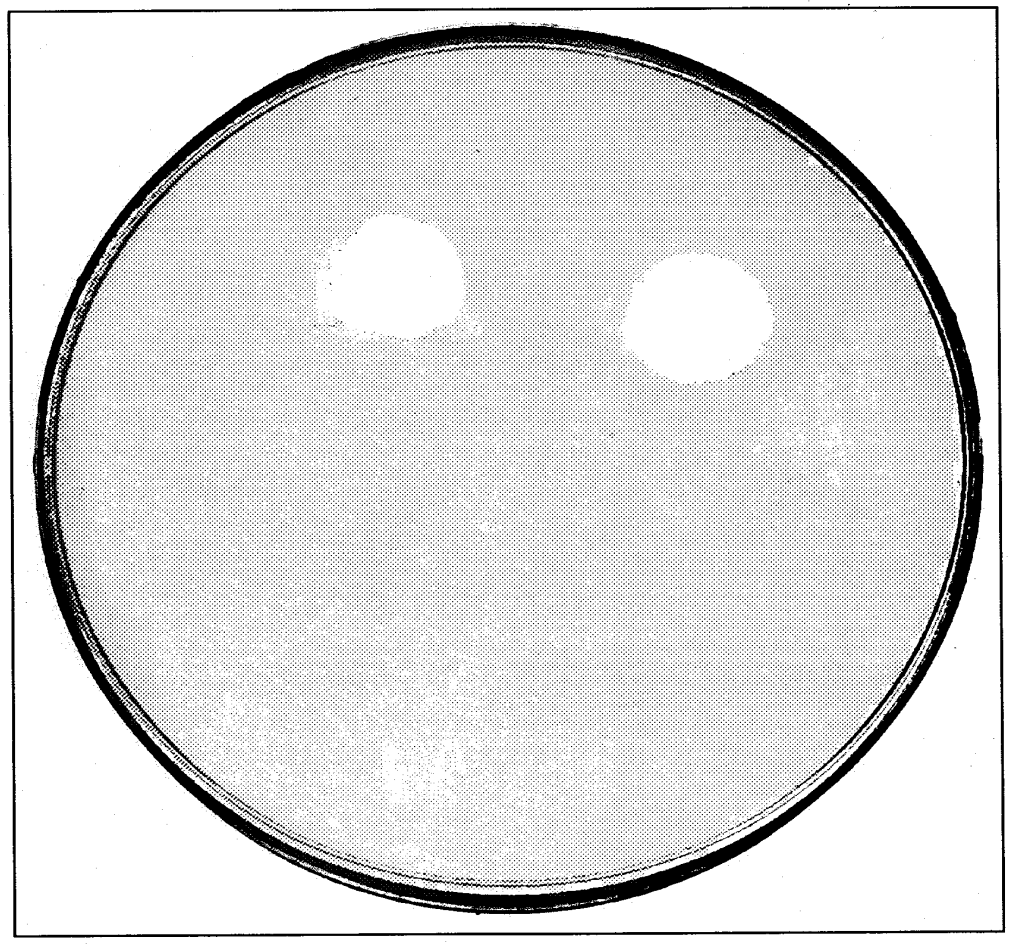


FIG-2



PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 9/70

A2

(11) International Publication Number: **WO 00/42992**

(43) International Publication Date: 27 July 2000 (27.07.00)

(21) International Application Number: PCT/US99/31327

(22) International Filing Date: 30 December 1999 (30.12.99)

(30) Priority Data:

60/116,823	21 January 1999 (21.01.99)	US
09/434,878	5 November 1999 (05.11.99)	US

(71) Applicant: LAVIPHARM LABORATORIES, INC. [US/US]; Suite 6, 131 Ethel Road West, Piscataway, NJ 08854 (US).

(72) Inventors: CHEN, Li–Lan, H.; 3906 Victory Court, Edison, NJ 08817 (US). PFISTER, William, R.; 16 Saxony Lane, Robbinsville, NJ 08691 (US). RENN, Donald, W.; 4 Brewster Point, Glen Cove, ME 04846–0088 (US). BURANA-CHOKPAISAN, Thitiwan; 4 Stout Court, Lawrenceville, NJ 08648 (US). OSBORNE, James; Lavipharm Laboratories, Inc., Suite 6, 131 Ethel Road West, Piscataway, NJ 08854 (US). TAN, Hock, Seng; 25 Jaime Court, Old Bridge, NJ 08857 (US). TAO, Li; Lavipharm Laboratories, Inc., Suite 6, 131 Ethel Road West, Piscataway, NJ 08854 (US).

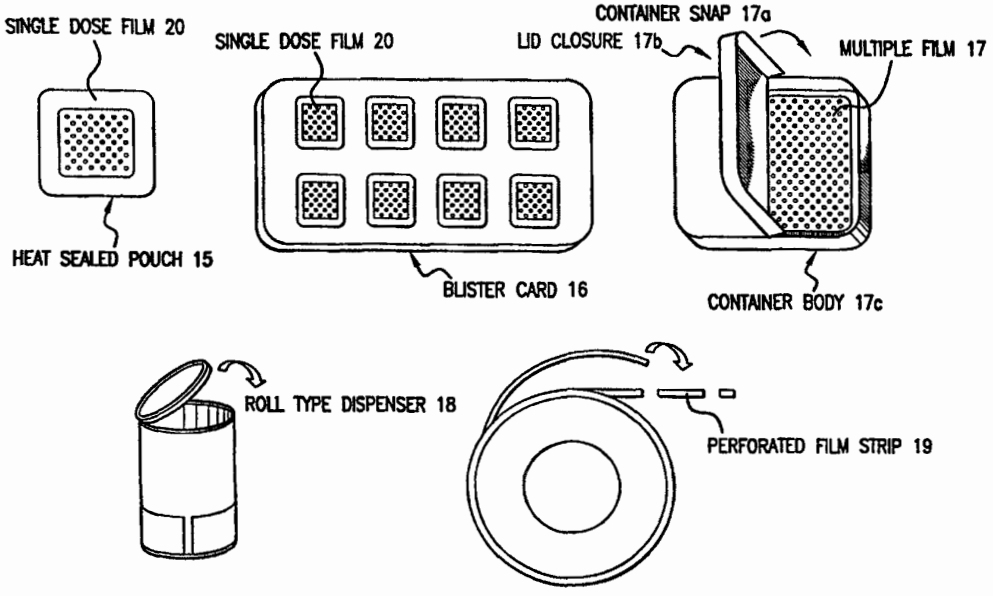
(74) Agent: STRIMPEL, Harriet, M.; Bromberg & Sunstein LLP, 125 Summer Street, Boston, MA 02110–1618 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: COMPOSITIONS AND METHODS FOR MUCOSAL DELIVERY



(57) Abstract

A dosage unit comprising a water–soluble hydrocolloid and a mucosal surface–coat–forming film, such film including an effective dose of active agent. In the dosage unit slidenafil citrate, nicotine, hydromorphone, oxybutynine or estradiol are used as active agents.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

COMPOSITIONS AND METHODS FOR MUCOSAL DELIVERY

Technical Description

The present invention is directed to a device and method for administering agents in a dissolving film configuration.

Background to the Invention

Many pharmaceutical dosage forms are administrated orally in the form of solid shaped articles such as tablets, pills, caplets and capsules that retain their shape under moderate pressure. Generally these dosage forms are designed to be swallowed whole or chewed to deliver the medication with adequate amounts of liquid. Some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Certain patients such as children or animals resist taking medication, and may try to hide a solid pill in order to spit it out later. In addition, many pediatric and geriatric patients are unwilling to take a solid dosage form because the active agent is difficult to swallow or is retained in the pharynx or gullet even when liquids are consumed with the dosage unit. Furthermore, the availability of liquids at the time of administering medications may be limited for certain patients and may be restricted for certain diseases and/or treatments. Chewable tablets provide some advantages over the conventional tablets. However, they are not suitable for children wearing braces and the taste of the medication may be unpleasant and difficult to mask in a chewable tablet. At the same time, water may be still required for the administration of chewable tablets.

In addition, the standard oral dosage forms, such as tablets, pills, caplets, and capsules, are designed for short residence time in the mouth. Absorption of the agent from these dosage forms occurs in the gastrointestinal (GI) tract, after the agent has separated from the dosage form and dissolved in the gastric fluids. For some active agents, it is desirable to achieve absorption through the oral mucosal tissues in order to accelerate onset of the therapeutic effect.

Many active agents are poorly absorbed, even after they are dispersed in the stomach, because of low solubility or slow dissolution rate in the gastric fluids. Tablets may be formulated so as to be quick dissolving. These tablets are commonly placed on the tongue and disintegrate rapidly in the oral cavity. However, these dosage units are

not fixed to a mucosal surface and may move around in the mouth. Consequently, they do not overcome a risk associated with choking or gagging that occurs with subjects having limited control of their swallowing reflexes. However, once placed in the mouth, these tablets dissolve rapidly in the saliva to provide a liquid formulation which is then swallowed. Quick dissolving tablets may be formed from a particulate support matrix containing the therapeutic agent, where the particulate support matrix is a protein (US 5,807,576, US 5,635,210, US 5,595,761). Alternatively, the tablet may be formed from a laminate with several layers and an outer coating (JP 100535518). Tablets have also been manufactured from shearform matrices which are substantially amorphous sugar formed when crystalline sugar is subjected to heat and shear (WO 95/07194; WO 95/35293). Other methods of forming quick dissolving tablets include wet granulation methods (EP 0627 218) and dry granulation methods (EP 0124027A1) and by freeze-drying techniques (EP 0084705A2). Generally, quick dissolving tablets are formed using complex multi-step manufacturing processes. In addition, these tablets may have poor mechanical strength, are fragile and friable and have insufficient holding capacity for active ingredients (US 5,720,974) and may be difficult to store and handle.

Therapeutic compounds are sometimes provided as powders or granules which may be difficult to swallow and cause unpleasant sensations in the mouth. Furthermore, many quick dissolving tablets contain particulates (>25 microns) which leave a "gritty" and unpleasant taste in the mouth. In the elderly, powders may cause choking and discomfort associated with trapping of granules in dentures. Powders and granules are generally packaged in a sealed pouch which requires tearing before use. This causes problems for geriatric patients and those suffering from arthritis in the fingers as well as for children. Consequently, problems of spillage of the contents arise in this group of patients. Furthermore, these oral preparations should be taken with water which for certain patients are inconvenient and may cause reduced patient compliance.

Liquid, syrups or suspensions are an alternative to solid dosage forms and are considered desirable for pediatric and geriatric patients who have problems in swallowing tablets. However, these dosage forms are often difficult to measure accurately and administer easily. Liquid formulations deteriorate rapidly upon exposure to heat or atmosphere and consequently have a relatively short shelf life. Furthermore, liquid formulations require a relatively large volume and are bulky to store.

In addition to solid and liquid dosage forms, rapidly dissolving buccal/oral delivery systems have been developed. These systems are commonly freeze dried preparations which are more expensive to manufacture as compared to tablets (US 5,648,093). Furthermore, freeze dried preparations are brittle and fragile when handled and must be kept in dry conditions to avoid disintegration. The instability of freeze-dried preparations has been reduced somewhat by the addition of mannitol (US 4,946,684). WO 9820862 reports a film that is formed according to a method that does not utilize freeze drying and avoids problems described in the art such as rigidity of the films, delayed softening and poor solubility in the mouth (US 4,876,092; EP 0200508; EPO 381194; CA-PS 1-26331; DE 2449865.5; DE 3630603; EP 0452446 and EP 0219762). However, the film described in WO 9820862 relies on the use of at least two different non-ionic surfactants to achieve immediate wettability.

It is desirable that a dosage unit should provide a non-invasive, effective and economic means to deliver an active agent to the target site. Where the target site is the plasma, additional issues arise concerning the rate of delivery of the active agent to that site as measured by bioavailability. For many types of active agent, fast onset of the therapeutic effect is desirable. Traditional oral dosages, such as tablets, are limited in onset time by the rate of absorption in the gastro-intestinal tract. Formulations have been developed which, when applied in the mouth, lead to faster onset that the traditional oral dosages because they target the oral mucosa. These formulations include dosage units containing 75%-90% polyethylene glycol that melt at body temperature, in the mouth.(US 5,004,601 and 5,135,752) Other formulations include liquid forms, lozenges or tablets that are administered sublingually or by a sweetened matrix on a stick. (US 5,770,606, Streisand et al. and Zhang et al., Christie et al., Sasaki et al.). Whereas the above references address the delivery route, they do not address the problems of bioavailability that arise from poor solubility or low dissolution rate.

A delivery device that addresses the above limitations would represent a desirable improvement on existing delivery systems.

Summary of the Invention

A novel dosage unit and its method of manufacture and use is provided. In an embodiment, the dosage unit includes a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an active agent.

In an embodiment of the invention, the hydrocolloid includes a polymer selected from the group consisting of a natural, semi-natural and synthetic biopolymer being exemplified by a polysaccharide and a polypeptide. In addition to the hydrocolloid, the film may further include one or more of an emulsifier, a plasticizer, a taste modifying agent, a water soluble inert filler, a preservative, a buffering agent, a coloring agent, a permeation enhancer, and a stabilizer. The film may further include an active agent selected from the group consisting of a therapeutic agent, a dietary supplement and a hygiene aid. Embodiments of the invention utilize effective amounts of sildenafil citrate, nicotine, hydromorphone , oxybutynine or estradiol as active agents in the dosage unit. The active agent may be encapsulated within a second polymer having dissolution properties that are different from those of the hydrocolloid. More than one active agent may be included in the film. In an embodiment of the invention, the emulsifier may have a concentration of 0.1-10%w. The water inert filler may include a concentration range of 0.5-50% and the preservative may include a concentration range of 0.01-10%. A mucosal adhesion enhancer such as starch graft copolymer may be included in the dosage unit.

In embodiments of the invention, the dosage unit may further include any of the following features: a dry film thickness in the range of 1-20 mil, more particularly less than 10 mils, a dry tack value of less than 3.5g, more particular less than 2 g, a wet tack value of greater than 35g, a tensile strength greater than 1500psi, a modulus in the range of 35,000-300,000 psi, a tear propagation resistance in the range 0.001N-1N, a disintegration time in a range from 1-300 seconds, a dissolution time in a range from 10-600 seconds, and a percentage elongation less than 20%.

In embodiments of the invention, methods are provided for making a dosage unit, that include in one embodiment, dissolving a hydrocolloid in a solvent so as to form a substantially homogeneous preparation; adding to the hydrocolloid preparation, an active agent and at least one reagent selected from the group consisting of an emulsifier, a plasticizer, a taste modifier, a water soluble inert filler, a coloring agent, a preservative, a permeation enhancer, a stabilizer and a buffering agent to form a coatable mixture; and forming a mucosal surface-coat forming film from the mixture for packaging as a dosage unit. The method may further include the step of coating the mixture onto a backing film. In a further embodiment, the reagents including: a hydrocolloid, an active agent,

and at least one reagent selected from the group consisting of an emulsifier, a plasticizer, a taste modifier, a water soluble inert filler, a coloring agent, a preservative, a permeation enhancer, a stabilizer, and a buffering agent, may be combined in any order in a vessel having a heating source and a mechanical mixing device, the combined ingredients being mixed during and after the addition of the ingredients to the vessel, an effective amount of heat being applied for melting a substantial portion of the mixture. The mixture may then be formed into a film in a dry extrusion process.

In an embodiment of the invention, a method is provided for administering an active agent to a subject, that includes obtaining a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an active agent; and placing the film on a mucosal surface coat forming film in the subject; so as to release the active agent.

In a further embodiment of the invention, a dosage unit is provided that includes a water soluble hydrocolloid and an effective dose of sildenafil citrate in a mucosal-surface contacting film. More particularly, an effective dose of sildenafil citrate is formed into a solid dispersion with xylitol for treating erectile dysfunction. The sildenafil/xylitol dispersion may be mixed with at least one reagent selected from the group consisting of an emulsifier, a plasticizer, a taste modifier, a coloring agent, a preservative, a permeation enhancer, a stabilizer and a buffering agent. The solid dispersion of sildenafil and xylitol may arise at a ratio of 9 parts sildenafil to one part xylitol. According to embodiments of the invention directed to a dosage unit and method of making a dosage unit suitable for erectile dysfunction, the water solubility of sildenafil in the solid dispersion is at least 20 mg/ml, more particularly about 50mg/ml. More particularly, the film may be capable of completely dissolution at the oral mucosal surface within 10-600 seconds.

Brief Description of the Figures

Figure 1 shows possible application sites in the oral cavity for the inventive dosage unit. (**1**) is the upper lip; (**2**) is the gingiva; (**3**) is the hard palate; (**4**) is the cheek; (**5**) is the lingual; (**6**) is the sublingual; (**7**) is the lower lip.

Figure 2 illustrates one manufacturing process for the dosage unit. (**8**) is the

mixing and degassing tank; (**9**) is the coating slot with thickness controller; (**10**) is the polyester backing belt; (**11**) is the drying oven with aeration controller; (**12**) is the intraoral film; (**13**) is the die cutting and (**14**) is the intraoral unit dose.

Figure 3 shows examples of packaging and dispensing devices for the intraoral delivery system. (**15**) is a heat sealed single pouch; (**16**) is a multi-unit blister card; (**17**) is a multi-unit dispensing pack, **17(a)** the container snap and **17(b)** the lid closure; (**18**) is a multi-unit roll-type dispenser cylinder; (**19**) is a perforated film strip; and (**20**) is a single dose film.

Figure 4 demonstrates the disintegration and dissolution time of the intraoral delivery system as a function of thickness.-- • -- is disintegration time and -- ○ -- is dissolving time.

Figure 5 shows the release profiles of -- ▾ -- nicotine, -- ▽ -- oxybutynin, -- • -- hydromorphone and -- ○ -- estradiol.

Figure 6 shows the pharmacokinetics in six subjects after administration of a dissolving film sildenafil formulation and after administration of the commercial tablet containing the same dosage of sildenafil. Sildenafil film -- ○ -- Viagra -- ▽ --.

Detailed Description of Invention

Delivery of active agents in solid form via the mouth causes problems to patients who may choke on the dosage unit. This effect is caused at least in part by the mobility of the dosage unit within the mouth. We have developed a new class of dosage units which are not mobile in the mouth because on contact with the moist mucosal surface, the film becomes a coating that adheres to the mucosal surface and then disintegrates and dissolves over a time frame controlled in the design of the dosage. The dosage unit, in an embodiment of the invention, is in the form of a flexible, non-tacky, dry conveniently packaged film. Once removed from the package and placed on a mucosal surface, the mucosal surface-coat-forming film hydrates substantially immediately to form a coating on the moist surface of the mucous membrane and then disintegrates and dissolves to release the active agent from the film.

The dosage unit may release the active agent over a period of time that is determined by a number of different factors. These factors include the dimensions of the

film, the concentration of the active agent, the solubility of the agent at the mucosal surface and how the agent is dispersed throughout the film. The thickness of the film is a factor in determining the rate of dissolution. A thick film will dissolve more slowly than an otherwise similar thin film. A thick film may be desirable for its holding capacity for active agents that are required in high dosages. Although the surface area of a film can be adjusted up to about 5 square centimeters, increased thickness may also be desirable for purposes of achieving effective active agent dosages. The active agent can form a solid dispersion with a water soluble inert filler for purposes of increasing the solubility of the agent when released from the film thereby enhancing bioavailability of the active agent. This is exemplified here by sildenafil which is incorporated in a film with a water soluble inert filler, for example, xylitol, which has been found here to enhance the bioavailability of this agent. Solubilizing agents that are well known in the art may be included in the film. The extent of uptake of the active agent from the dosage unit at the mucosal surface can be controlled by the dissolution rate of the film. A dissolving film will release the active agent and this in turn will cause the active agent to be swallowed and taken up in the GI tract. In contrast, slow release of the active agent at the mucosal surface will give rise to increased uptake by the mucosal surface. A further parameter governing the release of an active agent at the mucosal surface is the manner in which the agent is dispersed in the film. For example, the agent may be dispersed as colloidal particles or microencapsulated within the film or alternatively may be mixed throughout the film as a reagent during casting.

The dosage unit of the invention may be used as a vehicle for delivering a wide range of active agents. For example, the active agent may be a small molecule, a protein, a nucleic acid including antisense molecules or other biological or synthetic molecules.

The term "mucosal surface-coat-forming" as applied to a film as used in this description and in the following claims unless specified otherwise , means a film that coats the mucosal surface on contact, and may not thereafter be manually recovered or moved from the contact site; and subsequently disintegrates and dissolves so as to release the active agent. It should be noted that for purposes of the description of the invention and the claims,

"mucosal surface" refers to any moist surface of the body. This includes the surfaces identified in Figure 1. It further includes a wound surface where lymph fluid bathes the

tissue surface.

Embodiments of the present invention include a process, composition and method of use for a quick dissolving film for local and systemic delivery of pharmaceutical agents to a mucosal surface in a subject. In the following text, specific reference may be made to the oral cavity by way of example. However, it is not intended to limit the scope of the invention to the oral cavity. The dosage unit of the invention may be applied to any mucosal surface as deemed appropriate for the systemic or local delivery of an active agent including vaginal, rectal, and ocular surfaces. For purposes of oral delivery, the films may be applied on lingual, sub-lingual, buccal, gingival, and palatal surfaces (Figure 1).

For vaginal delivery of such agents as contraceptive agents including nonoxynol or anti-infectives including antifungal agents, antibacterial agents and anti-viral agents, or fragrant or hygiene agents; the film should be non-sticky when removed from the packaging but should have mucoadhesive properties when applied in the vagina. Although films containing active agents for use in the vagina have been used, they appear to have some significant drawbacks most particularly the lack of adhesive properties at the mucosal surface. This makes these films impractical to administer. (US 5,380,529; 5,595,980 and 5,529,782).

Embodiments of the invention provide improved dosage forms to deliver active agents that are appropriate for all age groups and that physician, parents, patients and family members can administer easily. These dosage forms are economical to prepare and have an extended shelf life. They are easy to handle and non-tacky before administration so as to avoid disintegration prior to use and are conveniently packaged for shelf life, ease of storage and distribution. The dosage form may be administered to the subject by placing the film on a mucous surface, at which time the film becomes a mucoadhesive coating, characterized by the property that it can no longer exist in an independent form and is subsequently dispersed in solution.

Embodiments of the invention provide a delivery system for active agents and other active agents that will dissolve and completely release their contents on a moist mucosal surface -for example in the oral cavity. The release of the active agent occurs without mastication or the need for intake of water. With particular reference to the oral cavity, an embodiment of the invention provides active agents that remain in the oral

cavity for treatment or modification of the oral environment; for example, for periodontal disease treatment or breath-odor control. Furthermore, embodiments of the invention further provide improvements that include: improved organoleptic properties (smell and taste), and texture and feel of dosage forms intended to be placed in the oral cavity; a dosage form which "melts" in the mouth and leaves a smooth pleasant after feel following dissolution; and a prolonged retention of the active agent in the mouth following dissolution of the quick dissolving dosage form to extend the residence time of the active agent cleared from the mouth by the production of saliva and subsequent swallowing. Depending on the optimal program for a specific application of the invention, the disintegration time and the dissolution time can be controlled within a prescribed range by adjustment of the formulation and the thickness of the film. In some cases, it is desirable for release of the active agent to occur after dissolution of the film. For these applications, the active agent may be encapsulated in a material with dissolution properties that are different from those of the hydrocolloid. Encapsulation of the active agent also may be utilized to achieve masking of taste for active agents that are bitter. In some cases, two or more different active agents may be included in the film. An example where multiple active agents frequently are administered is cold medications, which often contain several active agents.

"Coating solution" is defined here and in the claims as a viscous and homogeneous mixture of hydrocolloids, active agents and other additives in a solvent. The coating solution is treated according to the method of the invention to form a film.

"Subject" is defined here and in the claims as a human or animal species.

"Thickness" is defined here and in the claims by measurements in mil (a mil = one thousandth of an inch) determined when a film is placed between two microscopic slides.

"Permeation enhancer" as defined here and in the claims is a natural or synthetic molecule which facilitates the absorption of an active agent through a mucosal surface.

"Enzyme inhibitor" as defined here and in the claims is a natural or synthetic molecule which inhibits enzymatic metabolism of an active agent in the saliva or in a mucosal tissue.

"Water Content" is defined here and in the claims as % residual water content per unit dose as measured according to the Karl Fisher method and expressed as percent of

the dry weight of the film.

"The hydration rate" is defined here and in the claims as the speed of absorbing water at 25°C. and 75% relative humidity in 24 hours.

"Percentage of swelling" is defined here as a percentage of the initial volume that is increased before dissolving. In an embodiment of the invention, the percentage of swelling is less than 10% in 60 seconds.

Taste modifying agents include flavoring agents, sweetening agents and taste masking agents and are exemplified by: the essential oils or water soluble extracts of menthol, wintergreen, peppermint, sweet mint, spearmint, vanillin, cherry, chocolate, cinnamon, clove, lemon, orange, raspberry, rose, spice, violet, herbal, fruit, strawberry, grape, pineapple, peach, kiwi, papaya, mango, coconut, apple, coffee, plum, watermelon, nuts, durean, green tea, grapefruit, banana, butter, camomile, sugar, dextrose, lactose, mannitol, sucrose, xylitol, malitol, acesulfame potassium, talin, glycyrrhizin, sucralose, aspartame, saccharin, sodium saccharin, sodium cyclamate and honey.

Emulsifying agents include solubilizers and wetting agents and are exemplified by polyvinyl alcohol, sorbitan esters, cyclodextrins, benzyl benzoate, glyceryl monostearate, polyoxyethylene alkyl ethers, polyoxyethylene stearates, poloxamer, polyoxyethylene castor oil derivatives, hydrogenated vegetable oils, bile salts, polysorbates and ethanol.

Plasticizers may include glycerin, sorbitol, propylene glycol, polyethylene glycol, triacetin, triethyl citrate (TEC), acetyl triethyl citrate (ATEC) and other citrate esters.

Active agents (for human and veterinary applications) include therapeutic agents, nutritional supplements and hygiene aids. The therapeutic agents are exemplified by analgesics, a-adrenergic receptor blockers, anti-Alzheimer's disease medication, antianginal, antianxiety, antiarrythmics, antiarthritics, antibiotics, anticoagulants/thrombolytics, anticonvulsants/anti-Parkinson medication, anti-depressants, anti-diabetics, anti-diarrheal, anti-epileptics, anti-fungal, anti-gout, anti-heartworm medication for dogs, anti-histamines, anti-hypertensives, anti-inflammatories, anti-infectives, antimigraines, anti-nasuants/anti-emetics, anti-neoplastics/anti-tumor active agents, anti-pruitics, anti-psychotics, anti-pyretics, anti-spasmodics, anti-virals, bronchial dilators/anti-asthmatics, calcium antagonists, cardiac agents, cardiotonics, central nervous system actives, contraceptives, coronary vasodilators, cough/cold

remedies, dietary supplements, including vitamins and minerals, diuretics, fertility active agents, flea control agents for animals (Ivermectin), H_2 receptor antagonists, herbal actives, hormones, hypoglycemics, hypolipidemics, muscle relaxants, ovulation stimulators, peptide active agents, polypeptide active agents, proteins such as insulin, calcitonin, LHRH and the like. Sedatives and hypnotics, sexual dysfunction active agents, sleep aids, smoking cessation aids, steroids and steroidals, tranquilizers, laxatives, ophthalmic preparations, nutritional supplements, breath fresheners, breath deodorants, saliva substitutes, antigingivitis agents, anti-cavity agents, anti-plaque agents, diagnostic indicators, and local anesthetics. Also included are active agents for treatment of osteoporosis, hormone replacement, treatment of periodontal disease, antiseptics, corticosteroids, non steroidal anti-inflammatory agents, antiviral agents and vaccines.

Water soluble inert fillers include mannitol, xylitol, sucrose, lactose, maltodextrin, dextran, dextrin, modified starches, dextrose, sorbitol, and dextrates. The water soluble inert fillers may be used in embodiments of the invention as inert carriers to form a high water soluble dispersion with active agents.

Buffering agents include acidulants and alkalizing agents exemplified by citric acid, fumaric acid, lactic acid, tartaric acid, malic acid, as well as sodium citrate, sodium bicarbonate and carbonate, sodium or potassium phosphate and magnesium oxide.

Coloring agents may include FD & C coloring agents, natural coloring agents, and natural juice concentrates, pigments such as titanium oxide, silicon dioxide and zinc oxide.

Stabilizers as used here and in the claims, include anti-oxidants, chelating agents, and enzyme inhibitors as exemplified by ascorbic acid, vitamin E, butylated hyroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate, dilauryl thiodipropionate, thiodipropionic acid, gum guaiac, citric acid, edetic acid and its salts and glutathione.

Preservatives which here include anti-microbial agents and non-organic compounds are exemplified by sodium benzoate, parabens and derivatives, sorbic acid and its salts, propionic acids and its salts, sulfur dioxide and sulfites, acetic acid and acetates, nitrites and nitrates.

The mechanical properties of the film is determined by tensile strength modulus,

percent elongation (ASTM D882, standard test method for tensile properties of thin plastic sheet) and tear propagation resistance (ASTM D1938, standard test method for tear propagation resistance of plastic film and thin sheet by single tear method). The mechanical properties are measured here using standard protocols as described in Annual Book of ASTM Standards, American National Standards Institute, NY 1995.

The "tensile strength" (psi) is the property of film that requires a load to cause load deformation failure of film.

The "% elongation" is measured when the film snaps as sufficient force is applied so as to exceed the elastic limit.

The "release study" is the percentage of active agents released from the film as a function of time in a suitable dissolution vessel and medium under specified conditions of temperature and pH.

"Dry tack" is quantitative values for tackiness (grams) of dry film by Texture Analyzers (Model TA.XT2i with 6mm diameter stainless steel cylinder probe) from Texture Technologies Corp. The tackiness after the addition of 10 ml of water on the same surface area is defined as the wet tack (gram) to simulate the adhesion of film upon the contact with a moist mucosal surface. In an embodiment of the invention, the dry tack ranges from 0.2-3.5grams, with a preferred range of 0.4-2.0grams and the wet tack is in the range of 35-150 grams with a preferred range of 40-100 grams.

"Tear propagation resistance" is defined here and in the claims as the average force (N) necessary to propagate a tear across a film or sheet under a specified rate of extension as defined in ASTM D1938 and is interpreted from the load time chart. In a preferred embodiment of the invention, the tear resistance ranges from 0.001N-1N with a preferred range of 0.01-1N.

"Disintegration time" is defined here and in the claims as the time (second) at which a film breaks when brought into contact with water or saliva. In an embodiment of the invention, the disintegration time ranges from 1-300 seconds.

"Dissolving time" is defined here and in the claims as the time (seconds or minutes) at which not less than 80% of the tested film is dissolved in an aqueous media or saliva. In an embodiment of the invention, the dissolution time ranges from 10-600 seconds.

"Modulus" is a measurement of stiffness of a film.

A factor that plays a significant role in determining the properties of mucosal surface-coat-forming composition is the viscosity of the hydrocolloid. The viscosity of the hydrocolloid depends on its molecular size, derivation, hydrophobicity and hydrophilicity and the presence of other additives in the formulation. A comparison of films formed from the hydrocolloid, hydroxymethylcellulose, having different viscosity values is shown in Table 9a and 9b.

In embodiments of the invention, a hydrocolloid concentration in the range of 5-99% of the dry weight of the films is provided, more particularly greater than 10%. These films have dry tack and wet tack properties that improve ease of handling and use. The low dry tack properties of the film provide for a physically attractive and easily handled film that is neither fragile nor sticky and can be easily removed from packaging and placed on a mucosal surface. The wet tack properties of the film provide the advantage of stickiness of the moistened film such that when the film is placed on the mucosa, it remains attached at that site until it dissolves. In contrast, if the wet tack is too low, the film can move in the mouth and may be swallowed before dissolving and possibly give rise to choking. Furthermore, the low moisture content and low dry tack of the film enhances the shelf-life of the film and the flexibility of the dosage forms. These properties render the films suitable for easy making, packaging, handling and application.

In an embodiment of the invention, a water soluble polymer (2% polymer solution) is selected having a gelation temperature greater than 70°C. The hydration rate of a hydrocolloid having these features is rapid with a percentage moisture absorption of polymers in the range of 5-20% at 75% humidity at room temperature. The hydration rate is selected according to the desired wettability of the film thereby obviating the need for surfactants. The wet tack of the hydrated film ranges from 35-150 grams more particularly 40-100 grams. The percentage swelling may be less than 10% within 60 seconds. The film is cast so as to have a thickness of 1-20mil. The water content of the film ranges from 0.5-10% with a preferred range of 1-5%. In embodiments of the invention, the film may be formed using a mixture of two or more types of the same hydrocolloid that differ only in molecular weights and/or different degrees of substitution. The time of dissolution of the film is in the range of 10-600seconds, (see Figure 4), the time of disintegration of the film may be 1-300 seconds. The active agent

in the film may be encapsulated in a polymer having different chemical or physical properties from the hydrocolloid of the film and having dissolution properties different from those of the hydrocolloid. Examples of the films formed according to the invention having properties that fall into the above ranges are provided in Table 1,3,6 and 7.

The ease of handling is characterized by the dry tack of the film and the flexibility is reflected by the tensile strength, modulus, % elongation and tear resistance of the film. For example, the dry tack is in the range of 0.2-3.5 grams more particularly 0.4-2.0 grams. The tensile strength may be in the range of 1500-10,000 psi, more particularly 2000-8000, more particularly greater than 2000psi, the modulus is in the range of 35,000 -300,000 and the % elongation is less than 20% more particularly 1-10% for a film having a thickness of 2 mil.

In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling (at room temperature) natural polysaccharide or derivatives including pectin and derivatives, guar gum arabic, tragacanth gum, xanthan gum, gellan sodium salt, propyleneglycol alginate, starches (amylose, amylopectin), modified starches, hydroxyethyl starch, pullulan, carboxymethyl starch, gum ghatti, okra gum, karaya gum, dextrans, dextrins and maltodextrins, konjac, acemannan from *aloe*, locust bean gum, tara gum, quince seed gum, fenugreek seed gum, scleroglucan, gum arabic, psyllium seed gum, tamarind gum, oat gum, quince seed gum, carrageenans, scleraglucan, succinoglucan, larch arabinogalactan, flaxseed gum, chondroitin sulfates, hyaluronic acid, curdlan, chitosan, deacetylated konjac, and *rhizobium* gum.

In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling polypeptide or protein exemplified by gelatins, albumins, milk proteins, soy protein, and whey proteins. The hydrocolloid may further be selected from a group of synthetic hydrocolloids exemplified by any of the following: polyethylene-imine, hydroxyethyl cellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, polyacrylic acids, low molecular weight polyacrylamides and their sodium salts (carbomers), polyvinylpyrollidone, polyethylene glycols, polyethylene oxides, polyvinyl alcohols, pluronics, tetronics, and other block co-polymers, carboxyvinyl polymers, and colloidal silicon dioxide. A preferred embodiment of the invention

utilizes a hydroxypropyl methyl cellulose having a methoxy content of about 19-30% and hydroxypropyl content of 7-12% and a molecular weight of approximately 50,000 - 250,000 daltons (Table 9).

In addition to hydrocolloids and the active agents, the films may contain any or all of the following ingredients: emulsifying agents, solubilizing agents, wetting agents, taste modifying agents, plasticizers, active agents, water soluble inert fillers, preservatives, buffering agents, coloring agents, and stabilizers. In a preferred embodiment, the percentage dry weight concentration of at least single ingredients incorporated in a film in each of the following categories is as follows: emulsifying agent (0.1%-10%), plasticizer (0.5-20%), active agents (0.01-75%), taste modifying agents (0.1-10%), coloring agents (0.01-5%), water soluble inert fillers (0.5-50%), preservatives (0.01-10%), buffering agents (0.1-10%) and stabilizers (0.01-5%).

Methods for manufacturing the dosage unit of the invention include the solvent casting methods as shown in Figure 2 or alternatively extrusion methods as exemplified in Example 11. The extrusion method involves blending ingredients to form a film using mechanical force and moderate heat. Significantly, the above processes do not rely on a freeze drying step. Nor do the above processes rely on extremes of heat or cold during manufacture.

In an embodiment of the invention, the solvent casting method includes a natural or synthetic hydrocolloid that is completely dissolved or dispersed in water or in a water alcoholic solution under mixing to form a homogenous formulation. In addition to the active agent and the hydrocolloid, any of the ingredients listed above may be added and dispersed or dissolved uniformly in the hydrocolloid solution. The active ingredients and flavoring agents can be incorporated before or after film forming. This homogeneous mixture (coating solution) with a solid content of 5-50% and a viscosity of 500-15000cps was degassed (**8**) and coated on the non-siliconized side of a polyester film (**10**) at 5-50mil wet film thickness (**9**), more preferably 5-20mil wet film thickness and dried under aeration at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation (**11**). The manufacturing process for forming the dosage unit is illustrated in Figure 2. The dry film formed by this process is a glossy, stand alone, self supporting, non-tacky and flexible film (**12**). The dry film is

then cut into a suitable shape (**13**) and surface area for active agent delivery at the preferred site. For example, the cast film can be die-cut into different shapes and sizes using a rotary die. The film may be cut into a size that contains for example, a single dosage unit. For example, a dosage unit may include a film size with surface area of $5cm^2$ that contains a dosage of active agent in the range of 20-250 mg (**14**). The size of the film may be varied according to the dosage required. The dosage contained in each square centimeter is selected according to the active agent. Films are then packaged into a single pouch package, multi-unit blister card or multiple unit dispensers (Figure 3).

In contrast to the above method, the dry extrusion method does not rely on placing the hydrocolloid in a solvent. Instead, the ingredients of the dosage unit are mixed together in dry form and heated. The heated blend is then forced through an extrusion die to form a film of selected thickness. The film can then be cut and packaged.

The dry extrusion method has a number of advantages. First, it is an economical process. Second, because there is no drying oven, extrusion of the film is faster than solvent coating. Third, the dry extrusion avoids the step of removing residual solvent. Some residual solvent is generally present in the solvent coating process and can affect the safety or stability of the film. Where a film requires an organic solvent rather than water, removal of the solvent from the film may be required by environmental regulations. The extrusion process avoids any need for recovering solvent and avoids residual solvent in the film.

The dosage unit may be prepared for use by selecting a film that is capable of delivering an effective dose and administering the film to the patient by placing it on a mucosal surface such as the oral mucosa (Figure 1) where it dissolves in the body fluid for example, saliva (0.5-10 minutes) and is swallowed in liquid form. Figure 4 graphically represents the rate of disintegration and dissolution for different thickness films. Figure 5 shows the release profile of four active agents from films according to Examples 5-8. The fraction of the dose absorbed through the mucosal tissue can be facilitated by the use of a permeation enhancer into the film.

The overall bioavailability of the active agent which is absorbed both locally at the mucous membrane and systemically within the gastrointestinal system is improved

compared to the same dose of the active agent given in a conventional oral tablet or capsule dosage form. This is exemplified in Figure 6 and Table 11 which show the improved bioavailability of Sildenafil film over Viagra. The oral retention characteristics, mouth feel properties, flavor and taste of the film can be modified based on the hydrocolloid and other excipients used to prepare the films and the medications.

The invention is illustrated but not meant to be limited to the examples provided below. According to Examples 1-8, the hydrocolloid was dissolved in water under agitated mixing to form a uniform and viscous solution. Additional ingredients were then added sequentially to the viscous solution such as peppermint, aspartame, propyl glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid. The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed. The viscosity, pH and specific gravity were measured. The formulation was then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes. A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying. The dry film was cut into different shapes for measurement of dry tack, wet tack, tensile strength modulus, elongation, tear resistance, residual water content, disintegration and dissolution. The dosage form was 25-250 mg in various shapes, sizes, and thickness.

Example 9 shows how the properties of dosage units vary when different hydroxymethylcellulose polymers are utilized. Example 10 shows how mucoadhesion can be increased up to at least 84% using an enhancer exemplified by starch graft copolymer. In vivo studies of the dosage unit show that it is well tolerated by patients (Example 12) and shows enhanced bioavailability (Example 13).

Examples

Examples 1-3: Quick dissolving films, compositions and associated properties

The films were prepared as follows: a homogeneous mixture of ingredients was prepared in a coating solution in the amounts indicated in Table 1. The amounts are given as percentage weight of coating solution. The mixture was degassed in a vacuum chamber and coated on the non-siliconized side of a polyester film and dried in a hot air circulating oven to form a self supporting non-tacky and flexible film. The film was then cut into dosage units ready for packaging.

Table 1: Formulation of quick dissolving films using several different hydrocolloids.

Composition: coating solution %	Ex. 1	Ex. 2	Ex. 3
Pullalan (P-20) w%		17.5	
Methocel E5 w%	21.06		
POLYOX WSR N-10 w%			1.8
PVA (Vinol 125) w%		1.5	
Cellulose gum w%			8.1
Propylene glycol w%	1.0		2.5
Aspartame w%	0.8	0.475	0.46
Peppermint w%	1.0	1.0	0.6
Citric acid w%	0.7	0.8	
Cremphor EL40 w%	1.0	1.0	
Benzoic acid w%	0.013	0.1	0.01
FD&C blue #1 w%	qs.		
FD&C yellow #5 w%	qs.		
Ethanol w%		10.6	
Water w%	74.42	67.025	85.6

Table 2: Properties of the film formed from the coating solution of Table 1.

Properties of dry film	Ex. 1	Ex. 2	Ex. 3
Thickness (mil)	2.1	2.5	2.6
Water content %	1.7	8.5	8.0
Dry tack (g)	0.67	0.55	0.60
Wet tack (g)	60.16	86.64	72.27
Tensile strength (psi)	5242	2381	2036
% Elongation (sec)	2.9	4	2.9

Modulus (psi)	266834	272502	44566
Tear resistance (N)	0.02	0.16	0.01
Disintegration (sec)	12	20	12
Dissolving time (sec)	41	60	39

Table 3: Dry weight percentages for components of Example 1 according to Tables 1 and 2.

Ingredients	**Percentage (w/w)**
Methocel E5	82.35
Propylene glycol	3.91
Aspartame	3.13
Citric acid	2.74
Peppermint oil	3.91
PEG-40 Hydrogenated castor oil	3.91
Benzoic acid	0.5
FD&C blue #1	qs.
FD&C yellow #5	qs.