AO 120 (Rev. 3/04)

| TO: | REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK |
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In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Delaware on the following X Patents or Trademarks:

| DOCKET NO. | DATE FILED | U.S. DISTRICT COURT |
|---|---|---|
| 13cv1461-RGA | 8/20/2013 | DISTRICT OF DELAWARE |

| PLAINTIFF | DEFENDANT |
|---|---|
| Reckitt Benckiser Pharmaceuticals Inc., et al. | Par Pharmaceutical Inc., et al. |

| | PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
|---|---|---|---|
| 1 | 8,475,832 | 7/2/2013 | RB Pharmaceuticals Limited |
| 2 | 8,017,150 | 9/13/2011 | MonoSol RX LLC |
| 3 | 8,603,514 | 12/10/2013 | MonoSol RX LLC |
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

| DATE INCLUDED | INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading | |
|---|---|---|
| PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
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In the above—entitled case, the following decision has been rendered or judgement issued:

| DECISION/JUDGEMENT |
|---|
| See attached Order |

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| JOHN A. CERINO, CLERK OF COURT | | 5/28/2014 |

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AO 120 (Rev. 3/04)

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| DOCKET NO. | DATE FILED | U.S. DISTRICT COURT |
|---|---|---|
| 13cv2003-RGA | 12/6/2013 | DISTRICT OF DELAWARE |

| PLAINTIFF | DEFENDANT |
|---|---|
| Reckitt Benckiser Pharmaceuticals Inc., et al. | Alvogen Pine Brook Inc., et al. |

| | PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
|---|---|---|---|
| 1 | 8,475,832 | 7/2/2013 | RB Pharmaceuticals Limited |
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| JOHN A. CERINO, CLERK OF COURT | | 5/9/2014 |

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AO 120 (Rev. 08/10)

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☐ Trademarks or ☐ Patents. ( ☐ the patent action involves 35 U.S.C. § 292.):

| DOCKET NO. | DATE FILED | U.S. DISTRICT COURT |
|---|---|---|
| | 4/4/2014 | DELAWARE |

| PLAINTIFF | DEFENDANT |
|---|---|
| RECKITT BENCKISER PHARMACEUTICALS INC., RB PHARMACEUTICALS LIMITED, and MONOSOL RX LLC | PAR PHARMACEUTICAL, INC. and INTELGENX TECHNOLOGIES CORP. |

| | PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
|---|---|---|---|
| 1 | 8,475,832 | 7/2/2013 | RB Pharmaceuticals Limited |
| 2 | 8,017,150 | 9/13/2011 | MonoSol RX, LLC |
| 3 | 8,603,514 | 12/10/2013 | MonoSol RX, LLC |
| 4 | | | |
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

| DATE INCLUDED | INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading | |
|---|---|---|
| PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
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| DECISION/JUDGEMENT |
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AO 120 (Rev. 08/10)

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☐ Trademarks or ☑ Patents. ( ☐ the patent action involves 35 U.S.C. § 292.):

| DOCKET NO. | DATE FILED | U.S. DISTRICT COURT |
|---|---|---|
| 13-cv-1461-RGA | 8/20/2013 | of Delaware |

| PLAINTIFF | DEFENDANT |
|---|---|
| RECKITT BENCKISER PHARMACEUTICALS, INC., RB PHARMACEUTICALS LIMITED and MONOSOL RX, LLC, | PAR PHARMACEUTICAL, INC., INTELGENX TECHNOLOGIES CORP., and LTS LOHMANN THERAPY SYSTEMS CORP. |

| | PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
|---|---|---|---|
| 1 | U.S. 8,475,832 | 7/2/2013 | RB Pharmaceuticals Limited |
| 2 | U.S. 8,017,150 | 9/13/2011 | MonoSol Rx, LLC |
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| 4 | | | |
| 5 | | | |

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

| DATE INCLUDED | INCLUDED BY ☑ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading | |
|---|---|---|
| 2/18/2014 | | |
| PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
| 1 U.S. 8,603,514 | 12/10/2013 | MonoSol RX, LLC |
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| 4 | | |
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In the above—entitled case, the following decision has been rendered or judgement issued:

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☐ Trademarks or ☑ Patents. ( ☐ the patent action involves 35 U.S.C. § 292.):

| DOCKET NO. | DATE FILED | U.S. DISTRICT COURT |
|---|---|---|
| 13-cv-1674-RGA | 10/8/2013 | of Delaware |

| PLAINTIFF | DEFENDANT |
|---|---|
| RECKITT BENCKISER PHARMACEUTICALS, INC., RB PHARMACEUTICALS LIMITED and MONOSOL RX, LLC, | WATSON LABORATORIES, INC. |

| | PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
|---|---|---|---|
| 1 | U.S. 8,475,832 | 7/2/2013 | RB Pharmaceuticals Limited |
| 2 | U.S. 8,017,150 | 9/13/2011 | MonoSol Rx, LLC |
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|---|---|
| 2/18/2014 | ☑ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading |

| | PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
|---|---|---|---|
| 1 | U.S. 8,603,514 | 12/10/2013 | MonoSol RX, LLC |
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| DOCKET NO. | DATE FILED | U.S. DISTRICT COURT |
|---|---|---|
| 13-cv-2003-RGA | 12/6/2013 | DELAWARE |

| PLAINTIFF | DEFENDANT |
|---|---|
| Reckitt Benckiser Pharmaceuticals, Inc., RB Pharmaceuticals Limited, and MonoSol RX, LLC | Alvogen Pine Brook, Inc. |

| | PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
|---|---|---|---|
| 1 | 8,475,832 | 7/2/2013 | RB Pharmaceuticals Limited |
| 2 | 8,017,150 | 9/13/2011 | MonoSol RX, LLC |
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

| DATE INCLUDED | INCLUDED BY |
|---|---|
| 1/24/2014 | ☑ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading |

| | PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
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| 1 | 8,603,514 | 12/10/2013 | MonoSol RX, LLC |
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| | 12/6/2013 | DELAWARE |

| PLAINTIFF | DEFENDANT |
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| Reckitt Benckiser Pharmaceuticals, Inc., RB Pharmaceuticals Limited and MonoSol RX, LLC | Alvogen Pine Brook, Inc. and Alvogen Group, Inc. |

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| 1 | 8,475,832 | 7/2/2013 | RB Pharmaceuticals Limited |
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| | 10/8/2013 | of Delaware |

| PLAINTIFF | DEFENDANT |
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| RECKITT BENCKISER PHARMACEUTICALS, INC., RB PHARMACEUTICALS LIMITED and MONOSOL RX, LLC, | WATSON LABORATORIES, INC. and ACTAVIS, INC. |

| | PATENT OR TRADEMARK NO. | DATE OF PATENT OR TRADEMARK | HOLDER OF PATENT OR TRADEMARK |
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| 1 | U.S. 8,475,832 | 7/2/2013 | RB Pharmaceuticals Limited |
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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | ISSUE DATE | PATENT NO. | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/107,389 | 09/13/2011 | 8017150 | 1199-26 DIV | 9641 |

23869 7590 08/24/2011

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

# ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 364 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

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

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 12107389 |
| Filing Date | 2008-04-22 |
| First Named Inventor | Robert K. Yang |
| Art Unit | 1611 |
| Examiner Name | Gina C. Yu |
| Attorney Docket Number | 1199-26 DIV |

**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 | 4880416 | | 1989-11-14 | Horiuchi et al | |
| Change(s) applied to document, /M.C.E./ 7/28/2011 | 2 | 5800832 | | 1998 ~~1989~~-09-01 | Tapolsky et al | |
| | 3 | 6800329 | B2 | 2004-10-05 | Horstmann et al | |
| | 4 | 7579019 | B2 | 2009-08-25 | Tapolsky et al | |

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

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| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20040191302 | A1 | 2004-09-30 | Davidson | |
| | 2 | 20050048102 | A1 | 2005-03-03 | Tapolsky et al | |



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /G.Y./

[0117] 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.

[0118] The actives may be taste-masked prior to incorporation into the film composition, as set forth in co-pending PCT application titled, Uniform Films For Rapid Dissolve Dosage Form Incorporating Taste-Masking Compositions, (based on U.S. Provisional Application No. 60/414,276 Express Mail Label No.: EU552991605 US of the same title, filed September 27, 2003, ~~attorney docket No. 1199-15P~~) the entire subject matter of which is incorporated by reference herein.

Change(s) applied to document, /J.L.B./ 8/15/2011

**Actives**

[0119] When an active is introduced to the film, the amount of active per unit area is determined by the uniform distribution of the film. For example, when the films are cut into individual dosage forms, the amount of the active in the dosage form can be known with a great deal of accuracy. This is achieved because the amount of the active in a given area is substantially identical to the amount of active in an area of the same dimensions in another part of the film. The accuracy in dosage is particularly advantageous when the active is a medicament, i.e. a drug.

[0120] 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.

[0121] 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

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 12107389 |
| Filing Date | 2008-04-22 |
| First Named Inventor | Robert K. Yang |
| Art Unit | 1794 |
| Examiner Name | |
| Attorney Docket Number | 1199-26 DIV |

**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 | 6264981 | B1 | 2001-07-24 | Zhang et al. | |

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|---|---|---|---|---|---|---|
| | 1 | 20030069263 | A1 | 2003-04-10 | Breder et al. | |
| | 2 | 20070148097 | A1 | 2007-06-28 | Finn et al. | |

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| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 12107389 12107389 - GAU: 1611 |
| | Filing Date | 2008-04-22 |
| | First Named Inventor | Robert K. Yang |
| | Art Unit | 1794 |
| | Examiner Name | |
| | Attorney Docket Number | 1199-26 DIV |

| 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 | /Gina Yu/ | Date Considered | 04/08/2010 |
|---|---|---|---|

*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.



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /G.Y./

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV | 9641 |

23869 7590 07/27/2011
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

| EXAMINER | |
|---|---|
| YU, GINA C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 07/27/2011 | PAPER |

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The time period for reply, if any, is set in the attached communication.

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| APPLICATION NO./ CONTROL NO. | FILING DATE | FIRST NAMED INVENTOR / PATENT IN REEXAMINATION | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 12/107,389 | 22 April, 2008 | YANG ET AL. | 1199-26 DIV |

| | | EXAMINER | |
|---|---|---|---|
| HOFFMANN & BARON, LLP<br>6900 JERICHO TURNPIKE<br>SYOSSET, NY 11791 | | GINA C. YU | |
| | | ART UNIT | PAPER |
| | | 1617 | 20110706 |

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|---|---|
| | /GINA C. YU/<br>Primary Examiner, Art Unit 1617 |

PTO-90C (Rev.04-03)

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Bib Data Sheet

**CONFIRMATION NO. 9641**

| SERIAL NUMBER | FILING OR 371(c) DATE / RULE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 RULE | 424 | 1617 | 1199-26 DIV |

**APPLICANTS**

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

**** CONTINUING DATA ***************************

This application is a DIV of 10/856,176 05/28/2004 PAT 7,666,337 which claims benefit of 60/473,902 05/28/2003
and is a CIP of PCT/US2002/032575 10/11/2002
and is a CIP of PCT/US02/32594 10/11/2002
which claims benefit of 60/414,276 09/27/2002
and said 10/856,176 05/28/2004
is a CIP of PCT/US02/32542 10/11/2002
which claims benefit of 60/371,940 04/11/2002

**** FOREIGN APPLICATIONS *********************

**IF REQUIRED, FOREIGN FILING LICENSE GRANTED**
** 05/06/2008

| | | STATE OR COUNTRY | SHEETS DRAWING | TOTAL CLAIMS | INDEPENDENT CLAIMS |
|---|---|---|---|---|---|
| Foreign Priority claimed | ☐ yes ☐ no | NY | 26 | 18 | 2 |
| 35 USC 119 (a-d) conditions met | ☐ yes ☐ no ☐ Met after Allowance | | | | |
| Verified and Acknowledged | Examiner's Signature Initials | | | | |

**ADDRESS**
23869

**TITLE**

POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

| FILING FEE RECEIVED | | |
|---|---|---|
| 735 | FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following: | ☐ All Fees<br>☐ 1.16 Fees ( Filing )<br>☐ 1.17 Fees ( Processing Ext. of time )<br>☐ 1.18 Fees ( Issue )<br>☐ Other _____<br>☐ Credit |

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Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

| | |
|---|---|
| Debra Chambliss | (Depositor's name) |
| | (Signature) |
| July 22, 2011 | (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV | 9641 |

TITLE OF INVENTION:

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE | PUBLICATION FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|
| nonprovisional | YES | $755 | $300 | $1055 | 08/08/2011 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| | | |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
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(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Hoffmann & Baron, LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

| (A) NAME OF ASSIGNEE | (B) RESIDENCE: (CITY and STATE OR COUNTRY) |
|---|---|
| MonoSol Rx, LLC | Portage, IN |

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:
☑ Issue Fee
☑ Publication Fee (No small entity discount permitted)
☑ Advance Order - # of Copies 1

4b. Payment of Fee(s):
☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☑ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 082461

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Date July 22, 2011

Typed or printed name Nichole E. Martiak Registration No. 55,832

This collection of information is required by 37 CFR 1.311. 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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**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 disclosure of these records is required by the Freedom of Information Act.
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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 inspection 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.

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 12107389 |
| **Filing Date:** | 22-Apr-2008 |
| **Title of Invention:** | POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM |
| **First Named Inventor/Applicant Name:** | Robert K. Yang |
| **Filer:** | Nichole Elizabeth Martiak/Debra Chambliss |
| **Attorney Docket Number:** | 1199-26 DIV |

Filed as Large Entity

## Utility under 35 USC 111(a) Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| Utility Appl issue fee | 1501 | 1 | 1510 | 1510 |
| Publ. Fee- early, voluntary, or normal | 1504 | 1 | 300 | 300 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| Printed copy of patent - no color | 8001 | 1 | 3 | 3 |
| | | **Total in USD ($)** | | **1813** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 10580211 |
| **Application Number:** | 12107389 |
| **International Application Number:** | |
| **Confirmation Number:** | 9641 |
| **Title of Invention:** | POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM |
| **First Named Inventor/Applicant Name:** | Robert K. Yang |
| **Customer Number:** | 23869 |
| **Filer:** | Nichole Elizabeth Martiak/Debra Chambliss |
| **Filer Authorized By:** | Nichole Elizabeth Martiak |
| **Attorney Docket Number:** | 1199-26 DIV |
| **Receipt Date:** | 22-JUL-2011 |
| **Filing Date:** | 22-APR-2008 |
| **Time Stamp:** | 16:04:35 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

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| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $1813 |
| RAM confirmation Number | 2513 |
| Deposit Account | 082461 |
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## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Miscellaneous Incoming Letter | Ntc-re-Change-to-Large-Entity-Status.pdf | 90169<br>d3347419c0a0a5b4daea6d2d44c75970af3dc581 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Issue Fee Payment (PTO-85B) | ptol85b_Issue_Fee_Transmittal.pdf | 241213<br>0c55bd7b5c3458061fda11527d4f8654a9f43951 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Fee Worksheet (SB06) | fee-info.pdf | 33977<br>5e8a3e593ad46d938879b3a9136157d8e4efa360 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 365359 | | |

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**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Applicant(s): Yang et al. | Examiner: Yu, Gina |
| Application No.: 12/107,389 | Group Art Unit: 1617 |
| Filed: April 22, 2008 | Docket: 1199-26 DIV |
| For: POLYETHYLENE-OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM | Dated: July 22, 2011 |

Confirmation No.: 9641

Commissioner for Patents
P.O. Box 1450,
Alexandria, VA 22313

**NOTIFICATION OF CHANGE TO LARGE ENTITY STATUS PURSUANT TO 37 CFR § 1.27 (g)(2) AND CORRECTION OF ERROR IN CLAIMING SMALL ENTITY STATUS PURSUANT TO 37 CFR §1.28(c)**

Sir:

Applicant filed the above-referenced patent application claiming small entity status. The assertion of small entity status and the prior payments of fees as a small entity were made in good faith and were not made with any attempt to deceive the Office.

It has been discovered that this application incorrectly claimed small entity status and that such status as a small entity was continued in error. Pursuant to 37 C.F.R. §1.28(c)(1), please accept this statement to correct the erroneously claimed small entity status.

Submitted herewith is an itemized statement of the deficiencies owed pursuant to 37 C.F.R. §1.28(c)(2), as follows:

| Fee Description | Date Paid | Fee Paid as Small Entity | Current Large Entity Fee | Deficiency Owed |
|---|---|---|---|---|
| Basic Filing | | | | |
| Utility Fee | 4/22/2008 | $75.00 | $330.00 | $255.00 |
| Utility Search Fee | 4/22/2008 | $255.00 | $540.00 | $285.00 |
| Utility Examination Fee | 4/22/2008 | $105.00 | $220.00 | $115.00 |
| Other | | | | |
| Information Disclosure Statement | 7/29/2010 | $180.00 | $180.00 | $0.00 |
| Notice of Appeal | 1/13/2011 | $540.00 | $540.00 | $0.00 |
| **Total Fees Paid:** | | $1155.00 | | |
| **Total Fees Due as Large Entity:** | | | $1810.00 | |
| **Total Fees Due Herewith:** | | | | **$655.00** |

A fee of $655.00 is believed to be due with this submission. The Commissioner is hereby authorized to charge payment of the fees associated with this communication, or any additional fees, which may be due or credit any overpayment, to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. § 1.136.

Pursuant to 37 C.F.R. §1.28(d), it is respectfully submitted that the deficiency payment authorized herewith provides notification of a loss of entitlement to small entity status for this patent.

Please direct any questions regarding this submission to Applicant's undersigned attorney.

Respectfully submitted,

Nichole E. Martiak

Nichole E. Martiak, Esq.
Registration No. 55,832
Attorney for Applicant

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

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| | |
|---|---|
| Debra Chambliss | (Depositor's name) |
| Debra Chambliss | (Signature) |
| July 22, 2011 | (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV | 9841 |

TITLE OF INVENTION:

POLYETHYLENE OXIDE_BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE | PUBLICATION FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|
| nonprovisional | YES | $755 | $300 | $1055 | 08/08/2011 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| YU, GINA C | 1617 | 424-484000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Hoffmann & Baron, LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

| (A) NAME OF ASSIGNEE | (B) RESIDENCE: (CITY and STATE OR COUNTRY) |
|---|---|
| MonoSol Rx, LLC | Portage, IN |

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:
- ☑ Issue Fee
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- ☑ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 082481

5. Change in Entity Status (from status indicated above)
- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ☑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Nichole E. Martiak Date July 22, 2011

Typed or printed name Nichole E. Martiak Registration No. 55,832

# PART B - FEE(S) TRANSMITTAL

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Alexandria, Virginia 22313-1450
**or Fax** (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

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

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

| | |
|---|---|
| Debra Chambliss | (Depositor's name) |
| Debra Chambliss | (Signature) |
| July 22, 2011 | (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV | 9641 |

TITLE OF INVENTION:

POLYETHYLENE OXIDE BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE | PUBLICATION FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|
| nonprovisional | YES | $755 | $300 | $1055 | 08/08/2011 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| YU, GINA C | 1617 | 424-484000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Hoffmann & Baron, LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

| (A) NAME OF ASSIGNEE | (B) RESIDENCE: (CITY and STATE OR COUNTRY) |
|---|---|
| MonoSol Rx, LLC | Portage, IN |

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:
☑ Issue Fee
☑ Publication Fee (No small entity discount permitted)
☑ Advance Order - # of Copies 1

4b. Payment of Fee(s):
☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☑ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 082461

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Nichole E. Martiak Date July 22, 2011

Typed or printed name Nichole E. Martiak Registration No. 55,832

This collection of information is required by 37 CFR 1.311. 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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.

## EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Nichole Martiak on April 29, 2011.

The application has been amended as follows:

Change(s) applied to document, /K.D.D./ 6/28/2011

In specification, page 10, immediately after paragraph [0052] and immediately preceding the "**DETAILED DESCRIPTION OF THE INVENTION**" title, insert the following as a new paragraph:

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

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINA C. YU whose telephone number is (571)272-8605. The examiner can normally be reached on Monday through Friday, from 9:00AM until 5:00 PM..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun G. Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

# NOTICE OF ALLOWANCE AND FEE(S) DUE

23869 7590 05/06/2011
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

| EXAMINER |
|---|
| YU, GINA C |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

DATE MAILED: 05/06/2011

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV | 9641 |

TITLE OF INVENTION: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | YES | $755 | $300 | $0 | $1055 | 08/08/2011 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**

# PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail** **Mail Stop ISSUE FEE**
**Commissioner for Patents**
**P.O. Box 1450**
**Alexandria, Virginia 22313-1450**
**or Fax (571)-273-2885**

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CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23869 7590 05/06/2011
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

**Certificate of Mailing or Transmission**

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| |
|---|
| (Depositor's name) |
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV | 9641 |

TITLE OF INVENTION: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | YES | $755 | $300 | $0 | $1055 | 08/08/2011 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| YU, GINA C | 1617 | 424-484000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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UNITED STATES PATENT AND TRADEMARK OFFICE

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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23869 7590 05/06/2011

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

| EXAMINER | |
|---|---|
| YU, GINA C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

DATE MAILED: 05/06/2011

## Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 334 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 334 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## 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 disclosure of these records is required by the Freedom of Information Act.
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 inspection 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.

| Notice of Allowability | Application No. | Applicant(s) | |
|---|---|---|---|
| | 12/107,389 | YANG ET AL. | |
| | Examiner | Art Unit | |
| | GINA C. YU | 1617 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *pre-appeal request filed on January 13, 2011 and decision mailed on February 8, 2011*.

2. ☒ The allowed claim(s) is/are *claims 1-18*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE**.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20110503* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/GINA C. YU/
Primary Examiner, Art Unit 1617

| Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 12/107,389 | YANG ET AL. | |
| | Examiner | Art Unit | |
| | GINA C. YU | 1617 | |

All participants (applicant, applicant's representative, PTO personnel):

(1) *GINA C. YU*. (3)_____.

(2) *NICHOLE MARTIAK*. (4)_____.

Date of Interview: *29 April 2011*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Examiner called the above-named attorney to amend specification and to provide description for Fig 38; the attorney authorized an examiner's amendment to insert the same language which was added in the parent case case* .

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

| /GINA C. YU/<br>Primary Examiner, Art Unit 1617 | |
|---|---|

# Summary of Record of Interview Requirements

**Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record**
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

**Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews**
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

---

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

**Examiner to Check for Accuracy**

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

## EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Nichole Martiak on April 29, 2011.

The application has been amended as follows:

In specification, page 10, immediately after paragraph [0054] and immediately preceding the "**DETAILED DESCRIPTION OF THE INVENTION**" title, insert the following as a new paragraph:

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

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINA C. YU whose telephone number is (571)272-8605. The examiner can normally be reached on Monday through Friday, from 9:00AM until 5:00 PM..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun G. Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GINA C. YU/
Primary Examiner, Art Unit 1617

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 12107389 | YANG ET AL. |
| | **Examiner** | **Art Unit** |
| | GINA C YU | 1617 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 04/08/2010 | 10/05/2010 | 03/22/2011 | | | | | | |
| 1 | 1 | ✓ | ✓ | = | | | | | | |
| 2 | 2 | ✓ | ✓ | = | | | | | | |
| 3 | 3 | ✓ | ✓ | = | | | | | | |
| 4 | 4 | ✓ | ✓ | = | | | | | | |
| 5 | 5 | ✓ | ✓ | = | | | | | | |
| 6 | 6 | ✓ | ✓ | = | | | | | | |
| 7 | 7 | ✓ | ✓ | = | | | | | | |
| 8 | 8 | ✓ | ✓ | = | | | | | | |
| 9 | 9 | ✓ | ✓ | = | | | | | | |
| 10 | 10 | ✓ | ✓ | = | | | | | | |
| 11 | 11 | ✓ | ✓ | = | | | | | | |
| 12 | 12 | ✓ | ✓ | = | | | | | | |
| 13 | 13 | ✓ | ✓ | = | | | | | | |
| 14 | 14 | ✓ | ✓ | = | | | | | | |
| 15 | 15 | ✓ | ✓ | = | | | | | | |
| 16 | 16 | ✓ | ✓ | = | | | | | | |
| 17 | 17 | ✓ | ✓ | = | | | | | | |
| 18 | 18 | ✓ | ✓ | = | | | | | | |

# WEST Search History

Hide Items | Restore | Clear | Close

DATE: Tuesday, May 03, 2011

| Hide? | Set Name | Query | Hit Count |
|---|---|---|---|
| *Prior Art* | | | |
| *DB=PGPB,USPT; PLUR=YES; OP=OR* | | | |
| ☐ | L7 | L6 and @pd > 20100407 | 2 |
| ☐ | L6 | L4 AND POLYETHYL$ AND HYDRO$CELLULO$ | 5 |
| ☐ | L5 | L4 AND POLYETHYL$ AND CELLULO$ | 15 |
| ☐ | L4 | L2 AND ADHESIVE AND MUCOS$ | 20 |
| ☐ | L3 | L2 AND ADHESIVE | 30 |
| ☐ | L2 | 5393528 | 52 |
| *DB=USPT; PLUR=YES; OP=OR* | | | |
| ☐ | L1 | 5393528.PN. | 1 |

END OF SEARCH HISTORY

# Issue Classification

| Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|
| 12107389 | YANG ET AL. |
| **Examiner** | **Art Unit** |
| GINA C YU | 1617 |

| ORIGINAL | | INTERNATIONAL CLASSIFICATION | |
|---|---|---|---|
| CLASS | SUBCLASS | CLAIMED | NON-CLAIMED |
| 424 | 484 | A 6 1 K 9 / 14 | |

| CROSS REFERENCE(S) | | | | | |
|---|---|---|---|---|---|
| CLASS | SUBCLASS (ONE SUBCLASS PER BLOCK) | | | | |
| 424 | 486 | 488 | 434 | 435 | |

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 17 | 17 | | | | | | | | | | | | |
| 2 | 2 | 18 | 18 | | | | | | | | | | | | |
| 3 | 3 | | | | | | | | | | | | | | |
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| 16 | 16 | | | | | | | | | | | | | | |

| | | | |
|---|---|---|---|
| NONE<br><br>(Assistant Examiner) | (Date) | **Total Claims Allowed:**<br>18 | |
| /GINA C YU/<br>Primary Examiner.Art Unit 1617<br><br>(Primary Examiner) | 03/22/2011<br><br>(Date) | O.G. Print Claim(s)<br>1 | O.G. Print Figure<br>None |

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 12107389 | YANG ET AL. |
| | Examiner | Art Unit |
| | GINA C YU | 1617 |

| SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| 424 | 434, 435, 436, 443, 484 | 4/8/2010 | gy |
| updated | | 10/5/2010 | gy |
| update | | 3/22/2011 | gy |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| West, Inventor | 4/8/2010 | gy |
| updated | 10/5/2010 | gy |
| Pre-apeal conference held with Fereydoun Sajjadi and Jean Witz | 2/8/2011 | gy |
| updated | 3/22/2011 | gy |

| INTERFERENCE SEARCH | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| 424 | 434, 435, 436, 443, 484 | 3/22/2011 | gy |

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| | |

UNITED STATES PATENT AND TRADEMARK OFFICE

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Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV | 9641 |

23869 7590 02/08/2011
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

| EXAMINER | |
|---|---|
| YU, GINA C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 02/08/2011 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Notice of Panel Decision from Pre-Appeal Brief Review | Application/Control No. | Applicant(s)/Patent under Reexamination | |
|---|---|---|---|
| | 12/107,389 | YANG ET AL. | |
| | FEREYDOUN G. SAJJADI | Art Unit | |
| | | 1617 | |

This is in response to the Pre-Appeal Brief Request for Review filed 13 January 2011.

1. ☐ **Improper Request** – The Request is improper and a conference will not be held for the following reason(s):

☐ The Notice of Appeal has not been filed concurrent with the Pre-Appeal Brief Request.
☐ The request does not include reasons why a review is appropriate.
☐ A proposed amendment is included with the Pre-Appeal Brief request.
☐ Other: .

The time period for filing a response continues to run from the receipt date of the Notice of Appeal or from the mail date of the last Office communication, if no Notice of Appeal has been received.

2. ☐ **Proceed to Board of Patent Appeals and Interferences** – A Pre-Appeal Brief conference has been held. The application remains under appeal because there is at least one actual issue for appeal. Applicant is required to submit an appeal brief in accordance with 37 CFR 41.37. The time period for filing an appeal brief will be reset to be one month from mailing this decision, or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater. Further, the time period for filing of the appeal brief is extendible under 37 CFR 1.136 based upon the mail date of this decision or the receipt date of the notice of appeal, as applicable.

☐ The panel has determined the status of the claim(s) is as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: _____.
Claim(s) withdrawn from consideration: _____.

3. ☒ **Allowable application** – A conference has been held. The rejection is withdrawn and a Notice of Allowance will be mailed. Prosecution on the merits remains closed. No further action is required by applicant at this time.

4. ☐ **Reopen Prosecution** – A conference has been held. The rejection is withdrawn and a new Office action will be mailed. No further action is required by applicant at this time.

All participants:

(1) *FEREYDOUN G. SAJJADI*.

(2) *Jean Witz*.

(3) *Gina Yu*.

(4)_____.

/Fereydoun G Sajjadi/
Supervisory Patent Examiner, Art Unit 1617

Doc Code: AP.PRE.REQ

PTO/SB/33 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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.

# PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 1199-26 DIV

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

Signature _____

Typed or printed name _____

| Application Number | Filed |
|---|---|
| 12/107,389 | 04/22/2008 |

First Named Inventor: Robert K. Yang

| Art Unit | Examiner |
|---|---|
| 1617 | Gina C. Yu |

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 55,832.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

/Nichole E. Martiak, Reg. No. 55,832/
Signature

Nichole E. Martiak
Typed or printed name

973-331-1700
Telephone number

January 13, 2011
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. 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: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

# 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 disclosure of these records is required by the Freedom of Information Act.
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 inspection 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.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Appellant(s) | Yang | Examiner: | Yu, Gina C. |
| Serial No.: | 12/107,389 | Group Art Unit: | 1617 |
| Confirmation No.: | 9641 | Docket: | 1199-26 DIV |
| Filed: | April 22, 2008 | Dated: | January 13, 2010 |
| For: | Polyethylene Oxide-Based Films and Drug Delivery Systems Made Therefrom | | |

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

**STATEMENT IN SUPPORT OF PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Sir:

In support of the concurrently-filed Notice of Appeal and Pre-Appeal Brief Request for Review, please consider the patentability of the claims of the above-identified application in view of the following remarks.

**Appellants' Response to §103(a) Rejection over Schiraldi in view of Flick**

Claims 1-4, 8, 10-13 and 17 are rejected as allegedly obvious under 35 U.S.C. §103(a) over Schiraldi (U.S. 4,713,243) in view of Flick (Water Soluble Resins, an industrial guide, 1991). The Examiner acknowledges that the weight ratio of polyethylene oxide and hydrophilic cellulosic polymer is different than that claimed, but alleges that Schiraldi discloses a mucosally adhesive film including 40-95% hydroxypropyl cellulose, 5-60% homopolymer of ethylene oxide, up to 10% polyethylene or polypropylene, and 2-10% plasticizer, and an active. The Examiner then continues to rely upon Flick for allegedly indicating that polyethylene oxide polymers having various molecular weights are available.

Claim 1 includes the combination of polyethylene oxide (PEO) and a hydrophilic cellulosic polymer, specifically requiring greater than a 3:1 ratio of PEO to cellulosic polymer; and requires that the PEO component include both low MW PEO (100,000-300,000) and high MW PEO (600,000-900,000); and further requires that the low MW PEO be 60% or more in the polymer component. As previously stated, these limitations set forth very specific ranges, ratios, and amounts of particular polymeric materials.

The Examiner acknowledges the cited references do not include the particular combination of polymers in the specifically recited amounts and having the recited molecular

weights. Schiraldi does disclose the general combination of a hydroxypropyl cellulose and a homopolymer of ethylene oxide, but there is no disclosure or suggestion as to the claimed molecular weight combination. In fact, Schiraldi only states that the homopolymer of ethylene oxide should have a relatively high molecular weight "i.e., above 100,000 and preferably above 3,000,000." (Col. 4, lines 24-28). In fact, the most preferred ethylene oxide has a molecular weight of 4,000,000-5,000,000. (Col. 4, lines 28-31). One of ordinary skill in the art would simply not be led to using the claimed combination of molecular weights, which are both significantly below the "preferred" molecular weights in Schiraldi. There is simply no disclosure or guidance to select low MW polymers, and particularly there is no disclosure to select a particular combination of MW polymers, each having MW's far below Schiraldi's "preferred" ranges.

The Appellants have unexpectedly discovered that the particular combination of molecular weights and polymers claimed provides a suitable release profile for an opiate, and still provides a suitable dosage form. (See, for example, Examples DH-DZ). As explained in the application, and as is understood by those of skill in the art, different actives have quite different solubilities and release profiles. For example, an opiate (as claimed) has a significantly different solubility and release profile than other analgesics, such as those listed in Schiraldi. There is simply no expectation of success, **or any predictability** from a reading of Schiraldi that one would be able to achieve a suitable film having a successful release profile of an opiate by modifying Schiraldi's film. In fact, given Schiraldi's express preference for high molecular weight polymers, one of ordinary skill in the art would simply not expect successful results using the claimed components.

Appellants again respectfully submit that the present claims are not merely routine expermimentation. As can be appreciated by those of skill in the art, numerous film forming materials are known in the art. In fact, the reference cited by the Examiner (Flick) specifically states that "this ... guide contains descriptions of more than 1100 currently available water-soluble resins, supplied by 47 manufacturers or distributors of these products." (Description, Page 1) (emphasis added). Given the numerous possible combinations of film forming materials available, and in particular given the wide number of molecular weights available to choose from, one of ordinary skill in the art simply would not

be able to predict which particular combination of polymers having which particular molecular weights would be useful to form the claimed invention. Further, there certainly would be no expectation of success with respect to doing so, based upon the cited Schiraldi reference and its preferred molecular weights. The claims recite a particular combination of polymers, having a particular molecular weight, in a particular ratio. This is not a matter of simply testing different molecular weights, or simply testing different ratios. There are three distinct limitations in the claims, none of which are disclosed in Schiraldi or Flick. Furthermore, the Examiner fails to appreciate that is absolutely no predictability of results associated with randomly selecting a particular polymer having a particular molecular weight out of context from the cited reference.

Given the vast number of polymers and wide disparity of molecular weights to choose from, there is a significantly high degree of experimentation necessary to arrive at the narrow ranges claimed. Further, given Schiraldi's scant teachings as to the polymers and molecular weights, there is absolutely no direction or guidance that would direct one of skill in the art to the claimed invention. There is simply no predictability in the art to arrive at the presently claimed combination of polymers, molecular weights, and ratios to achieve a suitable delivery system with a suitable release profile of an opiate.

Appellants again respectfully submit that the Examiner's rejection is a merely a clear case of impermissible hindsight reconstruction, using the Appellants' claims as an instruction manual. Appellants again remind the Examiner that hindsight cannot provide the basis for an obviousness rejection.

As has been recently stated by the Board of Patent Appeals and Interferences, "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *Ex Parte Houze*, Appeal No. 2009-008650, March 16, 2010 (*quoting In Re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009)). As has been repeatedly stated, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *Ex Parte Howard*, Appeal No. 2009-005947 (B.P.A.I., May 25, 2010) (*quoting In Re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992)). "A factfinder should be aware, of course, of the distortion caused by hindsight bias

and must be cautious of arguments reliant upon ex post reasoning." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007).

The presently pending claims recite at least three specific numerical limitations, none of which is disclosed or even suggested in the cited references. There is no disclosure of the ratio of cellulosic polymer to PEO. There is also no disclosure of the combination of low *and* high molecular weight PEO. Finally, there is no disclosure of the particular amount of low molecular weight PEO. There is simply no basis to argue that the optimization of these limitations would be obvious to one of ordinary skill in the art without using the present claims as a roadmap or instruction manual. In fact, as stated above, Schiraldi specifically states that "preferred" molecular weights of PEO are above 3,000,000 – well above both of the presently claimed PEO weights. Accordingly, it is unclear how the Examiner could have arrived at the conclusion of obviousness without utilizing hindsight.

In response to Appellants' arguments that the prior art does not teach combining different molecular weights of PEO, the Examiner states the following: "...what is unobvious about combining two polymers of different molecular weights to obtain a polymer mixture of the median molecular weight?" (Office Action, at page 11). Appellants respectfully traverse.

The present combination of particular amounts of cellulosic polymers and particular molecular weight PEO's provides a film product that includes strength but also provides a desired dissolution rate and release profile for an opiate when provided to the user. The Appellants have found that the presently claimed combination provides a product which strikes a balance between these properties.

Appellants respectfully submit that the Examiner's statement that combining two polymers having different molecular weights to arrive at a median molecular weight is misplaced. One of skill would appreciate that the low MW PEO would release at different time than the high MW PEO. Accordingly, combining these two different types of PEO would not provide a new polymer having a "median molecular weight", which would release at the same time.

As stated above, there is no *prima facie* case of obviousness with this hypothetical combination of references. Claims 1-4 8, 10-13 and 17 are allowable over Schiraldi and

Flick, whether taken alone or in combination. Allowance of these claims is respectfully requested.

**Appellants' Response to §103(a) Rejection over Schiraldi in view of Flick and Khan**

Claims 5-9 and 14-18 have been rejected under 35 U.S.C. §103 (a) as allegedly being obvious over Schiraldi and Flick and further in view of Khan (U.S. 5,656,296). The Examiner acknowledged that Schiraldi and Flick fail to teach the claimed sweeteners and buffering agents. The Examiner relied upon Khan for teaching orally administered compositions including buffers and sweetening agents. The Examiner stated that one of ordinary skill in the art would be motivated to use Khan's agents to given an improved taste.

As explained above, neither of Schiraldi nor Flick discloses the presently claimed limitations, including (1) the ratio of cellulosic polymer to PEO, (2) the molecular weights of PEO, including both low and high molecular weight PEOs, and (3) the level of low molecular weight PEO. In fact, Flick specifically states that there are "more than 1100 ... water-soluble resins", one of which includes polyethylene oxide. There is simply no direction, suggestion or guidance to arrive at the claimed invention. It would not be obvious to one of ordinary skill in the art to arrive at the present combination of limitations without impermissible hindsight reconstruction. Khan's disclosure of buffers and sweeteners fails to remedy this clear defect. Thus, there is no *prima facie* case of obviousness with this hypothetical combination of references.

Claims 5-9 and 14-18 are allowable over Schiraldi, Flick and Khan, whether taken alone or in combination. Allowance of claims 1-18 is respectfully requested.

If the Examiner has any questions or comments relating to the present application, he or she is respectfully invited to contact Appellants' attorney at the telephone number set forth below.

Respectfully submitted,

HOFFMANN & BARON, LLP

6900 Jericho Turnpike
Syosset, New York 11791
(973) 331-1700

/Nichole E. Martiak, Reg No. 55,832/

Nichole E. Martiak
Registration No.: 55,832
Attorney for Appellant(s)

PTO/SB/31 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# NOTICE OF APPEAL FROM THE EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Docket Number (Optional): 1199-26 DIV

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]
on _____

Signature _____

Typed or printed name _____

In re Application of: Robert K. Yang et al.

| Application Number | Filed |
|---|---|
| 12/107,389 | 04/22/2008 |

For: Polyethylene Oxide-Based Films and Drug Delivery Systems Made Therefrom

| Art Unit | Examiner |
|---|---|
| 1617 | Gina C. Yu |

Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 540.00

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: $ _____

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☐ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. _____ .

☐ A petition for an extension of time under 37 CFR 1.136(a) (PTO/SB/22) is enclosed.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☐ attorney or agent of record.
Registration number _____.

☑ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. 55,832

/Nichole E. Martiak, Reg. No. 55,832/
Signature

Nichole E. Martiak
Typed or printed name

973-331-1700
Telephone number

January 13, 2011
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 41.31. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. 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.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

# 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 disclosure of these records is required by the Freedom of Information Act.
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 inspection 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.

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 12107389 |
| **Filing Date:** | 22-Apr-2008 |
| **Title of Invention:** | POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM |
| **First Named Inventor/Applicant Name:** | Robert K. Yang |
| **Filer:** | Nichole Elizabeth Martiak/Kathleen Goodhand |
| **Attorney Docket Number:** | 1199-26 DIV |

Filed as Large Entity

## Utility under 35 USC 111(a) Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| Notice of appeal | 1401 | 1 | 540 | 540 |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **540** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 9227637 |
| **Application Number:** | 12107389 |
| **International Application Number:** | |
| **Confirmation Number:** | 9641 |
| **Title of Invention:** | POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM |
| **First Named Inventor/Applicant Name:** | Robert K. Yang |
| **Customer Number:** | 23869 |
| **Filer:** | Nichole Elizabeth Martiak/Kathleen Goodhand |
| **Filer Authorized By:** | Nichole Elizabeth Martiak |
| **Attorney Docket Number:** | 1199-26 DIV |
| **Receipt Date:** | 13-JAN-2011 |
| **Filing Date:** | 22-APR-2008 |
| **Time Stamp:** | 16:57:29 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $540 |
| RAM confirmation Number | 3799 |
| Deposit Account | 082461 |
| Authorized User | |

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Pre-Brief Conference request | Pre-Appeal_Brief_Request_For_Review.pdf | 240108<br>9f2265adad7fa8e01ad092f591e47c3085102279 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Pre-Brief Conference request | Statement_in_Support_of_Pre-Appeal_Brief.pdf | 377385<br>6349bfa8458c2c869db019d412b76785d26d2dc6 | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Notice of Appeal Filed | Notice_of_Appeal.pdf | 258255<br>4c8d4feaf79ab896fd3331a0274dfae6b7d0cbe5 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Fee Worksheet (PTO-875) | fee-info.pdf | 30551<br>3202ef42346f849107e8701cd6f677d8557d8036 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 906299 | | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

UNITED STATES PATENT AND TRADEMARK OFFICE

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

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV | 9641 |

23869 7590 12/28/2010

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

| EXAMINER | |
|---|---|
| YU, GINA C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 12/28/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 12/107,389 | **Applicant(s)** YANG ET AL. | |
|---|---|---|---|
| | **Examiner** GINA C. YU | **Art Unit** 1617 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 13 December 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *None*.
   Claim(s) objected to: *1-18*.
   Claim(s) rejected: *None*.
   Claim(s) withdrawn from consideration: *None*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Applicants reinterate the same arguments presented in remarks filed on July 29, 2010. The arguments are unpersuasive for the reasons stated in Response to Applicant's Arguments, Office action dated October 13,2010. .
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/GINA C. YU/
Primary Examiner, Art Unit 1617

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | Yang | Examiner: | Yu, Gina C. |
| Serial No.: | 12/107,389 | Group Art Unit: | 1611 |
| Confirmation No.: | 9641 | Docket: | 1199-26 DIV |
| Filed: | April 22, 2008 | Dated: | December 13, 2010 |
| For: | Polyethylene Oxide-Based Films and Drug Delivery Systems Made Therefrom | | |

Please do not enter.
/G.Y./
December 23, 2010

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

**RESPONSE TO OFFICE ACTION**

Sir:

In response to the Office Action dated October 13, 2010, a response to which is due by January 13, 2011. As this submission is being filed by the two-month date of December 13, 2010, a response by the three-month date is respectfully requested.

**Remarks** begin on page 2 of this paper.

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | Yang | Examiner: | Yu, Gina C. |
| Serial No.: | 12/107,389 | Group Art Unit: | 1611 |
| Confirmation No.: | 9641 | Docket: | 1199-26 DIV |
| Filed: | April 22, 2008 | Dated: | December 13, 2010 |
| For: | Polyethylene Oxide-Based Films and Drug Delivery Systems Made Therefrom | | |

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

**RESPONSE TO OFFICE ACTION**

Sir:

In response to the Office Action dated October 13, 2010, a response to which is due by January 13, 2011. As this submission is being filed by the two-month date of December 13, 2010, a response by the three-month date is respectfully requested.

**Remarks** begin on page 2 of this paper.

**REMARKS**

Reconsideration of the present application is requested. Claims 1-18 are pending in this application.

**Applicants' Response to §103(a) Rejection over Schiraldi in view of Flick**

Claims 1-4, 8, 10-13 and 17 are rejected as allegedly obvious under 35 U.S.C. §103(a) over Schiraldi (U.S. 4,713,243) in view of Flick (Water Soluble Resins, an industrial guide, 1991). The Examiner acknowledges that the weight ratio of polyethylene oxide and hydrophilic cellulosic polymer is different than that claimed, but alleges that Schiraldi discloses a mucosally adhesive film including 40-95% hydroxypropyl cellulose, 5-60% homopolymer of ethylene oxide, up to 10% polyethylene or polypropylene, and 2-10% plasticizer, and an active. The Examiner then continues to rely upon Flick for allegedly indicating that polyethylene oxide polymers having various molecular weights are available.

Claim 1 includes the combination of polyethylene oxide (PEO) and a hydrophilic cellulosic polymer, specifically requiring greater than a 3:1 ratio of PEO to cellulosic polymer; and requires that the PEO component include both low MW PEO (100,000-300,000) and high MW PEO (600,000-900,000); and further requires that the low MW PEO be 60% or more in the polymer component. As previously stated, these limitations set forth very specific ranges, ratios, and amounts of particular polymeric materials.

The Examiner acknowledges the cited references do not include the particular combination of polymers in the specifically recited amounts and having the recited molecular weights. Schiraldi does disclose the general combination of a hydroxypropyl cellulose and a homopolymer of ethylene oxide, but there is no disclosure or suggestion as to the claimed molecular weight combination. In fact, Schiraldi only states that the homopolymer of ethylene oxide should have a relatively high molecular weight "i.e., above 100,000 and preferably above 3,000,000." (Col. 4, lines 24-28). In fact, the most preferred ethylene oxide has a molecular weight of 4,000,000-5,000,000. (Col. 4, lines 28-31). One of ordinary skill in the art would simply not be led to using the claimed combination of molecular weights,

which are both significantly below the "preferred" molecular weights in Schiraldi. There is simply no disclosure or guidance to select low MW polymers, and particularly there is no disclosure to select a particular combination of MW polymers, each having MW's far below Schiraldi's "preferred" ranges.

The Applicant has unexpectedly discovered that the particular combination of molecular weights and polymers claimed provides a suitable release profile for an opiate, and still provides a suitable dosage form. (See, for example, Examples DH-DZ). As explained in the application, and as is understood by those of skill in the art, different actives have quite different solubilities and release profiles. For example, an opiate (as claimed) has a significantly different solubility and release profile than other analgesics, such as those listed in Schiraldi. There is simply no expectation of success, **or any predictability** from a reading of Schiraldi that one would be able to achieve a suitable film having a successful release profile of an opiate by modifying Schiraldi's film. In fact, given Schiraldi's express preference for high molecular weight polymers, one of ordinary skill in the art would simply not expect successful results using the claimed components.

Applicants again respectfully submit that the present claims are not merely routine expermimentation. As can be appreciated by those of skill in the art, numerous film forming materials are known in the art. In fact, the reference cited by the Examiner (Flick) specifically states that "this … guide contains descriptions of more than 1100 currently available water-soluble resins, supplied by 47 manufacturers or distributors of these products." (Description, Page 1) (emphasis added). Given the numerous possible combinations of film forming materials available, and in particular given the wide number of molecular weights available to choose from, one of ordinary skill in the art simply would not be able to predict which particular combination of polymers having which particular molecular weights would be useful to form the claimed invention. Further, there certainly would be no expectation of success with respect to doing so, based upon the cited Schiraldi reference and its preferred molecular weights. The claims recite a particular combination of polymers, having a particular molecular weight, in a particular ratio. This is not a matter of

simply testing different molecular weights, or simply testing different ratios. There are three distinct limitations in the claims, none of which are disclosed in Schiraldi or Flick. Furthermore, the Examiner fails to appreciate that is absolutely no predictability of results associated with randomly selecting a particular polymer having a particular molecular weight out of context from the cited reference.

Given the vast number of polymers and wide disparity of molecular weights to choose from, there is a significantly high degree of experimentation necessary to arrive at the narrow ranges claimed. Further, given Schiraldi's scant teachings as to the polymers and molecular weights, there is absolutely no direction or guidance that would direct one of skill in the art to the claimed invention. There is simply no predictability in the art to arrive at the presently claimed combination of polymers, molecular weights, and ratios to achieve a suitable delivery system with a suitable release profile of an opiate.

Applicants again respectfully submit that the Examiner's rejection is a merely a clear case of impermissible hindsight reconstruction, using the Applicant's claims as an instruction manual. Applicants again remind the Examiner that hindsight cannot provide the basis for an obviousness rejection.

As has been recently stated by the Board of Patent Appeals and Interferences, "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *Ex Parte Houze*, Appeal No. 2009-008650, March 16, 2010 (*quoting In Re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009)). As has been repeatedly stated, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *Ex Parte Howard*, Appeal No. 2009-005947 (B.P.A.I., May 25, 2010) (*quoting In Re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992)). "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007).

The presently pending claims recite at least three specific numerical limitations, none of which is disclosed or even suggested in the cited references. There is no disclosure of the ratio of cellulosic polymer to PEO. There is also no disclosure of the combination of low *and* high molecular weight PEO. Finally, there is no disclosure of the particular amount of low molecular weight PEO. There is simply no basis to argue that the optimization of these limitations would be obvious to one of ordinary skill in the art without using the present claims as a roadmap or instruction manual. In fact, as stated above, Schiraldi specifically states that "preferred" molecular weights of PEO are above 3,000,000 – well above both of the presently claimed PEO weights. Accordingly, it is unclear how the Examiner could have arrived at the conclusion of obviousness without utilizing hindsight.

In response to Applicants' arguments that the prior art does not teach combining different molecular weights of PEO, the Examiner states the following: "…what is unobvious about combining two polymers of different molecular weights to obtain a polymer mixture of the median molecular weight?" (Office Action, at page 11). Applicants respectfully traverse.

The present combination of particular amounts of cellulosic polymers and particular molecular weight PEO's provides a film product that includes strength but also provides a desired dissolution rate and release profile for an opiate when provided to the user. The Applicants have found that the presently claimed combination provides a product which strikes a balance between these properties.

Applicants respectfully submit that the Examiner's statement that combining two polymers having different molecular weights to arrive at a median molecular weight is misplaced. One of skill would appreciate that the low MW PEO would release at different time than the high MW PEO. Accordingly, combining these two different types of PEO would not provide a new polymer having a "median molecular weight", which would release at the same time.

As stated above, there is no *prima facie* case of obviousness with this hypothetical combination of references. Claims 1-4 8, 10-13 and 17 are allowable over Schiraldi and Flick, whether taken alone or in combination. Allowance of these claims is respectfully requested.

**Applicants' Response to §103(a) Rejection over Schiraldi in view of Flick and Khan**

Claims 5-9 and 14-18 have been rejected under 35 U.S.C. §103 (a) as allegedly being obvious over Schiraldi and Flick and further in view of Khan (U.S. 5,656,296). The Examiner acknowledged that Schiraldi and Flick fail to teach the claimed sweeteners and buffering agents. The Examiner relied upon Khan for teaching orally administered compositions including buffers and sweetening agents. The Examiner stated that one of ordinary skill in the art would be motivated to use Khan's agents to given an improved taste.

As explained above, neither of Schiraldi nor Flick discloses the presently claimed limitations, including (1) the ratio of cellulosic polymer to PEO, (2) the molecular weights of PEO, including both low and high molecular weight PEOs, and (3) the level of low molecular weight PEO. In fact, Flick specifically states that there are "more than 1100 … water-soluble resins", one of which includes polyethylene oxide. There is simply no direction, suggestion or guidance to arrive at the claimed invention. It would not be obvious to one of ordinary skill in the art to arrive at the present combination of limitations without impermissible hindsight reconstruction. Khan's disclosure of buffers and sweeteners fails to remedy this clear defect. Thus, there is no *prima facie* case of obviousness with this hypothetical combination of references.

Claims 5-9 and 14-18 are allowable over Schiraldi, Flick and Khan, whether taken alone or in combination. Allowance of claims 1-18 is respectfully requested.

No fees are due with this submission. However, should any fees be due, the Commissioner is hereby authorized to charge payment of any required fees associated with this communication to Deposit Account No. 08-2461. This 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 or any future reply pursuant to 37 C.F.R. § 1.136, and also includes fees for consideration of any IDS, if necessary.

If the Examiner has any questions or comments relating to the present application, he or she is respectfully invited to contact Applicant's attorney at the telephone number set forth below.

Respectfully submitted,

/Nichole E. Martiak, Reg No. 55,832/

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(973) 331-1700

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 9021039 |
| **Application Number:** | 12107389 |
| **International Application Number:** | |
| **Confirmation Number:** | 9641 |
| **Title of Invention:** | POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM |
| **First Named Inventor/Applicant Name:** | Robert K. Yang |
| **Customer Number:** | 23869 |
| **Filer:** | Nichole Elizabeth Martiak |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | 1199-26 DIV |
| **Receipt Date:** | 13-DEC-2010 |
| **Filing Date:** | 22-APR-2008 |
| **Time Stamp:** | 15:30:33 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 1199-26_DIV-Response_After_Final.pdf | 125298<br>2751c0ab3faa928f18ccfdf55c4501753d81f53a | yes | 7 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Amendment After Final | 1 | 1 |
| | Applicant Arguments/Remarks Made in an Amendment | 2 | 7 |

| | |
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| **Warnings:** | |
| **Information:** | |
| **Total Files Size (in bytes):** | 125298 |

**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.**

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV | 9641 |

23869 7590 10/13/2010

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

| EXAMINER | |
|---|---|
| YU, GINA C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 10/13/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 12/107,389 | YANG ET AL. | |
| | Examiner | Art Unit | |
| | GINA C. YU | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *July 29, 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Receipt is acknowledged of response filed on July 29, 2010. No claim amendment has been made.

Claim rejections made under 35 U.S.C. § 103 (a) as indicated in the previous Office action which was mailed on April 29, 2010 are maintained for reasons of record.

Non-statutory double patenting rejection made in the same Office action is withdrawn in view of applicant's remarks.

### *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on July 29, 2010 was filed after the mailing date of the non-final Office action on April 29, 2010. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### *Claim Rejections - 35 USC § 103 (Maintained)*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

**Claims 1-4, 8, 10-13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi (US 4713243) in view of Flick (Water-soluble resins: an industrial guide, 1991).**

Schiraldi discloses a mucousally-adhesive bioadhesive thin film for intra-oral controlled-release delivery comprising a water soluble or swellable polymer matrix consisting of 40-95 wt % of hydroxypropyl cellulose, 5-60wt % a homopolymer of ethylene oxide, up to 10 wt % of polyethylene or polypropylene, and 2-10wt % of a

plasticizer, and a pharmaceutical active selected from anesthetics, analgesics, anti-inflammatory, etc. See abstract; col. 2, lines 30 -51. The thickness of the film ranges from 1 to 10 mil or 0.025-0.25 mm. The intended pharmaceuticals include analgesics such as aspirin, which is an opiate derivative according to applicant's own definition. See col. 3, lines 43. The reference also teaches an example of anesthetic film containing two pharmaceutical actives, thus incorporating an additional pharmaceutical agent as defined in instant claims 4 and 13 would have been obvious. Adding a flavor to the film product is suggested in col. 4, lines 50 – 54, meeting instant claims 8 and 17.

Although the weight ratio of the polyethylene oxide and the hydrophilic cellulosic polymer of the prior art is different from the present invention, Schiraldi teaches the ratio of the prior art polymers can be varied to control the solubility and the adhesive properties of each layer of film. See col. 3, lines 25 – 33. Other factors which affect this ratio are the desired delivery rate, the type of disorder to be treated, the area to be treated and the medication to be administered. See Id. The reference teaches the film can be custom designed by selecting and blending different polymers.

Although the polyethylene oxide used in examples is Polyox WSR 301 having MW 4,000,000-5,000,000, the reference suggests the lower limit of MW of polyethylene oxide useful for the purpose of the invention may be as low as 100,000. See col. 4, lines 24 -31.

Flick teaches polyethylene oxide polymers are supplied in a variety of viscosity grade and molecular weight. The reference teaches the polymers are effective as a rheology modifier, binder for additives, and produce visco-elastic behavior in solution.

See p. 389-390. The reference also indicates that polyethylene oxide polymers having molecular weight of 100K, 200K, 300, 600K and 900K are commercially available. See p. 391. Polyethylene oxide resin having MW 300 K has a viscosity up to 1100 cps, while the resins having MW 600K and 900K together have a viscosity ranges of 4500-17600 cps. See instant claim 2.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the Schiraldi film product by using polyethylene oxide resins of different molecular weight and varying the weight ratio of polyethylene oxide:hydrophilic cellulosic polymer as motivated by the combined teachings of Schiraldi and Flick. In this case, Such motivation is found in Schiraldi which teaches various type of film product may be formulated by varying the polymer weight ratio and choosing and blending different polymers. Flick also teaches polyethylene oxide resins of wide ranges of molecular weight and viscosity are effective as an adhesive, binder, thermoplastic and rheology modifier. Therefore, choosing polyethylene oxide resins of different lower molecular weight and varying the weight ratio of the polymers to produce a film product with a desired flexibility, rheology property, solubility, delivery rate, adhesiveness, etc. would have been an obvious modification to a skilled artisan. Since the Schiraldi teaches polyethylene oxide of a low molecular weight of 100,000 may be used, the skilled artisan would have had a reasonable expectation of successfully producing a stable film product of desired properties.

Furthermore, differences in concentration or temperature generally will not support the patentability of subject matter encompassed by the prior art unless there is

evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case, discovering an optimal weight ratio of a low molecular polyethylene oxide and cellulosic polymer to produce film products of intended uses (dosage, delivery rate, rheology, etc) by routine experimentations would only take ordinary skill in the art.

**Claims 5-9 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi and Flick as applied to claims 1-4, 8, 10-13 and 17 as above, and further in view of Khan et al. (US 5656296).**

Schiraldi and Flick fail to teach the sweeteners and buffering agents of the instant claims.

Khan teaches hard and soft orally administered compositions for controlled – release drug delivery and a method for preparing the said compositions. The reference teaches flavoring agents, sweetening agents and buffers are conventionally added to produce the pharmaceutically acceptable carriers. See col. 8, lines 24 - 39. The specific types and amounts of buffers and sweetening agents are taught in col. 10, lines 59 – 63 and col. 11, lines 6-27. Hydrogenated starch hydrolysates and the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide of instant claims 6, 7, 15 and 16 are disclosed in col. 11, line 6 and lines 23-24.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the teachings of Schiraldi/Flick by incorporating sweetening

agents and buffer as motivated Khan as the latter teaches such additives are conventionally added to make edible and pharmaceutically suitable drug systems. Since Schiraldi already teaches flavoring agents and other additives may be added to the intra-oral film products, the skilled artisan would have had a reasonable expectation of successfully producing a modified mucousally-adhesive film product with improved taste and stability.

***Response to Arguments***

Applicant's arguments filed July 29, 2010 have been fully considered but they are not persuasive.

Applicant mischaracterizes the rationales of the present obviousness rejections. Applicant asserts that the grounds of rejection are based on a presumption that the modification of the Schiraldi would be merely a matter of "routine experimentation". Applicant also separately argues that the only relevant disclosure from the Flick reference is a portion of the introductory paragraph form the resource provider (i.e., Knovel); the introduction indicates that the Water-soluble resins book contains "more than 1100 currently available water-soluble resins". Applicant's arguments are unpersuasive and fail to address the actual substance of the rejections – the specific reasons and motivation to modify the prior arts that have been cited.

**Schiraldi**

Applicant asserts that "preferred" molecular weight of PEO are above 3,000,000. However, it is well settled in patent law that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including

nonpreferred embodiments. See Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." See In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). In this case, the fact that the reference indicates a preferred embodiment does not mean that a skilled artisan would have determined not to use other PEO polymers of different molecular weight which are disclosed in the reference as suitable alternatives. In this case, the reference clearly indicates that the PEO useful for the invention has "a relatively high molecular weight, i.e., above 100,000"; applicant's polymers are within this range.

As indicated in the rejection above, Schiraldi states:

> [b]y varying the ratios of the above polymers both the solubility and 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.

See col. 3, lines 25 – 33. The reference teaches and suggests a person of ordinary skill in the art to select different polymers and modify the blend ratio in order to produce films of different solubility (i.e., dissolution rate in the mouth), adhesive properties, etc. Applicant has not addressed how the present invention is still

considered nonobvious in view of these specific parameters known to a person of ordinary skill in the art.

**Flick**

Referring to the resource provider's (Knovel) description paragraph for Water-Soluble Resins by Flick, applicant highlights only the fact that "there are more than 1100 currently available water-soluble resins". This disclosure alone, applicant argues, indicates that a skilled artisan "simply would not be able to predict which particular combination of polymers having which particular molecular weights available to choose from".

A reasonable person of ordinary skill in chemical art would not have agreed to applicant's assertion. Schiraldi specifically teaches using water-soluble or swellable cellulose polymer and PEO with a suitable molecular weight range. The introduction by Knovel in fact states that the Flick reference contains "description" and "information" of those commercially available water-soluble resins which would teach a person of ordinary skill how to use the polymers. The purpose of the introduction to the reference is obviously to persuade readers to buy and use the book, not to dissuade them away from reading the information contained therein. No reasonable chemist would have stopped at finding how many available water-soluble resins are discussed in the book, and then choose to ignore the actual teaching on the subject matter, which the introduction says is disclosed in the book.

As indicated above, Flick teaches that polyethylene oxide resin having MW 300K has a viscosity up to 1100 cps, while the resins having MW 600K and 900K together

have a viscosity ranges of 4500-17600 cps. The reference also indicates that these polymers are effective as a rheology modifier, binder for additives, and produce visco-elastic behavior in solution. Flick teaches the properties and utility of the POE polymers of different molecular weight, thus it would only take ordinary skill in the art to choose and select the polymers that are suitable for different viscosity in solution.

**Schiraldi in view of Flick**

Citing In re Wands, applicant asserts that Schiraldi's "scant teaching" and the number of water-soluble resin polymers which is quoted by the reference provider for Flick, would not have enabled a person of ordinary skill in the art to make the presently claimed invention. Applicant is reminded that the Wands factors are not the legal standard to determine obviousness of a claimed invention. It is well settled in patent law that the Wands factors are considered to determine whether a patent application sufficiently enables a person of ordinary skill in the art to make and use the claimed invention without undue experimentation.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In KSR, the Supreme Court particularly emphasized "the need for caution in granting a patent based on the combination of elements found in the prior art,"Id. at ___,

82 USPQ2d at 1395, and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."Id. at ___, 82 USPQ2d at 1395. The Supreme Court stated that there are "[t]hree cases decided after Graham [that] illustrate this doctrine." Id. at ___, 82 USPQ2d at 1395. (1) "In United States v. Adams, . . . [t]he Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." Id. at ___, 82 USPQ2d at 1395.

The Supreme Court further stated that:

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. Id. at ___, 82 USPQ2d at 1396.

When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id . at ___, 82 USPQ2d at 1396. See MPEP 2141.

Therefore, examiner will continue to make determination of patentability of the presently claimed film product under 35 U.S.C. § 103 (a) and the legal standards as set forth by holdings of Graham and KSR.

Applicant asserts, “there is simply no basis to argue that the optimization of these limitations would be obvious to one of ordinary skill in the art without using the present claims as a roadmap or instruction manual”. Applicant further states,”examiner has not provided a true and rational basis for one of ordinary skill in the art to be motivated to modify Schiraldi to arrive at the present claims”.

The argument is unpersuasive, as Schiraldi provides motivation to vary the type of polymers and modify the weight ratio of the polymers to make films of various properties, which include different solubility and adhesion properties. Flick teaches that the molecular weight of PEO is directly related to the viscosity of the polymer in a solution. Examiner also notes that Schiraldi teaches to use a plasticizer for the purpose "reducing the polymer melt viscosity and to impart flexibility to the final product". See Schiraldi, col. 4, lines 24 - 37. Thus, reducing viscosity of the polymer mixture to produce more flexible final product would have been obviously a driving force to choose a PEO of low viscosity.

Applicant asserts that the prior arts fail to teach or suggest combining PEO of two different weight ranges. In response, what is unobvious about combining two polymers of different molecular weight to obtain a polymer mixture of the median molecular weight?

**Schiraldi and Flick, and further in view of Khan**

Applicant argues Khan fails to cure the alleged deficiencies of Schiraldi and Flick. The Schiraldi/Flick rejection is viewed proper for reasons above, and applicant’s argument is unpersuasive.

***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINA C. YU whose telephone number is (571)272-8605. The examiner can normally be reached on Monday through Thursday, from 8:00AM until 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydown G. Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GINA C. YU/
Primary Examiner, Art Unit 1617

| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 12107389 | YANG ET AL. |
| | Examiner | Art Unit |
| | GINA C YU | 1617 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ✓ | Rejected | - | Cancelled | N | Non-Elected | A | Appeal |
| = | Allowed | ÷ | Restricted | I | Interference | O | Objected |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| CLAIM | | DATE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Final | Original | 04/08/2010 | 10/05/2010 | | | | | | | |
| | 1 | ✓ | ✓ | | | | | | | |
| | 2 | ✓ | ✓ | | | | | | | |
| | 3 | ✓ | ✓ | | | | | | | |
| | 4 | ✓ | ✓ | | | | | | | |
| | 5 | ✓ | ✓ | | | | | | | |
| | 6 | ✓ | ✓ | | | | | | | |
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| | 8 | ✓ | ✓ | | | | | | | |
| | 9 | ✓ | ✓ | | | | | | | |
| | 10 | ✓ | ✓ | | | | | | | |
| | 11 | ✓ | ✓ | | | | | | | |
| | 12 | ✓ | ✓ | | | | | | | |
| | 13 | ✓ | ✓ | | | | | | | |
| | 14 | ✓ | ✓ | | | | | | | |
| | 15 | ✓ | ✓ | | | | | | | |
| | 16 | ✓ | ✓ | | | | | | | |
| | 17 | ✓ | ✓ | | | | | | | |
| | 18 | ✓ | ✓ | | | | | | | |

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 12107389 | YANG ET AL. |
| | Examiner | Art Unit |
| | GINA C YU | 1611 |

| SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| 424 | 434, 435, 436, 443, 484 | 4/8/2010 | gy |
| updated | | 10/5/2010 | gy |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| West, Inventor | 4/8/2010 | gy |
| updated | 10/5/2010 | gy |

| INTERFERENCE SEARCH | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 12107389 |
| Filing Date | 2008-04-22 |
| First Named Inventor | Robert K. Yang |
| Art Unit | 1611 |
| Examiner Name | Gina C. Yu |
| Attorney Docket Number | 1199-26 DIV |

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| Receipt date: 07/29/2010 | Application Number | 12107389 | 12107389 - GAU: 1617 |
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| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2008-04-22 | |
| | First Named Inventor | Robert K. Yang | |
| | Art Unit | 1611 | |
| | Examiner Name | Gina C. Yu | |
| | Attorney Docket Number | 1199-26 DIV | |

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| | 1 | 08011194 | WO | A2 | 2008-01-24 | Biodelivery Sciences International, Inc. | | ☐ |

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(74) Agents: **HANLEY, Elizabeth, A.** et al.; Lahive & Cockfield, Llp, One Post Office Square, Boston, MA 02109-2127 (US).

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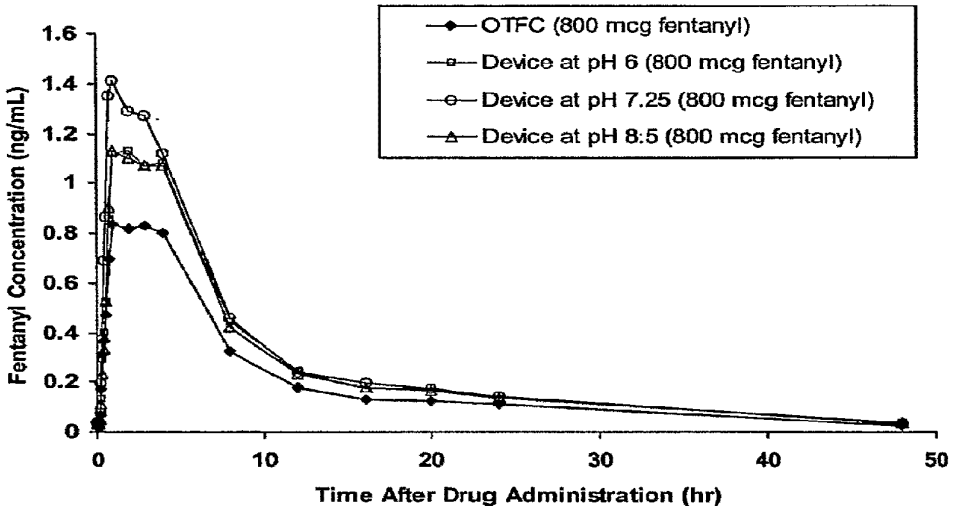
*[Continued on next page]*

(54) Title: TRANSMUCOSAL DELIVERY DEVICES WITH ENHANCED UPTAKE

**Mean Fentanyl Concentration-Time Plots For Three Exemplary Devices of the Invention and OTFC**




(57) Abstract: The present invention provides methods for enhancing transmucosal uptake of a medicament, e.g., fentanyl or buprenorphine, to a subject and related devices. The method includes administering to a subject a transmucosal drug delivery device comprising the medicament. Also provided are devices suitable for transmucosal administration of a medicament to a subject and methods of their administration and use. The devices include a medicament disposed in a mucoadhesive polymeric diffusion environment and a barrier environment.

WO 2008/011194 A2

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# TRANSMUCOSAL DELIVERY DEVICES WITH ENHANCED UPTAKE

## RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 60/832,725, filed July 21, 2006, U.S. Provisional Application No. 60/832,726, filed July 21, 2006, and U.S. Provisional Application No. 60/839,504, filed August 23, 2006. The entire contents of these applications are incorporated herein by this reference. This application is also related to U.S. Serial No. 11/639,408, filed December 13, 2006, and PCT/US2006/47686, also filed December 13, 2006, both of which claim priority to US Provisional Application No. 60/750,191, filed December 13, 2005, and 60/764,618, filed February 2, 2006. The entire contents of these applications are also incorporated herein by this reference.

## BACKGROUND

[0002] US Patent No. 6,264,981 (Zhang *et al.*) describes delivery devices, *e.g.*, tablets of compressed powders that include a solid solution micro-environment formed within the drug formulation. The micro-environment includes a solid pharmaceutical agent in solid solution with a dissolution agent that that facilitates rapid dissolution of the drug in the saliva. The micro-environment provides a physical barrier for preventing the pharmaceutical agent from being contacted by other chemicals in the formulation. The micro-environment may also create a pH segregation in the solid formulation. The pH of the micro-environment is chosen to retain the drug in an ionized form for stability purposes. The rest of the formulation can include buffers so that, upon dissolution in the oral cavity, the pH is controlled in the saliva such that absorption of the drug is controlled.

[0003] US Publication 2004/0253307 also describes solid dosage forms that include buffers that upon dissolution of the solid dosage form maintains the pharmaceutical agent at a desired pH to control absorption, *i.e.*, to overcome the influence of conditions in the surrounding environment, such as the rate of saliva secretion, pH of the saliva and other factors.

## BRIEF SUMMARY OF THE INVENTION

**[0004]** The present invention provides transmucosal devices for enhanced uptake of a medicament and methods of making and using the same. In some embodiments, the devices generally include a mucoadhesive polymeric diffusion environment that facilitates not only the absorption of the medicament across the mucosal membrane to which it is applied, but additionally, the permeability and/or motility of the medicament through the mucoadhesive polymeric diffusion environment to the mucosa.

**[0005]** Accordingly, in one embodiment, the present invention is directed to methods for enhancing direct transmucosal delivery of a fentanyl or fentanyl derivative to a subject. The method generally includes administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface and the fentanyl or fentanyl derivative is delivered to the subject.

**[0006]** In another embodiment, the present invention is directed to methods for treating pain in a subject. The method generally includes transmucosally administering to a subject a therapeutically effective amount of a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the fentanyl or fentanyl derivative is delivered in less than about 30 minutes. In some embodiments, chronic pain is alleviated in the subject. In other embodiments, acute pain is alleviated in the subject. In other embodiments, the pain is breakthrough cancer pain.

**[0007]** In yet another embodiment, the present invention is directed to mucoadhesive delivery devices suitable for direct transmucosal administration of an effective amount of a fentanyl or fentanyl derivative to a subject. The mucoadhesive device generally includes a fentanyl or fentanyl derivative disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is upon application to a mucosal surface.

**[0008]** In another embodiment, the present invention is directed to transmucosal delivery devices that deliver a fentanyl or fentanyl derivative with at least 50% direct buccal absorption and an absolute bioavailability of at least about 70%. In yet another embodiment, the present invention is directed to transmucosal delivery devices that

deliver a fentanyl or fentanyl derivative directly to the mucosa to achieve onset of pain relief ($T_{first}$) of about 0.20 hours or less and time to peak plasma concentration ($T_{max}$) of about 1.6 hours or more. In still another embodiment, the present invention is directed to devices comprising about 800 μg of fentanyl, which exhibit upon transmucosal administration to a subject at least one *in vivo* plasma profile as follows: a $C_{max}$ of about 1.10 ng/mL or more; a $T_{first}$ of about 0.20 hours or less; and an $AUC_{0-24}$ of about 10.00 hr·ng/mL or more. In yet another embodiment, the present invention is directed to transmucosal delivery devices which include a fentanyl or fentanyl derivative that delivers the fentanyl or fentanyl derivative in an amount effective to treat pain, wherein oral irritation, oral ulceration and/or constipation associated with the delivery of the fentanyl or fentanyl derivative is insignificant or eliminated. In one embodiment, the pH of the mucoadhesive polymeric diffusion environment is between about 6.5 and about 8, *e.g.*, about 7.25. In one embodiment, the device comprises about 800 μg of fentanyl. In another embodiment, the device further comprises at least one additional layer that facilitates unidirectional delivery of the fentanyl or fentanyl derivative to the mucosa. In another embodiment, the fentanyl is fentanyl citrate.

**[0009]** In one embodiment, more than 30% of the fentanyl, *e.g.*, more than 55% of the fentanyl, in the device becomes systemically available via mucosal absorption.

**[0010]** In one embodiment, the present invention is directed to methods for enhancing direct transmucosal delivery of buprenorphine to a subject. The method generally includes administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: buprenorphine disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface, and the buprenorphine is delivered to the subject.

**[0011]** In another embodiment, the present invention is directed to methods for treating pain in a subject. The method generally includes transmucosally administering to a subject a therapeutically effective amount of buprenorphine disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the buprenorphine is delivered in less than about 30 minutes. In some embodiments, chronic pain is alleviated in the subject. In other embodiments, acute pain is alleviated in the subject. In other embodiments, the pain is breakthrough cancer pain.

**[0012]** In yet another embodiment, the present invention is directed to mucoadhesive delivery devices suitable for direct transmucosal administration of an effective amount of buprenorphine to a subject. The mucoadhesive device generally includes buprenorphine disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to a mucosal surface. In one embodiment, the pH is between about 4.0 and about 7.5, *e.g.*, about 6.0 or about 7.25. In another embodiment, the device further comprises at least one additional layer that facilitates unidirectional delivery of the buprenorphine to the mucosa.

**[0013]** In one embodiment of the methods and devices of the present invention, the device comprises a pH buffering agent. In one embodiment of the methods and devices of the present invention, the device is adapted for buccal administration or sublingual administration.

**[0014]** In one embodiment of the methods and devices of the present invention, the device is a mucoadhesive disc. In one embodiment of the methods and devices of the present invention, the medicament is formulated as a mucoadhesive film formed to delineate different dosages. In one embodiment of the methods and devices of the present invention, the device comprises a backing layer disposed adjacent to the mucoadhesive polymeric diffusion environment.

**[0015]** In one embodiment of the methods and devices of the present invention, the device further comprises an opioid antagonist. In one embodiment of the methods and devices of the present invention, the device further comprises naloxone.

**[0016]** In one embodiment of the methods and devices of the present invention, the device is a layered, flexible device. In one embodiment of the methods and devices of the present invention, the mucoadhesive polymeric diffusion environment has a buffered environment for the transmucosal administration.

**[0017]** In one embodiment of the methods and devices of the present invention, there is substantially no irritation at the site of transmucosal administration. In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 30 minutes.

**[0018]** In one embodiment of the methods and devices of the present invention, the polymeric diffusion environment comprises at least one ionic polymer system, *e.g.*, polyacrylic acid (optionally crosslinked), sodium carboxymethylcellulose and mixtures

thereof. In one embodiment, the polymeric diffusion environment comprises a buffer system, *e.g.*, citric acid, sodium benzoate or mixtures thereof. In some embodiments, the device has a thickness such that it exhibits minimal mouth feel. In some embodiments, the device has a thickness of about 0.25 mm.

**[0019]** In some embodiments, the present invention provides a flexible, bioerodable mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative to a subject. The mucoadhesive device includes a mucoadhesive layer comprising a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative disposed in a polymeric diffusion environment, wherein the polymeric diffusion environment has a pH of about 7.25 for the fentanyl or fentanyl derivative or a pH of about 6 for the buprenorphine or buprenorphine derivative; and a backing layer comprising a barrier environment which is disposed adjacent to and coterminous with the mucoadhesive layer. The device has no or minimal mouth feel and is able to transmucosally deliver the effective amount of the , fentanyl derivative, buprenorphine or buprenorphine derivative in less than about 30 minutes; and wherein a unidirectional gradient is created upon application of the device to a mucosal surface.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0020]** The foregoing and other aspects, embodiments, objects, features and advantages of the invention can be more fully understood from the following description in conjunction with the accompanying figures.

**[0021]** *Figures 1 and 2* are graphs comparing fentanyl citrate uptake in humans over 2 days post-administration, and 1 hour post-administration, respectively, for exemplary embodiments of the present invention and a commercially available delivery device (Actiq ® Oral Transmucosal Fentanyl Citrate) as described in Examples 1 and 2.

**[0022]** *Figure 3* is a graph comparing buprenorphine uptake in humans over 16 hours post-administration, respectively, for exemplary embodiments of the present invention and a commercially available delivery devices as described in Examples 3 and 4.

**[0023]** *Figures 4A-C* are schematic representations of exemplary embodiments of the present invention.

## DETAILED DESCRIPTION OF THE INVENTION

**[0024]** The present invention is based, at least in part, on the discovery that transmucosal uptake of medicaments can be enhanced by employing a novel polymeric diffusion environment. Such a polymeric diffusion environment is advantageous, *e.g.*, because the absolute bioavailability of the medicament contained therein is enhanced, while also providing a rapid onset. Additionally, less medicament is needed in the device to deliver a therapeutic effect versus devices of the prior art. This renders the device less abusable, an important consideration when the medicament is a controlled substance, such as an opioid. The polymeric diffusion environment described in more detail herein, provides an enhanced delivery profile and more efficient delivery of the medicament. Additional advantages of a polymeric diffusion environment are also described herein.

**[0025]** In order to more clearly and concisely describe the subject matter of the claims, the following definitions are intended to provide guidance as to the meaning of terms used herein.

**[0026]** As used herein, the articles "a" and "an" mean "one or more" or "at least one," unless otherwise indicated. That is, reference to any element of the present invention by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present.

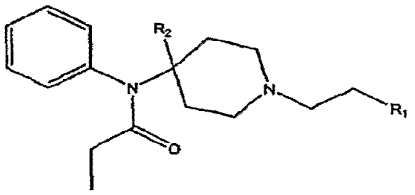
**[0027]** As used herein, the term "acute pain" refers to pain characterized by a short duration, e.g., three to six months. Acute pain is typically associated with tissue damage, and manifests in ways that can be easily described and observed. It can, for example, cause sweating or increased heart rate. Acute pain can also increase over time, and/or occur intermittently.

**[0028]** As used herein, the term "chronic pain" refers to pain which persists beyond the usual recovery period for an injury or illness. Chronic pain can be constant or intermittent. Common causes of chronic pain include, but are not limited to, arthritis, cancer, Reflex Sympathetic Dystrophy Syndrome (RSDS), repetitive stress injuries, shingles, headaches, fibromyalgia, and diabetic neuropathy.

**[0029]** As used herein, the term "breakthrough pain" refers to pain characterized by frequent and intense flares of moderate to severe pain which occur over chronic pain, even when a subject is regularly taking pain medication. Characteristics of breakthrough pain generally include: a short time to peak severity (*e.g.*, three to five minutes);

excruciating severity; relatively short duration of pain (*e.g.*, 15 to 30 minutes); and frequent occurrence (*e.g.*, one to five episodes a day). Breakthrough pain can occur unexpectedly with no obvious precipitating event, or it can be event precipitated. The occurrence of breakthrough pain is predictable about 50% to 60% of the time. Although commonly found in patients with cancer, breakthrough pain also occurs in patients with lower back pain, neck and shoulder pain, moderate to severe osteoarthritis, and patients with severe migraine.

**[0030]** As used herein, unless indicated otherwise, the term "fentanyl", includes any pharmaceutically acceptable form of fentanyl, including, but not limited to, salts, esters, and prodrugs thereof. The term "fentanyl" includes fentanyl citrate. As used herein, the term "fentanyl derivative" refers to compounds having similar structure and function to fentanyl. In some embodiments, fentanyl derivatives include those of the following formula:

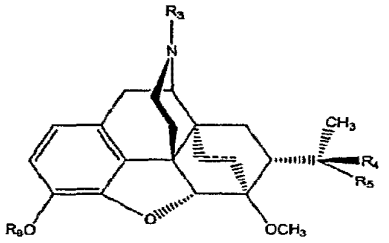



or pharmaceutically acceptable salts or esters thereof, wherein

$R_1$ is selected from an aryl group, a heteroaryl group or a –COO-$C_{1-4}$ alkyl group; and $R_2$ is selected from –H, a -$C_{1-4}$ alkyl-O-$C_{1-4}$ alkyl group or a –COO-$C_{1-4}$ alkyl group.

Fentanyl derivatives include, but are not limited to, alfentanil, sufentanil, remifentanil and carfentanil.

**[0031]** As used herein, unless indicated otherwise, the term "buprenorphine", includes any pharmaceutically acceptable form of buprenorphine, including, but not limited to, salts, esters, and prodrugs thereof. As used herein, the term "buprenorphine derivative" refers to compounds having similar structure and function to buprenorphine. In some embodiments, fentanyl derivatives include those of the following formula:



or pharmaceutically acceptable salts or esters thereof, wherein

is a double or single bond; $R_3$ is selected from a -$C_{1-4}$ alkyl group or a cycloalkyl-substituted-$C_{1-4}$ alkyl group; $R_4$ is selected from a -$C_{1-4}$ alkyl; $R_5$ is –OH, or taken together, $R_4$ and $R_5$ form a =O group; and $R_6$ is selected from –H or a -$C_{1-4}$ alkyl group.

Buprenorphine derivatives include, but are not limited to, etorphine and diprenorphine.

**[0032]** As used herein, "polymeric diffusion environment" refers to an environment capable of allowing flux of a medicament to a mucosal surface upon creation of a gradient by adhesion of the polymeric diffusion environment to a mucosal surface. The flux of a transported medicament is proportionally related to the diffusivity of the environment which can be manipulated by, *e.g.*, the pH, taking into account the ionic nature of the medicament and/or the ionic nature polymer or polymers included in the environment and.

**[0033]** As used herein, "barrier environment" refers to an environment in the form of, *e.g.*, a layer or coating, capable of slowing or stopping flux of a medicament in its direction. In some embodiments, the barrier environment stops flux of a medicament, except in the direction of the mucosa. In some embodiments, the barrier significantly slows flux of a medicament, *e.g.*, enough so that little or no medicament is washed away by saliva.

**[0034]** As used herein, the term "unidirectional gradient" refers to a gradient which allows for the flux of a medicament (*e.g.*, fentanyl or buprenorphine) through the device, *e.g.*, through a polymeric diffusion environment, in substantially one direction, *e.g.*, to the mucosa of a subject. For example, the polymeric diffusion environment may be a mucoadhesive polymeric diffusion environment in the form of a layer or film disposed adjacent to a backing layer or film. Upon mucoadministration, a gradient is created between the mucoadhesive polymeric diffusion environment and the mucosa, and the medicament flows from the mucoadhesive polymeric diffusion environment, substantially in one direction towards the mucosa. In some embodiments, some flux of the medicament is not entirely unidirectional across the gradient; however, there is typically not free flux of the medicament in all directions. Such unidirectional flux is described in more detail herein, *e.g.*, in relation to Figure 4.

[0035] As used herein, "treating" or "treatment" of a subject includes the administration of a drug to a subject with the purpose of preventing, curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving, stabilizing or affecting a disease or disorder, or a symptom of a disease or disorder (e.g., to alleviate pain).

[0036] The term "subject" refers to living organisms such as humans, dogs, cats, and other mammals. Administration of the medicaments included in the devices of the present invention can be carried out at dosages and for periods of time effective for treatment of a subject. In some embodiments, the subject is a human. In some embodiments, the pharmacokinetic profiles of the devices of the present invention are similar for male and female subjects. An "effective amount" of a drug necessary to achieve a therapeutic effect may vary according to factors such as the age, sex, and weight of the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

[0037] The term "transmucosal," as used herein, refers to any route of administration via a mucosal membrane. Examples include, but are not limited to, buccal, sublingual, nasal, vaginal, and rectal. In one embodiment, the administration is buccal. In one embodiment, the administration is sublingual. As used herein, the term "direct transmucosal" refers to mucosal administration via the oral mucosa, *e.g.*, buccal and/or sublingual.

[0038] As used herein, the term "water erodible" or "at least partially water erodible" refers to a substance that exhibits a water erodibility ranging from negligible to completely water erodible. The substance may readily dissolve in water or may only partially dissolve in water with difficulty over a long period of time. Furthermore, the substance may exhibit a differing erodibility in body fluids compared with water because of the more complex nature of body fluids. For example, a substance that is negligibly erodible in water may show an erodibility in body fluids that is slight to moderate. However, in other instances, the erodibility in water and body fluid may be approximately the same.

[0039] The present invention provides transmucosal delivery devices that uniformly and predictably deliver a medicament to a subject. The present invention also

provides methods of delivery of a medicament to a subject employing devices in accordance with the present invention. Accordingly, in one embodiment, the present invention is directed to mucoadhesive delivery devices suitable for direct transmucosal administration of an effective amount of a medicament, *e.g.*, fentanyl or fentanyl derivative or buprenorphine to a subject. The mucoadhesive device generally includes a medicament disposed in a polymeric diffusion environment; and a having a barrier such that a unidirectional gradient is created upon application to a mucosal surface, wherein the device is capable of delivering in a unidirectional manner the medicament to the subject. The present invention also provides methods of delivery of a medicament to a subject employing the devices in accordance with the present invention.

**[0040]** In another embodiment, the present invention is directed to methods for enhancing direct transmucosal delivery of a medicament, *e.g.*, fentanyl, fentanyl derivatives and/or buprenorphine, to a subject. The method generally includes administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: a medicament disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface, wherein an effective amount of the medicament is delivered to the subject.

**[0041]** In another embodiment, the present invention is directed to methods for treating pain in a subject. The method generally includes transmucosally administering to a subject a therapeutically effective amount of a medicament, *e.g.*, fentanyl, fentanyl derivatives and/or buprenorphine, disposed in a mucoadhesive polymeric diffusion environment having a thickness such that the effective amount of the medicament is delivered in less than about 30 minutes and such that pain is treated. In some embodiments, the medicament is delivered in less than about 25 minutes. In some embodiments, the medicament is delivered in less than about 20 minutes.

**[0042]** In some embodiments of the above methods and devices, an effective amount is delivered transmucosally. In other embodiments, an effective amount is delivered transmucosally and by gastrointestinal absorption. In still other embodiments, an effective amount is delivered transmucosally, and delivery though the gastrointestinal absorption augments and/or maintains treatment, *e.g.*, pain relief for a desired period of time, *e.g.*, at least 1, 1.5, 2, 2.5, 3, 3.5, or 4 or more hours.

**[0043]** In yet another embodiment, the present invention is directed to transmucosal delivery devices that deliver a fentanyl or fentanyl derivative directly to the mucosa to achieve onset of pain relief ($T_{first}$) of about 0.20 hours or less and time to peak plasma concentration ($T_{max}$) of about 1.6 hours or more. The combination of a rapid onset with a delayed maximum concentration is particularly advantageous when treating pain, *e.g.*, relief for breakthrough cancer pain (BTP) in opioid tolerant patients with cancer, because immediate relief is provided to alleviate a flare of moderate to severe pain but persistence is also provided to alleviate subsequent flares. Conventional delivery systems may address either the immediate relief or subsequent flare-ups, but the devices of this embodiment are advantageous because they address both.

***Table 1: Selected Pharmacokinetic properties of transmucosal devices.***

| | $T_{first}$ | $T_{max}$ | Total Bioavailability |
|---|---|---|---|
| BEMA pH 7.25 | 0.15 hours | 1.61 hours | 70% |
| Actiq® | 0.23 hours | 2.28 hours | 47% |
| Fentora® | 0.25 hours* | 0.50 hours | 65% |

* - reported as onset of main relief, first time point measured.

**[0044]** The devices of the present invention may have a number of additional or alternative desirable properties, as described in more detail herein. Accordingly, in another embodiment, the present invention is directed to transmucosal delivery devices that deliver a fentanyl or fentanyl derivative with at least 50% direct buccal absorption and an absolute bioavailability of at least about 70%. In still another embodiment, the present invention is directed to devices comprising about 800 $\mu$g of fentanyl, which exhibit upon transmucosal administration to a subject at least one *in vivo* plasma profile as follows: a $C_{max}$ of about 1.10 ng/mL or more; a $T_{first}$ of about 0.20 hours or less; and an $AUC_{0-24}$ of about 10.00 hr·ng/mL or more.

**[0045]** The pain can be any pain known in the art, caused by any disease, disorder, condition and/or circumstance. In some embodiments, chronic pain is alleviated in the subject using the methods of the present invention. In other embodiments, acute pain is alleviated in the subject using the methods of the present invention. Chronic pain can arise from many sources including, cancer, Reflex Sympathetic Dystrophy Syndrome (RSDS), and migraine. Acute pain is typically directly related to tissue damage, and lasts for a relatively short amount of time, *e.g.*, three to six months. In other embodiments, the pain is breakthrough cancer pain. In some embodiments, the methods and devices of the present invention can be used to

alleviate breakthrough pain in a subject. For example, the devices of the present invention can be used to treat breakthrough pain in a subject already on chronic opioid therapy. In some embodiments, the devices and methods of the present invention provide rapid analgesia and/or avoid the first pass metabolism of fentanyl, thereby resulting in more rapid breakthrough pain relief than other treatments, *e.g.*, oral medications.

**[0046]** In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 60% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 70% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 80% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 90% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 100% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 25 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 20 minutes.

**[0047]** Without wishing to be bound by any particular theory, it is believed that delivery of the medicament is particularly effective because the mucoadhesive polymeric diffusion environment (*e.g.*, the pH and the ionic nature of the polymers) is such that the medicament (*e.g.*, a weakly basic drug such as fentanyl or buprenorphine) can rapidly move through the mucoadhesive polymeric diffusion environment to the mucosa, while also allowing efficient absorption by the mucosa. For example, in some embodiments, the pH is low enough to allow movement of the medicament, while high enough for absorption.

**[0048]** In some embodiments, the mucoadhesive polymeric diffusion environement is a layer with a buffered pH such that a desired pH is maintained at the mucosal administration site. Accordingly, the effect of any variation in pH encountered

in a subject or between subjects (*e.g.*, due to foods or beverages recently consumed), including any effect on uptake, is reduced or eliminated.

**[0049]** Accordingly, one advantage of the present invention is that variability in the properties of the device (*e.g.*, due to changes in the pH of the ingredients) between devices, and from lot to lot is reduced or eliminated. Without wishing to be bound by any particular theory, it is believed that the polymeric diffusion environment of the present invention reduces variation, *e.g.*, by maintaining a buffered pH. Yet another advantage is pH variability at the administration site (e.g., due to what food or drink or other medications was recently consumed) is reduced or eliminated, such that, *e.g.*, the variability of the devices is reduced or eliminated.

**[0050]** A medicament for use in the present invention includes any medicament capable of being administered transmucosally. The medicament can be suitable for local delivery to a particular mucosal membrane or region, such as the buccal and nasal cavities, throat, vagina, alimentary canal or the peritoneum. Alternatively, the medicament can be suitable for systemic delivery via such mucosal membranes.

**[0051]** In one embodiment, the medicament can be an opioid. Opioids suitable for use in the present invention include, *e.g.*, alfentanil, allylprodine, alphaprodine, apomorphine, anileridine, apocodeine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclorphan, cyprenorphine, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, eptazocine, ethylmorphine, etonitazene, etorphine, fentanyl, fencamfamine, fenethylline, hydrocodone, hydromorphone, hydroxymethylmorphinan, hydroxypethidine, isomethadone, levomethadone, levophenacylmorphan, levorphanol, lofentanil, mazindol, meperidine, metazocine, methadone, methylmorphine, modafinil, morphine, nalbuphene, necomorphine, normethadone, normorphine, opium, oxycodone, oxymorphone, pholcodine, profadol remifentanil, sufentanil, tramadol, corresponding derivatives, physiologically acceptable compounds, salts and bases. In some embodiments, the medicament is fentanyl, *e.g.*, fentanyl citrate. In some embodiments, the medicament is buprenorphine.

**[0052]** The amount of medicament, *e.g.* fentanyl or buprenorphine, to be incorporated into the device of the present invention depends on the desired treatment dosage to be administered, *e.g.*, the fentanyl or fentanyl derivative can be present in

about 0.001% to about 50% by weight of the device of the present invention, and in some embodiments between about 0.005 and about 35% by weight or the buprenorphine can be present in about 0.001% to about 50% by weight of the device of the present invention, and in some embodiments between about 0.005 and about 35% by weight. In one embodiment, the device comprises about 3.5% to about 4.5% fentanyl or fentanyl derivative by weight. In one embodiment, the device comprises about 3.5% to about 4.5% buprenorphine by weight. In another embodiment, the device comprises about 800 μg of a fentanyl such as fentanyl citrate. In another embodiment the device comprises about 25, 50, 75, 100, 150, 200, 300, 400, 500, 600, 700, 900, 1000, 1200, 1500, 1600 or 2000 μg of a fentanyl such as fentanyl citrate or fentanyl derivative. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention. In another embodiment, the device comprises about 800 μg of buprenorphine. In another embodiment the device comprises about 100, 200, 300, 400, 500, 600, 700, 900, 1000, 1200, 1500, or 2000 μg of buprenorphine. In another embodiment the device comprises about 25, 50, 75, 100, 150, 200, 300, 400, 500, 600, 700, 900, 1000, 1200, 1500, 1600 or 2000 μg of any of the medicaments described herein.

**[0053]** One approach to reaching an effective dose is through titration with multiple dosage units such that patients start with a single 200 mcg unit and progressively increase the number of units applied until reaching an effective dose or 800 mcg (4 units) dose as the multiple discs once an effective dose has been identified. Accordingly, in some embodiments, the methods of the present invention also include a titration phase to identify a dose that relieves pain and produces minimal toxicity, because the dose of opioid, *e.g.*, fentanyl, required for control of breakthrough pain episodes is often not easily predicted. The linear relationship between surface area of the devices of the present invention and pharmacokinetic profile may be exploited in the dose titration process through the application of single or multiple discs to identify an appropriate dose, and then substitution of a single disc containing the same amount of medicament.

**[0054]** In one embodiment, the devices of the present invention are capable of delivering a greater amount of fentanyl systemically to the subject than conventional devices. According to the label for Actiq ® Oral Transmucosal Fentanyl Citrate, approximately 25% of the fentanyl in the ACTIQ product is absorbed via the buccal

mucosa, and of the remaining 75% that is swallowed, another 25% of the total fentanyl becomes available via absorption in the GI tract for a total of 50% total bioavailability. According to Fentora Fentanyl Buccal tablet literature, approximately 48% of the fentanyl in FENTORA product is absorbed via the buccal mucosa, and of the remainig 52%, another 17% of the total fentanyl becomes available via absorption in the GI tract for a total of 65% total bioavailability. Accordingly, in some embodiments, more than about 30% of the fentanyl disposed in the devices of the present invention becomes systemically available or bioavailable via absorption by the mucosa. In some embodiments, more than about 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% becomes systemically available via mucosal absorption. In some embodiments, more than about 55%, 60%, 65% or 70% of the fentanyl disposed in the devices of the present invention becomes systemically available or bioavailable by any route, mucosal and/or GI tract. In some embodiments, more than about 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% becomes systemically available.

**[0055]** Accordingly, another advantage of the devices and methods of the present invention is that because the devices of the present invention more efficiently deliver the medicament, *e.g.*, fentanyl or buprenorphine, than do conventional devices, less medicament can be included than must be included in conventional devices to deliver the same amount of medicament. Accordingly, in some embodiments, the devices of the present invention are not irritating to the mucosal surface on which it attaches. In some embodiments, the devices of the present invention cause little or no constipation, even when the devices include an opioid antagonist such as naloxone. In yet another embodiment, the present invention is directed to transmucosal delivery devices which include a fentanyl or fentanyl derivative that delivers the fentanyl or fentanyl derivative in an amount effective to treat pain, wherein oral irritation, oral ulceration and/or constipation associated with the delivery of the fentanyl or fentanyl derivative is not significant or eliminated.

**[0056]** Another advantage is the devices of the present invention are less subject to abuse than conventional devices because less medicament, *e.g.*, fentanyl or buprenorphine, is required in the device, *i.e.*, there is less medicament to be extracted by an abuser for injection into the bloodstream.

**[0057]** In some embodiments, the devices of the present invention have a dose response that is substantially directly proportional to the amount of medicament present

in the device. For example, if the $C_{max}$ is 10 ng/mL for a 500 dose, then it is expected in some embodiments that a 1000 $\mu$g dose will provide a $C_{max}$ of approximately 20 ng/mL. Without wishing to be bound by any particular theory, it is believed that this is advantageous in determining a proper dose in a subject.

**[0058]** In some embodiments, the devices of the present invention further comprise an opioid antagonist in any of various forms, e.g., as salts, bases, derivatives, or other corresponding physiologically acceptable forms. Opioid antagonists for use with the present invention include, but are not limited to, naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine, naluphine, cyclazocine, levallorphan and physiologically acceptable salts and solvates thereof, or combinations thereof. In one embodiment, the device further comprises naloxone.

**[0059]** In some embodiments, the properties of the polymeric diffusion environment are effected by its pH. In one embodiment, *e.g.*, when the medicament is fentanyl, the pH of the mucoadhesive polymeric diffusion environment in the devices of the present invention is between about 6.5 and about 8. In another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 7.25. In another embodiment, the pH is between about 7.0 and about 7.5, or between about 7.25 and 7.5. In other embodiments, the pH is about 6.5, 7.0, 7.5, 8.0 or 8.5, or any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

**[0060]** In one embodiment, *e.g.*, when the medicament is buprenorphine, the pH of the mucoadhesive polymeric diffusion environment in the devices of the present invention is between about 4.0 and about 7.5. In another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 6.0. In one embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 5.5 to about 6.5, or between about 6.0 and 6.5. In yet another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 7.25. In another embodiment, the pH is between about 7.0 and 7.5, or between about 7.25 and 7.5. In other embodiments, the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5, or any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

**[0061]** The pH of the mucoadhesive polymeric diffusion environment can be adjusted and/or maintained by methods including, but not limited to, the use of buffering

agents, or by adjusting the composition of the device of the present invention. For example, adjustment of the components of the device of the present invention that influence pH, e.g., the amount of anti-oxidant, such as citric acid, contained in the device will adjust the pH of the device.

**[0062]** In some embodiments, the properties of the polymeric diffusion environment are effected by its buffering capacity. In some embodiments, buffering agents are included in the mucoadhesive mucoadhesive polymeric diffusion environment. Buffering agents suitable for use with the present invention include, for example, phosphates, such as sodium phosphate; phosphates monobasic, such as sodium dihydrogen phosphate and potassium dihydrogen phosphate; phosphates dibasic, such as disodium hydrogen phosphate and dipotassium hydrogen phosphate; citrates, such as sodium citrate (anhydrous or dehydrate); bicarbonates, such as sodium bicarbonate and potassium bicarbonate may be used. In one embodiment, a single buffering agent, *e.g.*, a dibasic buffering agent is used. In another embodiment, a combination of buffering agents is employed, *e.g.*, a combination of a tri-basic buffering agent and a monobasic buffering agent.

**[0063]** In one embodiment, the mucoadhesive polymeric diffusion environment of the device will have a buffered environment, *i.e.*, a stabilized pH, for the transmucosal administration of a medicament. The buffered environment of the device allows for the optimal administration of the medicament to a subject. For example, the buffered environment can provide a desired pH at the mucosa when in use, regardless of the circumstances of the mucosa prior to administration.

**[0064]** Accordingly, in various embodiments, the devices include a mucoadhesive polymeric diffusion environment having a buffered environment that reduces or eliminates pH variability at the site of administration due to, for example, medications, foods and/or beverages consumed by the subject prior to or during administration. Thus, pH variation encountered at the site of administration in a subject from one administration to the next may have minimal or no effect on the absorption of the medicament. Further, pH variation at the administration site between different patients will have little or no effect on the absorption of the medicament. Thus, the buffered environment allows for reduced inter- and intra- subject variability during transmucosal administration of the medicament. In another embodiment, the present invention is directed to methods for enhancing uptake of a medicament that include administering to

a subject a device including a medicament disposed in a mucoadhesive polymeric diffusion environment having a buffered environment for the transmucosal administration. In yet another embodiment, the present invention is directed to methods of delivering a therapeutically effective amount of a medicament to a subject that include administering a device including a medicament disposed in a mucoadhesive polymeric diffusion environment having a buffered environment for the transmucosal administration.

**[0065]** The devices of the present invention can include any combination or sub-combination of ingredients, layers and/or compositions of, *e.g.*, the devices described in US Patent No. 6,159,498, US Patent No. 5,800,832, US Patent No. 6,585,997, US Patent No. 6,200,604, US Patent No. 6,759,059 and/or PCT Publication No. WO 05/06321. The entire contents of these patent and publications are incorporated herein by reference in their entireties.

**[0066]** In some embodiments, the properties of the polymeric diffusion environment are effected by the ionic nature of the polymers employed in the environment. In one embodiment, the mucoadhesive polymeric diffusion environment is water-erodible and can be made from a bioadhesive polymer(s) and optionally, a first film-forming water-erodible polymer(s). In one embodiment, the polymeric diffusion environment comprises at least one ionic polymer system, *e.g.*, polyacrylic acid (optionally crosslinked), sodium carboxymethylcellulose and mixtures thereof.

**[0067]** In some embodiments, the mucoadhesive polymeric diffusion environment can include at least one pharmacologically acceptable polymer capable of bioadhesion (the "bioadhesive polymer") and can optionally include at least one first film-forming water-erodible polymer (the "film-forming polymer"). Alternatively, the mucoadhesive polymeric diffusion environment can be formed of a single polymer that acts as both the bioadhesive polymer and the first film-forming polymer. Additionally or alternatively, the water-erodible mucoadhesive polymeric diffusion environment can include other first film-forming water-erodible polymer(s) and water-erodible plasticizer(s), such as glycerin and/or polyethylene glycol (PEG).

**[0068]** In some embodiments, the bioadhesive polymer of the water-erodible mucoadhesive polymeric diffusion environment can include any water erodible substituted cellulosic polymer or substituted olefinic polymer wherein the substituents may be ionic or hydrogen bonding, such as carboxylic acid groups, hydroxyl alkyl

groups, amine groups and amide groups. For hydroxyl containing cellulosic polymers, a combination of alkyl and hydroxyalkyl groups will be preferred for provision of the bioadhesive character and the ratio of these two groups will have an effect upon water swellability and disperability. Examples include polyacrylic acid (PAA), which can optionally be partially crosslinked, sodium carboxymethyl cellulose (NaCMC), moderately to highly substituted hydroxypropylmethyl cellulose (HPMC), polyvinylpyrrolidone (PVP, which can optionally be partially crosslinked), moderately to highly substituted hydroxyethylmethyl cellulose (HEMC) or combinations thereof. In one embodiment, HEMC can be used as the bioadhesive polymer and the first film forming polymer as described above for a mucoadhesive polymeric diffusion environment formed of one polymer. These bioadhesive polymers are preferred because they have good and instantaneous mucoadhesive properties in a dry, system state.

**[0069]** The first film-forming water-erodible polymer(s) of the mucoadhesive polymeric diffusion environment can be hydroxyalkyl cellulose derivatives and hydroxyalkyl alkyl cellulose derivatives preferably having a ratio of hydroxyalkyl to alkyl groups that effectively promotes hydrogen bonding. Such first film-forming water-erodible polymer(s) can include hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), hydroxyethylmethyl cellulose (HEMC), or a combination thereof. Preferably, the degree of substitution of these cellulosic polymers will range from low to slightly above moderate.

**[0070]** Similar film-forming water-erodible polymer(s) can also be used. The film-forming water-erodible polymer(s) can optionally be crosslinked and/or plasticized in order to alter its dissolution kinetics.

**[0071]** In some embodiments, the mucoadhesive polymeric diffusion environment, *e.g.*, a bioerodable mucoadhesive polymeric diffusion environment, is generally comprised of water-erodible polymers which include, but are not limited to, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, polyacrylic acid (PAA) which may or may not be partially crosslinked, sodium carboxymethyl cellulose (NaCMC), and polyvinylpyrrolidone (PVP), or combinations thereof. Other mucoadhesive water-erodible polymers may also be used in the present invention. The term "polyacrylic acid" includes both uncrosslinked and partially crosslinked forms, *e.g.*, polycarbophil.

[0072] In some embodiments, the mucoadhesive polymeric diffusion environment is a mucoadhesive layer, e.g, a bioerodable mucoadhesive layer. In some embodiments, the devices of the present invention include a bioerodable mucoadhesive layer which comprises a mucoadhesive polymeric diffusion environment.

[0073] In some embodiments, the properties of the polymeric diffusion environment are effected by the barrier environment. The barrier environment is disposed such that the flux of medicament is substantially unidirectional. For example, in an exemplary layered device of the present invention, having a layer comprising a medicament dispersed in a polymeric diffusion environment and a co-terminus barrier layer (see, *e.g.*, Figure 4B), upon application to the mucosa, some medicament may move to and even cross the boundary not limited by the mucosa or barrier layer. In another exemplary layered device of the present invention, a barrier layer does not completely circumscribe the portion of the mucoadhesive polymeric diffusion environment that will not be in direct contact with the mucosa upon application of the device (see, *e.g.*, Figure 4C). A majority of the medicament in both of these cases, however, flows towards the mucosa. In another exemplary layered device of the present invention, having a barrier layer which circumscribes the portion of the mucoadhesive polymeric diffusion environment that will not be in direct contact with the mucosa upon application of the device (see, *e.g.*, Figure 4A), upon application to the mucosa, substantially all of the medicament typically flows towards the mucosa.

[0074] The barrier environment can be, *e.g.*, a backing layer. A backing layer can be included as an additional layer disposed adjacent to the mucoadhesive polymeric diffusion environment. The layers can be coterminous, or, *e.g.*, the barrier layer may circumscribe the portion of the mucoadhesive polymeric diffusion environment that will not be in direct contact with the mucosa upon application of the device. In one embodiment, the device comprises a backing layer disposed adjacent to the mucoadhesive polymeric diffusion environment. The device of the present invention can also comprise a third layer or coating. A backing layer can be also included in the devices of the present invention as a layer disposed adjacent to a layer which is, in turn, disposed adjacent to the mucoadhesive polymeric diffusion environment (i.e., a three layer device).

[0075] In one embodiment, the device further comprises at least one additional layer that facilitates unidirectional delivery of the medicament to the mucosa. In one

embodiment, the device of the present invention further comprises at least one additional layer disposed adjacent to the mucoadhesive polymeric diffusion environment. Such layer can include additional medicament or different medicaments, and/or can be present to further reduce the amount of medicament (originally in the mucoadhesive polymeric diffusion environment) that is washed away in the saliva.

**[0076]** Specialty polymers and non-polymeric materials may also optionally be employed to impart lubrication, additional dissolution protection, drug delivery rate control, and other desired characteristics to the device. These third layer or coating materials can also include a component that acts to adjust the kinetics of the erodability of the device.

**[0077]** The backing layer is a non-adhesive water-erodible layer that may include at least one water-erodible, film-forming polymer. In some embodiments, the backing layer will at least partially or substantially erode or dissolve before the substantial erosion of the mucoadhesive polymeric diffusion environment.

**[0078]** The barrier environment and/or backing layer can be employed in various embodiments to promote unidirectional delivery of the medicament (*e.g.*, fentanyl) to the mucosa and/or to protect the mucoadhesive polymeric diffusion environment against significant erosion prior to delivery of the active to the mucosa. In some embodiments, dissolution or erosion of the water-erodible non-adhesive backing layer primarily controls the residence time of the device of the present invention after application to the mucosa. In some embodiments, dissolution or erosion of the barrier environment and/or backing layer primarily controls the directionality of medicament flow from the device of the present invention after application to the mucosa.

**[0079]** The barrier environment and/or backing layer (*e.g.*, a water-erodible non-adhesive backing layer) can further include at least one water erodible, film-forming polymer. The polymer or polymers can include polyethers and polyalcohols as well as hydrogen bonding cellulosic polymers having either hydroxyalkyl group substitution or hydroxyalkyl group and alkyl group substitution preferably with a moderate to high ratio of hydroxyalkyl to alkyl group. Examples include, but are not limited to, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), hydroxyethylmethyl cellulose (HEMC), polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyethylene oxide (PEO), ethylene oxide-propylene oxide co polymers, and combinations thereof. The water-erodible non-adhesive backing layer

component can optionally be crosslinked. In one embodiment, the water erodible non-adhesive backing layer includes hydroxyethyl cellulose and hydroxypropyl cellulose. The water-erodible non-adhesive backing layer can function as a slippery surface, to avoid sticking to mucous membrane surfaces.

**[0080]** In some embodiments, the barrier environment and/or backing layer, *e.g.*, a bioerodible non-adhesive backing layer, is generally comprised of water-erodible, film-forming pharmaceutically acceptable polymers which include, but are not limited to, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, polyvinylalcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, or combinations thereof. The backing layer may comprise other water-erodible, film-forming polymers.

**[0081]** The devices of the present invention can include ingredients that are employed to, at least in part, provide a desired residence time. In some embodiments, this is a result of the selection of the appropriate backing layer formulation, providing a slower rate of erosion of the backing layer. Thus, the non-adhesive backing layer is further modified to render controlled erodibility which can be accomplished by coating the backing layer film with a more hydrophobic polymer selected from a group of FDA approved Eudragit™ polymers, ethyl cellulose, cellulose acetate phthalate, and hydroxyl propyl methyl cellulose phthalate, that are approved for use in other pharmaceutical dosage forms. Other hydrophobic polymers may be used, alone or in combination with other hydrophobic or hydrophilic polymers, provided that the layer derived from these polymers or combination of polymers erodes in a moist environment. Dissolution characteristics may be adjusted to modify the residence time and the release profile of a drug when included in the backing layer.

**[0082]** In some embodiments, any of the layers in the devices of the present invention may also contain a plasticizing agent, such as propylene glycol, polyethylene glycol, or glycerin in a small amount, 0 to 15% by weight, in order to improve the "flexibility" of this layer in the mouth and to adjust the erosion rate of the device. In addition, humectants such as hyaluronic acid, glycolic acid, and other alpha hydroxyl acids can also be added to improve the "softness" and "feel" of the device. Finally, colors and opacifiers may be added to help distinguish the resulting non-adhesive backing layer from the mucoadhesive polymeric diffusion environment. Some opacifers include titanium dioxide, zinc oxide, zirconium silicate, etc.

**[0083]** Combinations of different polymers or similar polymers with definite molecular weight characteristics can be used in order to achieve preferred film forming capabilities, mechanical properties, and kinetics of dissolution. For example, polylactide, polyglycolide, lactide-glycolide copolymers, poly-e-caprolactone, polyorthoesters, polyanhydrides, ethyl cellulose, vinyl acetate, cellulose, acetate, polyisobutylene, or combinations thereof can be used.

**[0084]** The device can also optionally include a pharmaceutically acceptable dissolution-rate-modifying agent, a pharmaceutically acceptable disintegration aid (*e.g.*, polyethylene glycol, dextran, polycarbophil, carboxymethyl cellulose, or poloxamers), a pharmaceutically acceptable plasticizer, a pharmaceutically acceptable coloring agent (e.g., FD&C Blue #1), a pharmaceutically acceptable opacifier (e.g., titanium dioxide), pharmaceutically acceptable anti-oxidant (e.g., tocopherol acetate), a pharmaceutically acceptable system forming enhancer (*e.g.*, polyvinyl alcohol or polyvinyl pyrrolidone), a pharmaceutically acceptable preservative, flavorants (e.g., saccharin and peppermint), neutralizing agents (e.g., sodium hydroxide), buffering agents (*e.g.*, monobasic, or tribasic sodium phosphate), or combinations thereof. Preferably, these components are individually present at no more than about 1% of the final weight of the device, but the amount may vary depending on the other components of the device.

**[0085]** The device can optionally include one or more plasticizers, to soften, increase the toughness, increase the flexibility, improve the molding properties, and/or otherwise modify the properties of the device. Plasticizers for use in the present invention can include, *e.g.*, those plasticizers having a relatively low volatility such as glycerin, propylene glycol, sorbitol, ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol, polypropylene glycol, dipropylene glycol, butylene glycol, diglycerol, polyethylene glycol (*e.g.*, low molecular weight PEG's), oleyl alcohol, cetyl alcohol, cetostearyl alcohol, and other pharmaceutical-grade alcohols and diols having boiling points above about 100°C at standard atmospheric pressure. Additional plasticizers include, *e.g.*, polysorbate 80, triethyl titrate, acetyl triethyl titrate, and tributyl titrate. Additional suitable plasticizers include, *e.g.*, diethyl phthalate, butyl phthalyl butyl glycolate, glycerin triacetin, and tributyrin. Additional suitable plasticizers include, *e.g.*, pharmaceutical agent grade hydrocarbons such as mineral oil (*e.g.*, light mineral oil) and petrolatum. Further suitable plasticizers include, e.g., triglycerides such as medium-chain triglyceride, soybean oil, safflower oil, peanut oil,

and other pharmaceutical agent grade triglycerides, PEGylated triglycerides such as Labrifil®, Labrasol® and PEG-4 beeswax, lanolin, polyethylene oxide (PEO) and other polyethylene glycols, hydrophobic esters such as ethyl oleate, isopropyl myristate, isopropyl palmitate, cetyl ester wax, glyceryl monolaurate, and glyceryl monostearate.

**[0086]** One or more disintegration aids can optionally be employed to increase the disintegration rate and shorten the residence time of the device of the present invention. Disintegration aids useful in the present invention include, *e.g.*, hydrophilic compounds such as water, methanol, ethanol, or low alkyl alcohols such as isopropyl alcohol, acetone, methyl ethyl acetone, alone or in combination. Specific disintegration aids include those having less volatility such as glycerin, propylene glycol, and polyethylene glycol.

**[0087]** One or more dissolution-rate-modifying agents can optionally be employed to decrease the disintegration rate and lengthen the residence time of the device of the present invention. Dissolution-rate modifying agents useful in the present invention include, *e.g.*, hydrophobic compounds such as heptane, and dichloroethane, polyalkyl esters of di and tricarboxylic acids such as succinic and citric acid esterified with C6 to C20 alcohols, aromatic esters such as benzyl benzoate, triacetin, propylene carbonate and other hydrophobic compounds that have similar properties. These compounds can be used alone or in combination in the device of the invention.

**[0088]** The devices of the present invention can include various forms. For example, the device can be a disc or film. In one embodiment, the device comprises a mucoadhesive disc. In one embodiment of the methods and devices of the present invention, the device is a layered, flexible device. The thickness of the device of the present invention, in its form as a solid film or disc, may vary, depending on the thickness of each of the layers. Typically, the bilayer thickness ranges from about 0.01 mm to about 1 mm, and more specifically, from about 0.05 mm to about 0.5 mm. The thickness of each layer can vary from about 10% to about 90% of the overall thickness of the device, and specifically can vary from about 30% to about 60% of the overall thickness of the device. Thus, the preferred thickness of each layer can vary from about 0.005 mm to about 1.0 mm, and more specifically from about 0.01 mm to about 0.5 mm.

**[0089]** In one embodiment, the mucoadhesive polymeric diffusion environment of the device of the present invention has a thickness of about 0.03 mm to about 0.07 mm. In one embodiment, the mucoadhesive polymeric diffusion environment of the

device of the present invention has a thickness of about 0.04 mm to about 0.06 mm. In yet another embodiment, the mucoadhesive polymeric diffusion environment of the present invention has a thickness of about 0.05mm. The thickness of the mucoadhesive polymeric diffusion environment is designed to be thick enough so that it can be easily manufactured, yet thin enough to allow for maximum permeability of the medicament through the layer, and maximum absorption of the medicament into the mucosal layer.

**[0090]** In one embodiment, the backing layer of the device of the present invention has a thickness of about 0.050 mm to about 0.350 mm. In one embodiment, the backing layer of the device of the present invention has a thickness of about 0.100 mm to about 0.300 mm. In yet another embodiment, the backing layer of the present invention has a thickness of about 0.200 mm. The thickness of the backing layer is designed to be thick enough so that it allows for substantially unidirectional delivery of the medicament (towards the mucosa), yet thin enough to dissolve so that it does not have to be manually removed by the subject.

**[0091]** In these embodiments, there is relatively minimal mouth feel and little discomfort because of the thinness and flexibility of the devices as compared to conventional tablet or lozenge devices. This is especially advantageous for patients who have inflammation of the mucosa and/or who may otherwise not be able to comfortably use conventional devices. The devices of the present invention are small and flexible enough so that they can adhere to a non-inflamed area of the mucosa and still be effective, *i.e.*, the mucosa does not need to be swabbed with the device of the present invention.

**[0092]** In various embodiments, the devices of the present invention can be in any form or shape such as a sheet or disc, circular or square in profile or cross-section, etc., provided the form allows for the delivery of the active to the subject. In some embodiments, the devices of the present invention can be scored, perforated or otherwise marked to delineate certain dosages. For example, a device may be a square sheet, perforated into quarters, where each quarter comprises a 200 $\mu$g dose. Accordingly, a subject can use the entire device for an 800 $\mu$g dose, or detach any portion thereof for a 200 $\mu$g, 400 $\mu$g or 600 $\mu$g dose.

**[0093]** The devices of the present invention can be adapted for any mucosal administration. In some embodiments of the methods and devices of the present

invention, the device is adapted for buccal administration and/or sublingual administration.

**[0094]** Yet another advantage of the devices of the present invention is the ease with which they are administered. With conventional devices, the user must hold the device in place, or rub the device over the mucosa for the duration of administration, which may last from twenty to thirty minutes or more. The devices of the present invention adhere to the mucosal surface in less than about five seconds, and naturally erode in about twenty to thirty minutes, without any need to hold the device in place.

**[0095]** Without wishing to be bound by any particular theory, it is also believed that the devices of the present invention are substantially easier to use than devices of the prior art. When devices of the prior art are used, they are often subject to much variability, *e.g.*, due to variation in mouth size, diligence of the subject in correctly administering the device and amount of saliva produced in the subject's mouth. Accordingly, in some embodiments, the present invention provides a variable-free method for treating pain in a subject. The term "variable-free" as used herein, refers to the fact that the devices of the present invention provide substantially similar pharmacokinetic profile in all subjects, regardless of mouth size and saliva production.

**[0096]** Without wishing to be bound by any particular theory, it is also believed that the presence of a backing layer also imparts a resistance to the devices of the present invention. Accordingly, in some embodiments, the devices of the present invention are resistant to the consumption of food or beverage. That is, the consumption of food or beverage while using the devices of the present invention does not substantially interfere with the effectiveness of the device. In some embodiments, the performance of the devices of the present invention, *e.g.*, peak fentanyl concentrations and/or overall exposure to the medicament is unaffected by the consumption of foods and/or hot beverages.

**[0097]** In various embodiments, the devices can have any combination of the layers, ingredients or compositions described herein including but not limited to those described above.

## EXEMPLIFICATION

Example 1: Preparation of Devices in Accordance with the Present Invention

**[0098]** Transmucosal devices were configured in the form of a disc, rectangular in shape with round corners, pink on one side and white on the other side. The drug is

present in the pink layer, which is the mucoadhesive polymeric diffusion environment, and this side is to be placed in contact with the buccal mucosa (inside the cheek). The drug is delivered into the mucosa as the disc erodes in the mouth. The white side is the non-adhesive, backing layer which provides a controlled erosion of the disc, and minimizes the oral uptake of the drug induced by constant swallowing, thus minimizing or preventing first pass metabolism. The mucoadhesive polymeric diffusion environment and backing layer are bonded together and do not delaminate during or after application.

**[0099]** The backing layer was prepared by adding water (about 77% total formulation, by weight) to a mixing vessel followed by sequential addition of sodium benzoate(about 0.1% total formulation, by weight), methylparaben (about 0.1% total formulation, by weight) and propylparaben (about 0.03% total formulation, by weight), citric acid (about 0.1% total formulation, by weight) and vitamin E acetate (about 0.01% total formulation, by weight), and sodium saccharin(about 0.1% total formulation, by weight). Subsequently, a mixture of the polymers hydroxypropyl cellulose (Klucel EF, about 14% total formulation, by weight) and hydroxyethyl cellulose (Natrosol 250L, about 7% total formulation, by weight) was added and stirred at a temperature between about 120 and 130°F, until evenly dispersed. Upon cooling to room temperature, titanium dioxide (about 0.6% total formulation, by weight) and peppermint oil (about 0.2% total formulation, by weight) were then added to the vessel and stirred. The prepared mixture was stored in an air-sealed vessel until it was ready for use in the coating operation.

**[0100]** The mucoadhesive polymeric diffusion environment was prepared by adding water (about 89% total formulation, by weight) to a mixing vessel followed by sequential addition of propylene glycol (about 0.5% total formulation, by weight), sodium benzoate (about 0.06% total formulation, by weight), methylparaben (about 0.1% total formulation, by weight) and propylparaben (about 0.03% total formulation, by weight), vitamin E acetate (about 0.01% total formulation, by weight) and citric acid (about 0.06% total formulation, by weight), red iron oxide (about 0.01% total formulation, by weight), and monobasic sodium phosphate (about 0.04% total formulation, by weight). After the components were dissolved, 800 μg fentanyl citrate (about 0.9% total formulation, by weight) was added, and the vessel was heated to 120 to 130°F. After dissolution, the polymer mixture [hydroxypropyl cellulose (Klucel EF,

about 0.6% total formulation, by weight), hydroxyethyl cellulose (Natrosol 250L, about 1.9% total formulation, by weight), polycarbophil (Noveon AA1(about 0.6% total formulation, by weight), and carboxy methyl cellulose (Aqualon 7LF, about 5.124% total formulation, by weight)] was added to the vessel, and stirred until dispersed. Subsequently, heat was removed from the mixing vessel. As the last addition step, tribasic sodium phosphate and sodium hydroxide were added to adjust the blend to a desired pH. For example, about 0.6% total formulation, by weight of sodium hydroxide and about 0.4% total formulation, by weight of tribasic sodium phosphate can be added to the formulation. Batches were made having pHs of about 6, 7.25, and 8.5. The blend was mixed under vacuum for a few hours. Each prepared mixture was stored in an air-sealed vessel until its use in the coating operation.

**[0101]** The layers were cast in series onto a St. Gobain polyester liner. First, the backing layer was cast using a knife-on-a-blade coating method. The backing layer was then cured in a continuous oven at about 65 to 95°C and dried. After two coating and drying iterations, an approximately 8 mil (203 to 213 micrometers) thick backing layer is obtained. Subsequently, the mucoadhesive polymeric diffusion environment was cast onto the backing layer, cured in an oven at about 65 to 95 °C and dried. The devices were then die-cut by kiss-cut method and removed from the casting surface.

Example 2: Study of Fentanyl Citrate Uptake in Humans for Delivery Devices of the Present Invention and a Commercially Available Delivery Device

**[0102]** The effect of system pH on the uptake of fentanyl citrate in three exemplary delivery devices of the present invention was evaluated, and compared to that observed in Actiq® Oral Transmucosal Fentanyl Citrate product (Cephalon, Inc., Salt Lake City, UT), referred to herein as "OTFC". A randomized, open-label, single-dose, four-period, Latin-square crossover study was conducted in 12 healthy volunteers. An Ethical Review Board approved the study and all subjects gave informed consent before participating. Bioanalytical work using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method was performed by CEDRA Clinical Research, LLC (Austin, TX).

**[0103]** Twelve (9 male, 3 female) healthy volunteers ranging in age from 21 to 44 years were recruited for the instant study. Subjects tested were free from any significant clinical abnormalities on the basis of medical history and physical examination, electrocardiogram, and screening laboratories. Subjects weighed between about 50 kg

and 100 kg and were within 15% of their ideal body weight based on Metropolitan Life tables for height and weight. Subjects were instructed to not consume alcohol, caffeine, xanthine, or foods/beverages containing grapefruit for 48 hours prior to the first dose of study medication and for the entire duration of the study. Subjects were also instructed not to use tobacco or nicotine containing products for at least 30 days prior to the first dose of medication. No subject had participated in any investigational drug study for at least 30 days prior to the instant study; had any significant medical condition either at the time of the study or in the past (including glaucoma and seizure disorders); had a positive drug screen; had used any concomitant medication other than oral contraceptives or acetaminophen for at least 72 hours prior to the first dose; or had a history of allergic reaction or intolerance to narcotics. Premenopausal women not using contraception or having a positive urine beta HCG test were excluded. Table 2, below, shows the demographics of the subjects included in this study.

***Table 2. Subject Demographics (N=12)***

| | |
|---|---|
| Age, years | |
| Mean (standard deviation) | 32 (7) |
| Median | 31 |
| Range | 21-44 |
| Gender, n (%) | |
| Female | 3 (25) |
| Male | 9 (75) |
| Race, n (%) | |
| Black | 3 (25) |
| Caucasian | 4 (33) |
| Hispanic | 5 (42) |
| Height (cm) | |
| Mean (standard deviation) | 171.6 (9.3) |
| Median | 172.0 |
| Range | 155.0 – 183.5 |
| Weight (kg) | |
| Mean (standard deviation) | 70.5 (9.0) |
| Median | 70.7 |
| Range | 52.0 – 86.5 |

**[0104]** The study consisted of a screening visit and a 9-day inpatient period during which each subject received single buccal transmucosal doses of each of the four study treatments with 48 hours separating the doses. The four study treatments, each including 800 μg of fentanyl citrate, were: the OTFC and devices prepared as described

in Example 1 and buffered at a pH of about 6 ("device at pH 6"), a pH of about 7.25 ("device at pH 7.25"), and a pH of about 8.5 ("device at pH 8.5").

**[0105]** Subject eligibility was determined at the screening visit, up to 21 days prior to entering the study facility. Subjects arrived at the study facility at 6:00 PM the day prior to dosing (day 0). Predose procedures (physical examination, clinical laboratory tests, electrocardiogram, and substance abuse screen) were performed. After an overnight fast of at least 8 hours, subjects received an oral dose of naltrexone at 6 AM. A standard light breakfast was served approximately 1 hour prior to study drug dosing. A venous catheter was placed in a large forearm or hand vein for blood sampling, and a pulse oximeter and noninvasive blood pressure cuff were attached. Subjects were placed in a semi-recumbent position, which they maintained for 8 hours after each dose.

**[0106]** Subjects received the first dose of drug at 8 AM on day 1 and subsequent doses at the same time on days 3, 5, and 7. Blood samples (7 mL) were collected in ethylenediaminetetraacetic acid (EDTA) for measurement of plasma fentanyl just prior to dose 1 and 5, 7.5, 10, 15, 20, 25, 30, 45, and 60 minutes, and 2, 3, 4, 8, 12, 16, 20, 24, and 48 hours after each dose. The 48-hour post dose sample was collected just prior to administration of the subsequent dose. A total of 511 mL of blood was collected over the study period for pharmacokinetic analysis. Samples were centrifuged and the plasma portion drawn off and frozen at -20°C or colder.

**[0107]** Finger pulse oximetry was monitored continuously for 8 hours after each dose and then hourly for an additional four hours. If the subject's oxyhemoglobin saturation persistently decreased to less than 90%, the subject was prompted to inhale deeply several times and was observed for signs of decreased oxyhemoglobin saturation. If the oxyhemoglobin saturation value immediately increased to 90% or above, no further action was taken. If the oxyhemoglobin saturation remained below 90% for more than 1 minute, oxygen was administered to the subject via a nasal cannula. Heart rate, respiratory rate, and blood pressure were measured just prior to the dose, and every 15 minutes for 120 minutes, and at 4, 6, 8, and 12 hours post dose. Throughout the study, subjects were instructed to inform the study personnel of any adverse events.

**[0108]** Each subject received a single buccal dose of each of the 4 study treatments in an open-label, randomized crossover design. The measured pH on the three devices during the manufacturing process in accordance with Example 1 were 5.95 for the device at pH 6.0, 7.44 for the device at pH 7.25, and 8.46 for the device at pH

8.5. After subjects rinsed their mouths with water, the delivery devices of the present invention were applied to the oral mucosa at a location approximately even with the lower teeth. The devices were held in place for 5 seconds until the device was moistened by saliva and adhered to the mucosa membrane. After application, subjects were instructed to avoid rubbing the device with their tongues, as this would accelerate the dissolution of the device.

**[0109]** OTFC doses were administered according to the package insert. After each mouth was rinsed with water, the OTFC unit was placed in the mouth between the cheek and lower gum. The OTFC unit was occasionally moved from one side of the mouth to the other. Subjects were instructed to suck, not chew, the OTFC unit over a 15-minute period. To block the respiratory depressive effects of fentanyl, a 50 mg oral dose of naltrexone was administered to each subject at approximately 12 hours and 0.5 hours prior to each dose of study drug and 12 hours after study drug. Naltrexone has been shown not to interfere with fentanyl pharmacokinetics in opioid naïve subjects. Lor M, et al., *Clin Pharmacol Ther*; 77: P76 (2005).

**[0110]** At the end of the study, EDTA plasma samples were analyzed for plasma fentanyl concentrations using a validated liquid chromatography with tandem mass spectrophotometry (LC/MS/MS) procedure. Samples were analyzed on a SCIEX API 3000 spectrophotometer using pentadeuterated fentanyl as an internal standard. The method was validated for a range of 0.0250 to 5.00 ng/mL based on the analysis of 0.500 mL of EDTA human plasma. Quantitation was performed using a weighted (1/X2) linear least squares regression analysis generated from calibration standards.

**[0111]** Pharmacokinetic data were analyzed by noncompartmental methods in WinNonlin (Pharsight Corporation). In the pharmacokinetic analysis, concentrations below the limit of quantitation (<0.0250 ng/mL) were treated as zero from time-zero up to the time at which the first quantifiable concentration ($C_{first}$) was observed. Subsequent to $C_{first}$, concentrations below this limit were treated as missing. Full precision concentration data were used for all pharmacokinetic and statistical analyses. $C_{first}$ was defined as the first quantifiable concentration above the pre-dose concentration because quantifiable data were observed in the pre-dose samples in some subjects. $\lambda_z$ was calculated using unweighted linear regression analysis on at least three log-transformed concentrations visually assessed to be on the linear portion of the terminal slope. The $t_{1/2}$ was calculated as the ratio of 0.693 to $\lambda_z$. Pharmacokinetic parameters

were summarized by treatment using descriptive statistics. Values of $t_{first}$, $t_{max}$, $C_{max}$, and $AUC_{inf}$ of the three exemplary devices of the present invention were compared to OTFC using an analysis of variance (ANOVA) model and Tukey's multiple comparison test. Statistical analysis was performed using SAS (SAS Institute Inc.). Table 3, below, presents the fentanyl pharmacokinetics for all 4 treatments after a single dose.

***Table 3. Pharmacokinetic Parameters of OTFC and Three Formulations of BEMA Fentanyl Citrate***

| Parameter | OTFC 800 μg (N=12) | | Device at pH 6 Fentanyl 800 μg (N=12) | | Device at pH 7.25 Fentanyl 800 μg (N=12) | | Device at pH 8.5 Fentanyl 800 μg (N=12) | |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | CV% | Mean (SD) | CV % | Mean (SD) | CV% | Mean (SD) | CV % |
| $t_{first}$ (hr) | 0.23 (0.18) | 78.03 | 0.13 (0.04) | 27.99 | 0.15 (0.08) | 54.18 | 0.21 (0.11) | 55.21 |
| $C_{first}$ (ng/mL) | 0.07 (0.05) | 64.95 | 0.05 (0.02) | 35.25 | 0.06 (0.02) | 41.59 | 0.06 (0.02) | 30.08 |
| $t_{max}$ (hr) | 2.28 (1.32) | 58.04 | 2.15 (1.14) | 53.23 | 1.61 (1.04) | 64.49 | 2.21 (1.34) | 60.64 |
| $C_{max}$ (ng/mL)[1] | 1.03 (0.25) | 24.19 | 1.40 (0.49) | 35.12 | 1.67 (0.75) | 45.07 | 1.39 (0.41) | 29.44 |
| $AUC_{last}$ (hr•ng/mL) | 9.04 (3.53) | 39.01 | 12.17 (4.28) | 35.19 | 12.98 (5.59) | 43.04 | 11.82 (4.54) | 38.37 |
| $AUC_{0-24}$ (hr•ng/mL) | 7.75 (2.52) | 32.48 | 10.43 (3.00) | 28.74 | 11.38 (4.30) | 37.78 | 10.18 (3.20) | 31.44 |
| $AUC_{inf}$ (hr•ng/mL) | 10.30 (3.84) | 37.29 | 13.68 (4.55) | 33.24 | 14.44 (5.39) | 37.33 | 13.11 (4.77) | 36.40 |
| % $AUC_{extrap}$ | 12.15 (8.31) | 68.40 | 11.53 (6.84) | 59.33 | 11.72 (6.91) | 58.96 | 10.31 (4.49) | 43.49 |
| $\lambda z$ ($hr^{-1}$) | 0.05 (0.02) | 37.83 | 0.05 (0.02) | 31.10 | 0.05 (0.01) | 21.18 | 0.06 (0.02) | 26.98 |
| $t_{1/2}$ (hr) | 15.33 (6.85) | 44.67 | 15.12 (5.09) | 33.66 | 14.28 (2.75) | 19.23 | 13.33 (4.14) | 31.04 |
| MRT | 15.92 (6.17) | 38.73 | 15.73 (4.19) | 26.63 | 14.45 (3.12) | 21.61 | 14.31 (4.45) | 31.09 |

1. Mean differences of BEMA fentanyl formulations and OTFC significantly different by ANOVA, p=0.0304.

**[0112]** Abbreviations used herein are as follows: $C_{first}$ is the first quantifiable drug concentration in plasma determined directly from individual concentration-time data; $t_{first}$ is the time to the first quantifiable concentration; $C_{max}$ is the maximum drug concentration in plasma determined directly from individual concentration-time data; $t_{max}$ is the time to reach maximum concentration; $\lambda_z$ is the observed elimination rate constant; $t_{1/2}$ is the observed terminal elimination half-life calculated as $\ln(2)/\lambda_z$; $AUC_{0-24}$ is the area under the concentration-time curve from time zero to 24 hours post-dose; calculated using the linear trapezoidal rule and extrapolated using the elimination rate

constant if quantifiable data were not observed through 24 hours; $AUC_{last}$ is the area under the concentration-time curve from time zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule; $AUC_{inf}$ is the area under the concentration-time curve from time zero extrapolated to infinity, calculated as $AUC_{last} + C_{last} / \lambda_z$; $AUC_{extrap}$ (%) is the percentage of $AUC_{inf}$ based on extrapolation; MRT is the mean residence time, calculated as $AUMC_{inf}/AUC_{inf}$, where $AUMC_{inf}$ is the area under the first moment curve (concentration-time vs. time), calculated using the linear trapezoidal rule form time zero to $T_{last}$ ($AUMC_{last}$) and extrapolated to infinity. It should be noted that, because quantifiable data were observed in the pre-dose samples for some subjects, $C_{first}$ was redefined as the first quantifiable concentration above the pre-dose concentration, which was set to zero in calculating mean fentanyl concentrations.

**[0113]** Figure 1 illustrates the plasma fentanyl concentration from 0 to 48 hours post-dose for the OTFC dose and the doses provided by the three exemplary devices of the present invention. The device at pH 7.25 provided the highest peak concentrations of fentanyl of the three devices of the present invention used in this study. In general, OTFC provided lower fentanyl concentrations for most time points as compared with the devices of the present invention. The device at pH 6 and the device at pH 8.5 yielded very similar concentration-time profiles, with $C_{max}$ values of 1.40 ng/mL and 1.39 ng/mL, respectively. These values are midway between the maximum plasma fentanyl values of 1.03 ng/mL for OTFC and 1.67 ng/mL for the device at pH 7.25. After approximately 6 hours post-dose, the fentanyl concentration-time profiles for the three devices of the present invention were similar. The differences in fentanyl $C_{max}$ values were statistically significant when comparing all of the devices of the present invention to OTFC ($p=0.0304$), and for pairwise comparisons of the device at pH 7.25 to OTFC ($p<0.05$).

**[0114]** In general, quantifiable fentanyl concentrations were observed earlier after administration of one of the three exemplary devices of the present invention (mean $t_{first}$ of 8 to 13 minutes) compared with OTFC (mean $t_{first}$ of 14 minutes). The device at pH 7.25 yielded the earliest average $t_{max}$ (1.61 hours) and highest $C_{max}$ (mean 1.67 ng/mL). As shown in Figure 2, fentanyl absorption from a device at pH 7.25 was more rapid over the first hour post dose than from OTFC, with 30-minute mean plasma concentrations of 0.9 ng/mL for the device at pH 7.25 and 0.5 ng/mL for OTFC.

**[0115]** The delivery devices of the present invention provided overall greater exposure to fentanyl, based on $AUC_{0\,24}$ as compared to OTFC. Fentanyl exposure as measured by $AUC_{0-24}$ values, were similar across groups treated with one of the devices of the present invention, suggesting that comparable amounts of fentanyl enter the systemic circulation from each of the devices. The device at pH 7.25, however, demonstrated approximately 19% greater maximum plasma fentanyl concentration.

**[0116]** Overall, fentanyl concentrations were observed earlier and increased more rapidly after administration of a device of the present invention compared with OTFC. Mean 30 and 60 minute plasma fentanyl concentrations observed with use of the device at pH 7.25 were 1.8 and 1.7 times higher than with OTFC, respectively. Similarly, the maximum plasma fentanyl concentration was 60% higher using a device of the present invention (mean 1.67 ng/mL) when compared to use of OTFC (mean 1.03 ng/mL). The $C_{max}$ for OTFC identified in this study is nearly identical to the 1.1 ng/mL $C_{max}$ value reported by Lee and co-workers with both a single 800 mcg lozenge as well as two 400 mcg lozenges. Lee, M., et al., *J Pain Symptom Manage* 2003; 26:743-747. Overall, fentanyl exposure for the fentanyl formulations of the present invention were greater than for OTFC. Mean estimates of $AUC_{last}$ and $AUC_{inf}$ were slightly larger, but the same general trends were observed. This indicates that the transmucosal uptake is significantly improved in the devices of the present invention as compared to OTFC.

**[0117]** Mean $t_{1/2}$ values and MRT values were similar for all treatment groups and the values in both cases followed the same trend. Additionally, because MRT after extravascular administration is dependent on the absorption and elimination rates, the MRT values suggest that fentanyl absorbs faster from a delivery device of the present invention, particularly with the device at pH 7.25 and the device at pH 8.5. This observation is consistent with the $t_{max}$ for the delivery devices of the present invention relative to OTFC.

**[0118]** Adverse events were similar across treatment groups and confounded by the co-administration of naltrexone with each study treatment. The most frequent adverse events were sedation and dizziness. One subject experienced oral mucosal irritation with OTFC. No subject experienced mucosal irritation with any of the three exemplary devices of the present invention. All reported adverse events were mild or moderate in nature.

[0119] As demonstrated above, the delivery devices of the present invention provide significantly higher plasma fentanyl concentrations than OTFC. The delivery device at pH 7.25 appeared to provide enhanced uptake believed to be attributable to a favorable balance between drug solubility and ionization. Similar studies have shown that the delivery devices of the present invention provide an absolute bioavailability of about 70.5% and buccal absorption was about 51% (estimated by subtracting the $AUC_{inf}$ following an oral dose of fentanyl from the $AUC_{inf}$ following BEMA fentanyl applied to the buccal mucosa, dividing by the single disc BEMA Fentanyl $AUC_{inf}$, and multiplying by 100).

Example 3: Preparation of Devices in Accordance with the Present Invention

[0120] Devices containing buprenorphine were also produced using the same method as described in Example 1, except that buprenorphine was added to the mucoadhesive polymeric diffusion environment, rather than fentanyl citrate.

Example 4: Study of Buprenorphine Uptake in Humans for Delivery Devices of the Present Invention

*[0121]* A study similar to that described in Example 2 was also performed with buprenorphine in exemplary devices of the present invention (at pH 6 and 7.25), suboxone sublingual and buprenex intramuscular. Results from this study are summarized in the graph in Figure 3. As demonstrated in Table 4, the delivery devices of the present invention at pH 6 appeared to provide enhanced uptake believed to be attributable to a favorable balance between drug solubility and ionization.

***Table 4: Pharmacokinetic data for buprenorphine***

| pH | 6 | 7.25 |
|---|---|---|
| $t_{first}$ (hr) | 0.75 | 0.75 |
| $C_{first}$ (ng/mL) | 0.0521 | 0.0845 |
| $t_{max}$ (hr) | 3 | 3 |
| $C_{max}$ (ng/mL)[1] | 1.05 | 0.86 |

EQUIVALENTS

[0122] Numerous modifications and alternative embodiments of the present invention will be apparent to those skilled in the art in view of the foregoing description. Accordingly, this description is to be construed as illustrative only and is for the purpose

of teaching those skilled in the art the best mode for carrying out the present invention. Details of the structure may vary substantially without departing from the spirit of the invention, and exclusive use of all modifications that come within the scope of the appended claims is reserved. It is intended that the present invention be limited only to the extent required by the appended claims and the applicable rules of law.

**[0123]** All literature and similar material cited in this application, including, patents, patent applications, articles, books, treatises, dissertations and web pages, regardless of the format of such literature and similar materials, are expressly incorporated by reference in their entirety. In the event that one or more of the incorporated literature and similar materials differs from or contradicts this application, including defined terms, term usage, described techniques, or the like, this application controls.

**[0124]** The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described in any way.

**[0125]** While the present inventions have been described in conjunction with various embodiments and examples, it is not intended that the present teachings be limited to such embodiments or examples. On the contrary, the present inventions encompass various alternatives, modifications, and equivalents, as will be appreciated by those of skill in the art.

**[0126]** The claims should not be read as limited to the described order or elements unless stated to that effect. It should be understood that various changes in form and detail may be made without departing from the scope of the appended claims. Therefore, all embodiments that come within the scope and spirit of the following claims and equivalents thereto are claimed.

**Claims:**

1. A method for enhancing direct transmucosal delivery of a fentanyl or fentanyl derivative to a subject, said method comprising:

administering a bioerodable drug delivery device to an oral mucosal surface of a subject, the device comprising: a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface and the fentanyl or fentanyl derivative is delivered to the subject.

2. A method for treating pain in a subject comprising transmucosally administering to a subject a therapeutically effective amount of a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the fentanyl or fentanyl derivative is delivered in less than about 30 minutes.

3. The method of any of the preceding claims wherein chronic pain is alleviated in the subject.

4. The method of any of the preceding claims wherein acute pain is alleviated in the subject.

5. The method or device of any of the preceding claims, wherein the pain is breakthrough cancer pain.

6. A mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of a fentanyl or fentanyl derivative to a subject, the mucoadhesive device comprising: a fentanyl or fentanyl derivative disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is upon application to a mucosal surface.

7. A transmucosal delivery device that delivers a fentanyl or fentanyl derivative with at least 50% direct buccal absorption and an absolute bioavailability of at least about 70%.

8. A transmucosal delivery device that delivers a fentanyl or fentanyl derivative directly to the mucosa to achieve onset of pain relief ($T_{first}$) of about 0.20 hours or less and time to peak plasma concentration ($T_{max}$) of about 1.6 hours or more.

9. A device comprising about 800 μg of fentanyl, which exhibits upon transmucosal administration to a subject at least one *in vivo* plasma profile selected from the group consisting of:

a $C_{max}$ of about 1.10 ng/mL or more;

a $T_{first}$ of about 0.20 hours or less; and

an $AUC_{0-24}$ of about 10.00 hr·ng/mL or more.

10. A transmucosal delivery device comprising a fentanyl or fentanyl derivative that delivers the fentanyl or fentanyl derivative in an amount effective to treat pain, wherein oral irritation, oral ulceration and/or constipation associated with the delivery of the fentanyl or fentanyl derivative is insignificant or eliminated.

11. The method or device of any of the preceding claims, wherein the pH of the mucoadhesive polymeric diffusion environment is between about 6.5 and about 8.

12. The method or device of any of the preceding claims, wherein the pH of the mucoadhesive polymeric diffusion environment is about 7.25.

13. The method or device of any of the preceding claims, wherein the device comprises about 800 μg of fentanyl.

14. The method or device of any of the preceding claims, wherein the device further comprises at least one additional layer that facilitates unidirectional delivery of the fentanyl or fentanyl derivative to the mucosa.

15. The method or device of any of the preceding claims, wherein the fentanyl is fentanyl citrate.

16. The method or device of any of the preceding claims, wherein more than 30% of the fentanyl in the device becomes systemically available via mucosal absorption.

17. The method or device of any of the preceding claims, wherein more than 55% of the fentanyl in the device becomes systemically available.

18. A method for enhancing direct transmucosal delivery of buprenorphine to a subject, said method comprising:

administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: buprenorphine disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the

polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface, and the buprenorphine is delivered to the subject.

19. A method for treating pain in a subject comprising transmucosally administering to a subject a therapeutically effective amount of buprenorphine disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the buprenorphine is delivered in less than about 30 minutes.

20. The method of any of the preceding claims wherein chronic pain is alleviated in the subject.

21. The method of any of the preceding claims wherein acute pain is alleviated in the subject.

22. A mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of buprenorphine to a subject, the mucoadhesive device comprising: buprenorphine derivative disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to a mucosal surface.

23. The method or device of any of claims 18-22, wherein the pH is between about 4.0 and about 7.5.

24. The method or device of any of claims 18-23, wherein the pH is about 6.0.

25. The method or device of any of claims 18-24, wherein the pH is about 7.25.

26. The method or device of any of claims 18-25, wherein the device further comprises at least one additional layer that facilitates unidirectional delivery of the buprenorphine to the mucosa.

27. The method or device of any of the preceding claims, wherein the device comprises a pH buffering agent.

28. The method or device of any of the preceding claims, wherein the device is adapted for buccal administration.

29. The method or device of any of the preceding claims, wherein the device is adapted for sublingual administration.

30. The method or device of any of the preceding claims, wherein the device is a mucoadhesive disc.

31. The method or device of any of the preceding claims, wherein the medicament is formulated as a mucoadhesive film formed to delineate different dosages.

32. The method or device of any of the preceding claims, wherein the device comprises a backing layer disposed adjacent to the mucoadhesive polymeric diffusion environment.

33. The method or device of any of the preceding claims, wherein the device further comprises an opioid antagonist.

34. The method or device of any of the preceding claims, wherein the device further comprises naloxone.

35. The method or device of any of the preceding claims, wherein the device is a layered, flexible device.

36. The method or device of any of the preceding claims, wherein the mucoadhesive polymeric diffusion environment has a buffered environment for the transmucosal administration.

37. The method or device of any of the preceding claims, wherein there is substantially no irritation at the site of transmucosal administration.

38. The method or device of any of the preceding claims, wherein there is about a 50% decrease in pain over about 30 minutes.

39. The method or device of any of the preceding claims, wherein the polymeric diffusion environment comprises at least one ionic polymer system.

40. The method or device of claim 39, wherein the ionic polymer system is selected from the group consisting of POLYCARBOPHIL, sodium carboxymethylcellulose and mixtures thereof.

41. The method or device of any of the preceding claims, wherein the polymeric diffusion environment comprises a buffer system.

42. The method or device of claim 41, wherein the buffer system comprises citric acid, sodium benzoate or mixtures thereof.

43. The method or device of any of the preceding claims, wherein the device has a thickness such that it exhibits minimal mouth feel.

44. The method or device of any of the preceding claims, wherein the device has a thickness of about 0.25 mm.

45. A flexible, bioerodable mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative to a subject, the mucoadhesive device comprising:

a mucoadhesive layer comprising a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative disposed in a polymeric diffusion environment, wherein the polymeric diffusion environment has a pH of about 7.25 for the fentanyl or fentanyl derivative or a pH of about 6 for the buprenorphine or buprenorphine derivative; and

a backing layer comprising a barrier environment which is disposed adjacent to and coterminous with the mucoadhesive layer,

wherein the device has no or minimal mouth feel and is able to transmucosally deliver the effective amount of the , fentanyl derivative, buprenorphine or buprenorphine derivative in less than about 30 minutes; and

wherein a unidirectional gradient is created upon application of the device to a mucosal surface.

**Figure 1. Mean Fentanyl Concentration-Time Plots For Three Exemplary Devices of the Invention and OTFC**

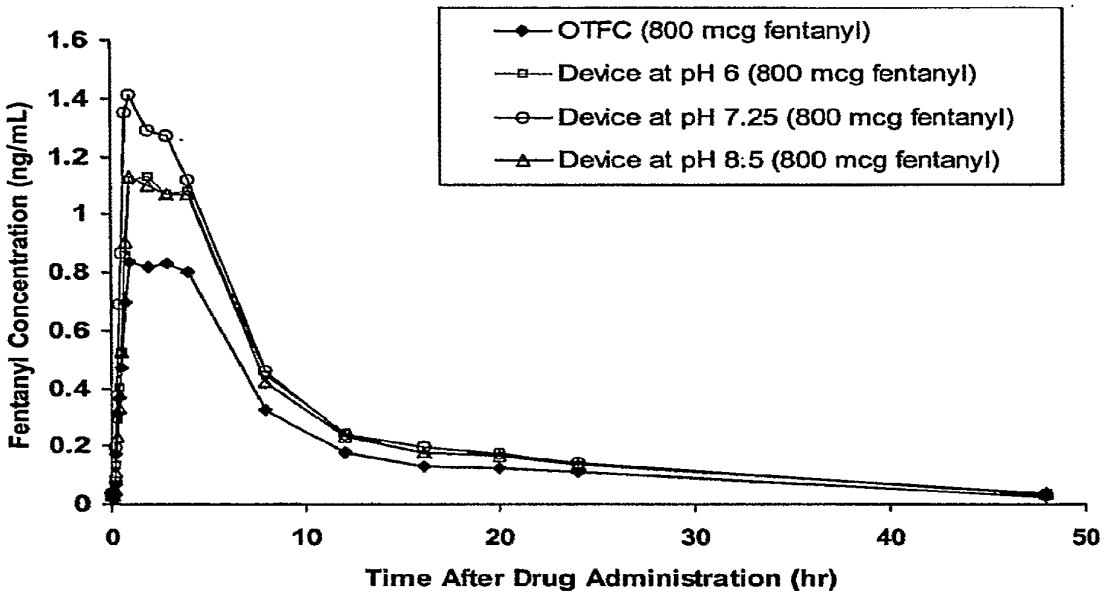


**Figure 2. Mean (SD) Fentanyl Concentration Over Time Comparing an Exemplary Device According To The Present Invention and OTFC**

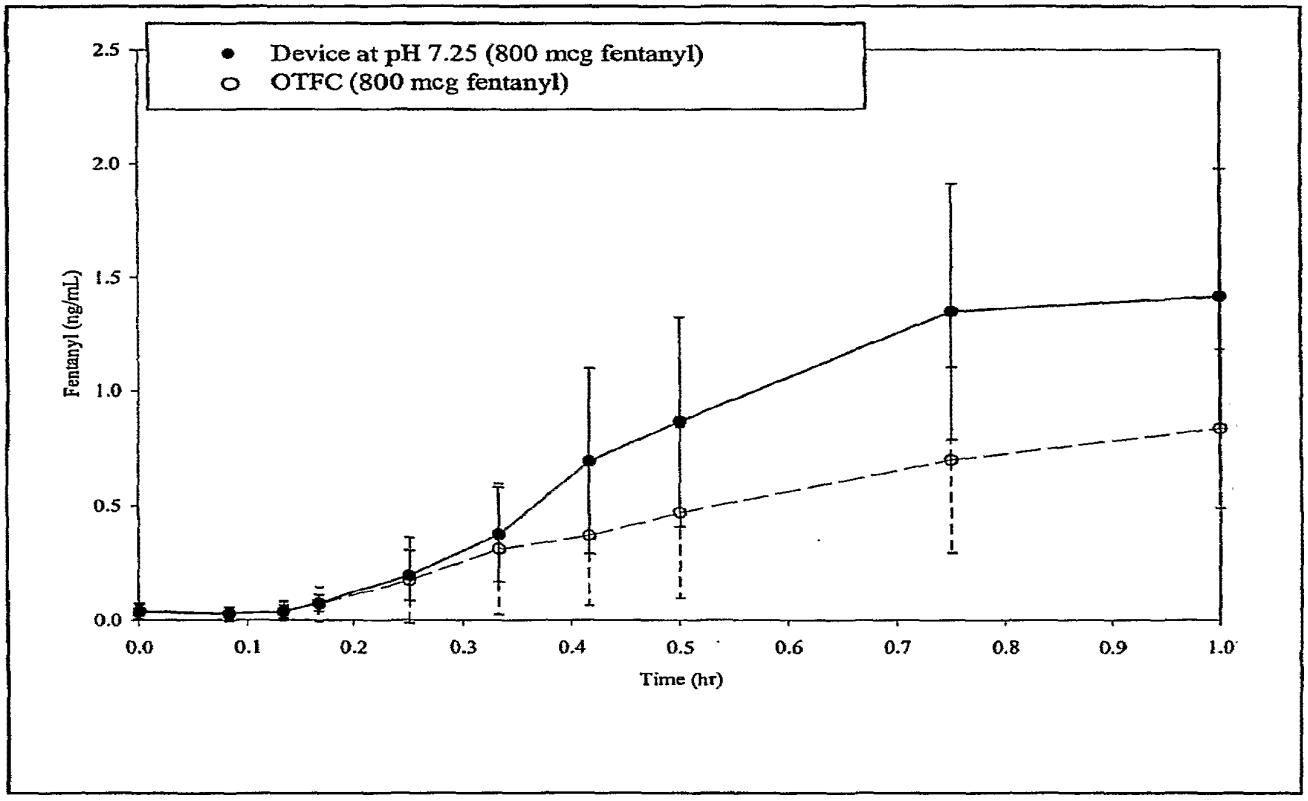


**Figure 3. Mean (SD) Buprenorphine Concentration Over Time Comparing an Exemplary Device According To The Present Invention and Conventional Buprenorphine Delivery**

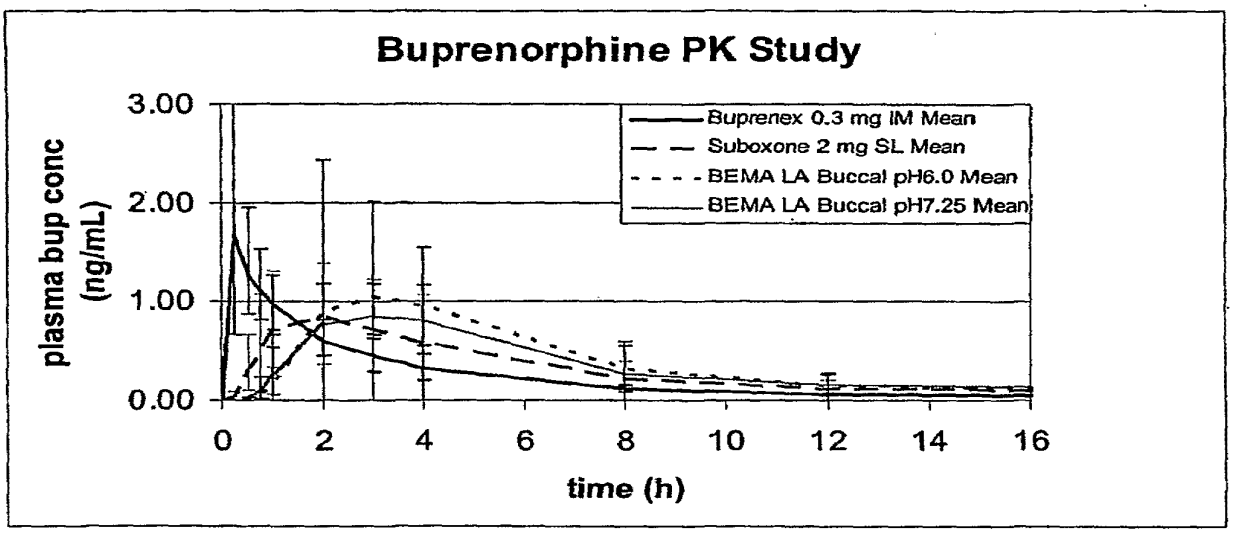


**Figure 4: Exemplary Embodiments of the Present Invention**

Figure 4A

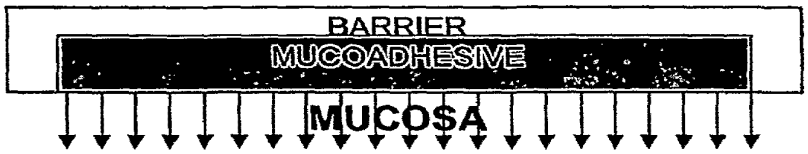



Figure 4B

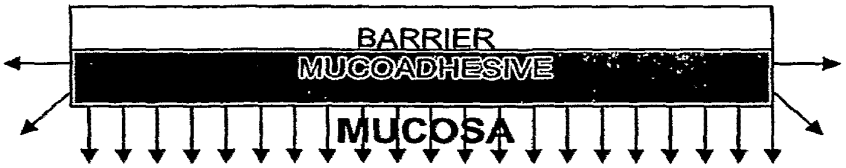
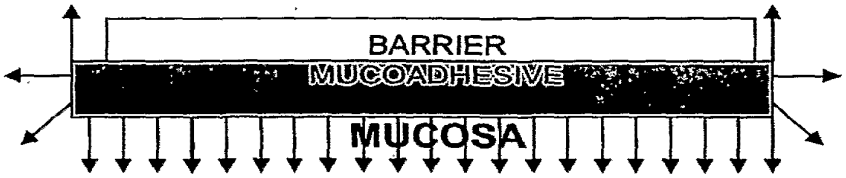



Figure 4C



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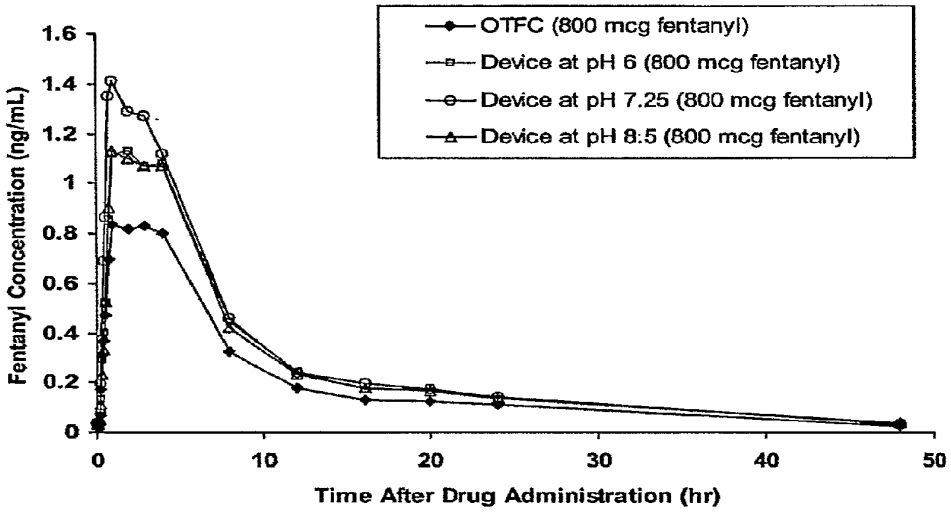
*[Continued on next page]*

(54) Title: TRANSMUCOSAL DELIVERY DEVICES WITH ENHANCED UPTAKE

**Mean Fentanyl Concentration-Time Plots For Three Exemplary Devices of the Invention and OTFC**




(57) Abstract: The present invention provides methods for enhancing transmucosal uptake of a medicament, e.g., fentanyl or buprenorphine, to a subject and related devices. The method includes administering to a subject a transmucosal drug delivery device comprising the medicament. Also provided are devices suitable for transmucosal administration of a medicament to a subject and methods of their administration and use. The devices include a medicament disposed in a mucoadhesive polymeric diffusion environment and a barrier environment.

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 1 642 579 A (TEIKOKU SEIYAKU KK [JP]) 5 April 2006 (2006-04-05)<br><br>claims; examples | 1-8,10, 14-17, 20,21, 28, 30-32, 35,37, 38,43 |
| X | WO 01/43728 A (LOHMANN THERAPIE SYST LTS [DE]; ASMUSSEN BODO [DE]; KRUMME MARKUS [DE]) 21 June 2001 (2001-06-21)<br><br>page 7, line 9 - page 11, line 29; claims | 1,3-6, 10,14, 20,21, 28-35, 37,43 |

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Couckuyt, Philippe |

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 01/58447 A (EURO CELTIQUE SA [LU]; OSHLACK BENJAMIN [US]; CURTIS WRIGHT [US]) 16 August 2001 (2001-08-16)<br><br>example 11 | 18-22,<br>30,<br>32-35,<br>37,43 |
| Y | example 11 | 11,12,<br>23-25,<br>27,36,<br>41,42,45 |
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| Y | claims 1,2,4,22; table 1 | 11,12,<br>23-25,<br>27,36,<br>41,42,45 |
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Information on patent family members

International application No
PCT/US2007/016634

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# INTERNATIONAL SEARCH REPORT

Interna[redacted]nal Application No
PCT/US2004/017076

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K47/34 A61K47/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 May 2005 | 09. 06. 2005 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Skjöldebrand, C |

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/017076

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: 1-33, 35,36 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-33, 35, 36

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] *The additional search fees were accompanied by the applicant's protest.*

[X] No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-33

   A rapid-dissolve film comprising polyethylene oxide, said film being free of added plasticizers. Processes for making such films.

   ---

2. claim: 34

   A premixture of a hydrophilic cellulosic polymer in a ratio of up to 4:1 with polyethylene oxide, which when deposited as a film and dried forms a rapid-dissolve delivery for active components.

   ---

3. claims: 35, 36

   A final film product comprising at least one water soluble polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer, which can be randomly divided and wherein no divided-out portion varies more than about 10% in composition of components.

   ---

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box II.2

Claims Nos.: 1-33, 35,36 (in part)

The claimed films are to be be free of plasticizers. Polyethylene glycol, falling under the definition polyethylene oxide, is however a frequently used plasticizer in films of HPC and HPMC. The current set of claims is therefore contradictive and not clear (Art. 6 PCT). Moreover, the functional term "plasticizer" relate to a compound defined by reference to a desirable characteristic or property.
Due to the unclear draft of the claim, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to films that also comprise hydrophilic cellulosic polymers. Also with this restriction, such a great number of potentially novelty destroying documents were retrieved, that only a fraction of them could be cited.

Product claims 35 and 36 relate to films comprising polyethylene oxide and, optionally, a hydrophilic cellulosic polymer. The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to:
films comprising both polyethylene oxide and the hydrophilic cellulosic polymer.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/017076

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# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 12107389 |
| **Filing Date:** | 22-Apr-2008 |
| **Title of Invention:** | POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM |
| **First Named Inventor/Applicant Name:** | Robert K. Yang |
| **Filer:** | Jon Anthony Chiodo |
| **Attorney Docket Number:** | 1199-26 DIV |

Filed as Small Entity

## Utility under 35 USC 111(a) Filing Fees

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

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| Submission- Information Disclosure Stmt | 1806 | 1 | 180 | 180 |
| | | **Total in USD ($)** | | **180** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 8117795 |
| **Application Number:** | 12107389 |
| **International Application Number:** | |
| **Confirmation Number:** | 9641 |
| **Title of Invention:** | POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM |
| **First Named Inventor/Applicant Name:** | Robert K. Yang |
| **Customer Number:** | 23869 |
| **Filer:** | Jon Anthony Chiodo |
| **Filer Authorized By:** | |
| **Attorney Docket Number:** | 1199-26 DIV |
| **Receipt Date:** | 29-JUL-2010 |
| **Filing Date:** | 22-APR-2008 |
| **Time Stamp:** | 15:44:35 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

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|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $180 |
| RAM confirmation Number | 2107 |
| Deposit Account | 082461 |
| Authorized User | |

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | response.pdf | 116480<br>4dafc1cfd5e6d4fcd6d2fae6d4981e655f9c2202 | yes | 8 |
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| | **Document Description** | | **Start** | **End** | |
| | Amendment/Req. Reconsideration-After Non-Final Reject | | 1 | 1 | |
| | Applicant Arguments/Remarks Made in an Amendment | | 2 | 8 | |
| **Warnings:** | | | | | |
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| 2 | Information Disclosure Statement (IDS) Filed (SB/08) | 1199-26_DIV_IDS.pdf | 3228075<br>405fa3e2f5dde136afb7b3599349b36b4c757990 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Foreign Reference | WO2008011194A2A3.pdf | 2717019<br>d60b9f9927a5beb33c7ef9cd17938a4d2a9459de | no | 53 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | NPL Documents | international_search_report.pdf | 267492<br>82c4ff00682701ddf5677cbdfea5f574f8e9ec0f | no | 7 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
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| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 6359679 | | |

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**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | Yang | Examiner: | Yu, Gina C. |
| Serial No.: | 12/107,389 | Group Art Unit: | 1611 |
| Confirmation No.: | 9641 | Docket: | 1199-26 DIV |
| Filed: | April 22, 2008 | Dated: | July 29, 2010 |
| For: | Polyethylene Oxide-Based Films and Drug Delivery Systems Made Therefrom | | |

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

**RESPONSE TO OFFICE ACTION**

Sir:

In response to the Office Action dated April 29, 2010, a response to which is due by July 29, 2010, please amend the application as follows:

**Remarks** begin on page 2 of this paper.

**REMARKS**

Reconsideration of the present application is requested. Claims 1-18 are pending in this application.

The Obviousness Rejection over Schiraldi in view of Flick

In the Office Action, claims 1-4, 8, 10-13 and 17 were rejected as allegedly obvious under 35 U.S.C. §103(a) over Schiraldi (U.S. 4,713,243) in view of Flick (Water Soluble Resins, an industrial guide, 1991). The Examiner alleged that Schiraldi discloses a mucosally adhesive film including 40-95% hydroxypropyl cellulose, 5-60% homopolymer of ethylene oxide, up to 10% polyethylene or polypropylene, and 2-10% plasticizer, and an active. The Examiner acknowledged that the weight ratio of polyethylene oxide and hydrophilic cellulosic polymer is different than that claimed. The Examiner also acknowledged that the particular MW polyethylene oxide used in Schiraldi is different than that claimed, but alleged that Schiraldi suggests a lower MW may be useful. The Examiner relied upon Flick for allegedly indicating that polyethylene oxide polymers having various molecular weights are available. The Examiner ultimately asserted that choosing the particular MW polyethylene oxides and the ratio of polyethylene oxide : cellulosic polymer would have been obvious. The Examiner stated that such modification is simply "routine experimentation".

The Applicant respectfully disagrees and traverses the instant rejection. Each of the pending claims recites very specific limitations with regard to the polymers. In particular, claim 1 includes the combination of polyethylene oxide (PEO) and a hydrophilic cellulosic polymer, specifically requiring greater than a 3:1 ratio of PEO to cellulosic polymer; and requires that the PEO component include both low MW PEO (100,000-300,000) and high MW PEO (600,000-900,000); and further requires that the low MW PEO be 60% or more in the polymer component. Independent claim 10 further recites that the cellulosic polymer is in a ratio of up to 4:1 with the PEO. These limitations set forth very specific ranges, ratios, and amounts of particular polymeric materials.

It is not asserted that either of the cited references includes the particular combination of polymers in the specifically recited amounts and having the recited molecular weights. Schiraldi does disclose the general combination of a hydroxypropyl cellulose and a

homopolymer of ethylene oxide, but there is no disclosure or suggestion as to the claimed molecular weight combination. In fact, Schiraldi only states that the homopolymer of ethylene oxide should have a relatively high molecular weight "i.e., above 100,000 and preferably above 3,000,000." (Col. 4, lines 24-28). In fact, the most preferred ethylene oxide has a molecular weight of 4,000,000-5,000,000. (Col. 4, lines 28-31). One of ordinary skill in the art would simply not be led to using the claimed combination of molecular weights, which are both significantly below the "preferred" molecular weights in Schiraldi. There is simply no disclosure or guidance to select low MW polymers, and particularly there is no disclosure to select a particular combination of MW polymers, each having MW's far below Schiraldi's "preferred" ranges.

As explained in the application, and as is understood by those of skill in the art, different actives have quite different solubilities and release profiles. For example, an opiate (as claimed) has a significantly different solubility and release profile than other analgesics, such as those listed in Schiraldi. The Applicant has discovered that the particular combination of molecular weights and polymers claimed provides a suitable release profile for an opiate, and still provides a suitable dosage form. (See, for example, Examples DH-DZ). There is simply no expectation of success, or any predictability from a reading of Schiraldi that one would be able to achieve a suitable film having a successful release profile of an opiate by modifying Schiraldi's film. In fact, given Schiraldi's express preference for high molecular weight polymers, one of ordinary skill in the art would simply not expect successful results using the claimed components.

Further, Schiraldi at best only includes a general disclosure of ratios, generally disclosing 5-60% the homopolymer of ethylene oxide, which is far below the level recited in the claim. Schiraldi fails to suggest to the claimed ratio of cellulosic polymer to PEO, only disclosing 40-95% hydroxypropyl cellulose and 5-60% homopolymer of ethylene oxide. Again, claim 1, for example, specifically recites "greater than 75%" PEO. Schiraldi simply fails to disclose or suggest the claimed polymers.

The Examiner, however, somehow asserts that it would be mere routine experimentation to arrive at the present limitations - including the particular ratios recited, the particular molecular weights recited, and the particular amounts recited. The Applicant

respectfully asserts that the recited combination goes above and beyond that of mere routine experimentation, and thus there is no *prima facie* case of obviousness.

As can be appreciated by those of skill in the art, numerous film forming materials are known in the art. In fact, the reference cited by the Examiner (Flick) specifically states that "this … guide contains descriptions of more than 1100 currently available water-soluble resins, supplied by 47 manufacturers or distributors of these products." (Description, Page 1) (emphasis added). Given the numerous possible combinations of film forming materials available, and in particular given the wide number of molecular weights available to choose from, one of ordinary skill in the art simply would not be able to predict which particular combination of polymers having which particular molecular weights would be useful to form the claimed invention. Further, there certainly would be no expectation of success with respect to doing so, based upon the cited Schiraldi reference and its preferred molecular weights. The claims recite a particular combination of polymers, having a particular molecular weight, in a particular ratio. This is not a matter of simply testing different molecular weights, or simply testing different ratios. There are three distinct limitations in the claims, none of which are disclosed in Schiraldi or Flick. Accordingly, there is absolutely no predictability of results associated with randomly selecting a particular polymer having a particular molecular weight out of context from the cited reference.

A look at the factors set forth in *In Re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), discussing undue experimentation, may be useful in further demonstrating the high degree of experimentation required. These factors include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Given the vast number of polymers and wide disparity of molecular weights to choose from, there is a significantly high degree of experimentation necessary to arrive at the narrow ranges claimed. Further, given Schiraldi's scant teachings as to the polymers and molecular weights, there is absolutely no direction or guidance that would direct one of skill in the art to the claimed invention. There is simply no predictability in the art to arrive at the

presently claimed combination of polymers, molecular weights, and ratios to achieve a suitable delivery system with a suitable release profile of an opiate.

Perhaps more glaringly, the Examiner's rejection is a clear case of impermissible hindsight reconstruction, using the Applicant's claims as an instruction manual. Hindsight cannot provide the basis for an obviousness rejection.

As has been recently stated by the Board of Patent Appeals and Interferences, "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *Ex Parte Houze*, Appeal No. 2009-008650, March 16, 2010 (*quoting In Re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009)). As has been repeatedly stated, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *Ex Parte Howard*, Appeal No. 2009-005947 (B.P.A.I., May 25, 2010) (*quoting In Re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992)). "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007).

Hindsight reconstruction cannot provide a rationale for combining teachings of prior art. *Ex Parte Howard* ("...we see no rational basis to combine the respective teachings of the cited references as the Examiner proposes apart from impermissible hindsight reconstruction of the invention using Appellant's own invention as a blueprint."); *Ex Parte Knauseder*, Appeal No. 2009-012617 (B.P.A.I. May 10, 2010) ("...the Examiner's conclusion of obviousness is based upon the use of impermissible hindsight reconstruction in view of Appellant's Specification rather than upon the suggestion of the prior art.").

The presently pending claims recite at least three specific numerical limitations, none of which is disclosed or even suggested in the cited references. There is no disclosure of the ratio of cellulosic polymer to PEO. There is also no disclosure of the combination of low *and* high molecular weight PEO. Finally, there is no disclosure of the particular amount of low molecular weight PEO. There is simply no basis to argue that the optimization of these limitations would be obvious to one of ordinary skill in the art without using the present claims as a roadmap or instruction manual. The Examiner has not provided a true and

rational basis for one of ordinary skill in the art to be motivated to modify Schiraldi to arrive at the present claims. In fact, as stated above, Schiraldi specifically states that "preferred" molecular weights of PEO are above 3,000,000 – well above both of the presently claimed PEO weights.

The present combination of particular amounts of cellulosic polymers and particular molecular weight PEO's provides a film product that includes strength but also provides a desired dissolution rate and release profile for an opiate when provided to the user. As may be appreciated, varying the type and level of polymers, as well as the molecular weights and amounts of polymers, may provide drastically different results in the film profile. This is especially true given the high number of possible film forming materials, including those stated in the cited Flick reference. The Applicants have found that the presently claimed combination provides a product which strikes a balance between these properties.

As stated above, there is no *prima facie* case of obviousness with this hypothetical combination of references. Claims 1-4 8, 10-13 and 17 are allowable over Schiraldi and Flick, whether taken alone or in combination. Allowance of these claims is respectfully requested.

Schiraldi in view of Flick and Khan

Next, in the Office Action, the Examiner rejected claims 5-9 and 14-18 as allegedly obvious over Schiraldi and Flick and further in view of Khan (U.S. 5,656,296). The Examiner acknowledged that Schiraldi and Flick fail to teach the claimed sweeteners and buffering agents. The Examiner relied upon Khan for teaching orally administered compositions including buffers and sweetening agents. The Examiner stated that one of ordinary skill in the art would be motivated to use Khan's agents to given an improved taste.

As explained above, neither of Schiraldi nor Flick discloses the presently claimed limitations, including (1) the ratio of cellulosic polymer to PEO, (2) the molecular weights of PEO, including both low and high molecular weight PEOs, and (3) the level of low molecular weight PEO. In fact, Flick specifically states that there are "more than 1100 … water-soluble resins", one of which includes polyethylene oxide. There is simply no direction, suggestion or guidance to arrive at the claimed invention. It would not be obvious to one of ordinary

skill in the art to arrive at the present combination of limitations without impermissible hindsight reconstruction. Khan's disclosure of buffers and sweeteners fails to remedy this clear defect. Thus, there is no *prima facie* case of obviousness with this hypothetical combination of references.

Claims 5-9 and 14-18 are allowable over Schiraldi, Flick and Khan, whether taken alone or in combination. Allowance of these claims is respectfully requested.

Double Patenting

Finally, in the Office Action, the Examiner rejected claims 1-18 on the ground of nonstatutory obviousness-type double patenting over claims 37, 38, 40, 42-52 and 56 of Application No. 10/856,176. The Applicant respectfully traverses the double patenting rejection, since the pending application is a divisional of the prior application. The double patenting rejection proposed by the Examiner is improper under 35 U.S.C. §121 (as discussed at MPEP 804.01). Specifically, 35 U.S.C. §121 states that

> A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

In the parent application (10/856,176), the Examiner issued a restriction requirement, requiring that the product claims and the method claims be separated into different groups, with the product claims being designated as Group I and the method claims as Group II. The Applicant elected to prosecute the method claims in the previous application, and has now filed the instant divisional application directed to the product claims. Thus, the claims as pending in the present application are specifically directed to those identified in the parent application as "Group I", which were not elected by the Applicant.

Since the parent application upon which the present application claims priority was subjected to a restriction requirement, and the Applicant has now filed a divisional application directed to the non-elected claims, the present double patenting rejection is

improper. The present application states the relationship between the two applications in the first paragraph of the specification. Thus, pursuant to 35 U.S.C. §121, the Applicant respectfully requests that the present rejection be withdrawn.

Supplemental Information Disclosure Statement

Finally, the Applicant submits herewith a Supplemental Information Disclosure Statement in accordance with the provisions of 37 C.F.R. §1.97 and 1.98, in fulfillment of the requirements of candor and good faith set forth in 37 C.F.R. §1.56.

The fee for a late submitted IDS is currently due, and the Commissioner is authorized to charge the required fee to Deposit Account No. 08-2461. No other fees are due with this submission. However, should any fees be due, the Commissioner is hereby authorized to charge payment of any required fees associated with this communication to Deposit Account No. 08-2461. This 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 or any future reply pursuant to 37 C.F.R. § 1.136, and also includes fees for consideration of any IDS, if necessary.

If the Examiner has any questions or comments relating to the present application, he or she is respectfully invited to contact Applicant's attorney at the telephone number set forth below.

Respectfully submitted,

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV | 9641 |

23869 7590 04/29/2010

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| EXAMINER | |
|---|---|
| YU, GINA C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1611 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 04/29/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 12/107,389 | YANG ET AL. | |
| | Examiner | Art Unit | |
| | GINA C. YU | 1611 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/01/2008, 08/15/2008, 09/18/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 1-4, 8, 10-13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi (US 4713243) in view of Flick (Water-soluble resins: an industrial guide, 1991).**

Schiraldi discloses a mucousally-adhesive bioadhesive thin film for intra-oral controlled-release delivery comprising a water soluble or swellable polymer matrix consisting of 40-95 wt % of hydroxypropyl cellulose, 5-60wt % a homopolymer of ethylene oxide, up to 10 wt % of polyethylene or polypropylene, and 2-10wt % of a plasticizer, and a pharmaceutical active selected from anesthetics, analgesics, anti-

inflammatory, etc. See abstract; col. 2, lines 30 -51. The thickness of the film ranges fro m1to 10 mils or 0.025-0.25 mm. The intended pharmaceuticals include analgesics such as aspirin, which is an opiate derivative according to applicant's own definition. See col. 3, lines 43. The reference also teaches an example of anesthetic film containing two pharmaceutical actives, thus incorporating an additional pharmaceutical agent as defined in instant claims 4 and 13 would have been obvious. Adding a flavor to the film product is suggested in col. 4, lines 50 – 54, meeting instant claims 8 and 17.

Although the weight ratio of the polyethylene oxide and the hydrophilic cellulosic polymer of the prior art is different from the present invention, Schiraldi teaches the ratio of the prior art polymers can be varied to control the solubility and the adhesive properties of each layer of film. See col. 3, lines 25 – 33. Other factors which affect this ratio are the desired delivery rate, the type of disorder to be treated, the area to be treated and the medication to be administered. See Id. The reference teaches the film can be custom designed by selecting and blending different polymers.

Although the polyethylene oxide used in examples is Polyox WSR 301 having MW 4,000,000-5,000,000, the reference suggests the lower limit of MW of polyethylene oxide useful for the purpose of the invention may be as low as 100,000. See col. 4, lines 24 -31.

Flick teaches polyethylene oxide polymers are supplied in a variety of viscosity grade and molecular weight. The reference teaches the polymers are effective as a rheology modifier, binder for additives, and produce visco-elastic behavior in solution. See p. 389-390. The reference also indicates that polyethylene oxide polymers having

molecular weight of 100K, 200K, 300, 600K and 900K are commercially available. See p. 391. Polyethylene oxide resin having MW 300 K has a viscosity up to 1100 cps, while the resins having MW 600K and 900K together have a viscosity ranges of 4500-17600 cps. See instant claim 2.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the Schiraldi film product by using polyethylene oxide resins of different molecular weight and varying the weight ratio of polyethylene oxide:hydrophilic cellulosic polymer as motivated by the combined teachings of Schiraldi and Flick. In this case, Such motivation is found in Schiraldi which teaches various type of film product may be formulated by varying the polymer weight ratio and choosing and blending different polymers. Flick also teaches polyethylene oxide resins of wide ranges of molecular weight and viscosity are effective as an adhesive, binder, thermoplastic and rheology modifier. Therefore, choosing polyethylene oxide resins of different lower molecular weight and varying the weight ratio of the polymers to produce a film product with a desired flexibility, rheology property, solubility, delivery rate, adhesiveness, etc. would have been an obvious modification to a skilled artisan. Since the Schiraldi teaches polyethylene oxide of a low molecular weight of 100,000 may be used, the skilled artisan would have had a reasonable expectation of successfully producing a stable film product of desired properties.

Furthermore, differences in concentration or temperature generally will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general

conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case, discovering an optimal weight ratio of a low molecular polyethylene oxide and cellulosic polymer to produce film products of intended uses (dosage, delivery rate, rheology, etc) by routine experimentations would only take ordinary skill in the art.

**Claims 5-9 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi and Flick as applied to claims 1-4, 8, 10-13 and 17 as above, and further in view of Khan et al. (US 5656296).**

Schiraldi and Flick fail to teach the sweeteners and buffering agents of the instant claims.

Khan teaches hard and soft orally administered compositions for controlled – release drug delivery and a method for preparing the said compositions. The reference teaches flavoring agents, sweetening agents and buffers are conventionally added to produce the pharmaceutically acceptable carriers. See col. 8, lines 24 - 39. The specific types and amounts of buffers and sweetening agents are taught in col. 10, lines 59 – 63 and col. 11, lines 6-27. Hydrogenated starch hydrolysates and the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide of instant claims 6, 7, 15 and 16 are disclosed in col. 11, line 6 and lines 23-24.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the teachings of Schiraldi/Flick by incorporating sweetening agents and buffer as motivated Khan as the latter teaches such additives are

conventionally added to make edible and pharmaceutically suitable drug systems. Since Schiraldi already teaches flavoring agents and other additives may be added to the intra-oral film products, the skilled artisan would have had a reasonable expectation of successfully producing a modified mucousally-adhesive film product with improved taste and stability.

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**Claims 1-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37, 38, 40, 42-52 and 56 of copending Application No. 10/856176.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims are directed to a method of producing a film product which has overlapping limitations with the presently claimed composition. The product of the '176 claims results in a film comprising polyoxyethylene oxide of MW 100K-900K and hydrophilic cellulosic polymer in an overlapping weight ratio or the ratio of 1:4 as defined in claims 40 and 42 of the copending application, which renders the inventions of instant claims 1 and 10 obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINA C. YU whose telephone number is (571)272-8605. The examiner can normally be reached on Monday through Thursday, from 8:00AM until 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GINA C. YU/
Primary Examiner, Art Unit 1611

| Notice of References Cited | Application/Control No. 12/107,389 | Applicant(s)/Patent Under Reexamination YANG ET AL. | |
|---|---|---|---|
| | Examiner GINA C. YU | Art Unit 1611 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-5,656,296 | 08-1997 | Khan et al. | 424/473 |
| | B | US- | | | |
| | C | US- | | | |
| | D | US- | | | |
| | E | US- | | | |
| | F | US- | | | |
| | G | US- | | | |
| | H | US- | | | |
| | I | US- | | | |
| | J | US- | | | |
| | K | US- | | | |
| | L | US- | | | |
| | M | US- | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
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| | N | | | | | |
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| | Q | | | | | |
| | R | | | | | |
| | S | | | | | |
| | T | | | | | |

**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | Flick, E., Water-Soluble Resins-An Industrial Guide, 1991, (2nd Ed.) William Andrew Publishing/Noyes, pages 389-391. |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 12107389 |
| Filing Date | 2008-04-22 |
| First Named Inventor | Robert K. Yang |
| Art Unit | 1794 |
| Examiner Name | |
| Attorney Docket Number | 1199-26 DIV |

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| | Application Number | 12107389 12107389 - GAU: 1611 |
| | Filing Date | 2008-04-22 |
| | First Named Inventor | Robert K. Yang |
| | Art Unit | 1794 |
| | Examiner Name | |
| | Attorney Docket Number | 1199-26 DIV |

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| Index of Claims | Application/Control No. | Applicant(s)/Patent Under Reexamination |
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| | Examiner | Art Unit |
| | GINA C YU | 1611 |

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| CLAIM | | DATE | | | | | | | | |
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| Final | Original | 04/08/2010 | | | | | | | | |
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| | Examiner Name | |
| | Attorney Docket Number | 1199-26 DIV |

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| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( Not for submission under 37 CFR 1.99) | | |
|---|---|---|
| | Application Number | 12107389 12107389 - GAU: 1611 |
| | Filing Date | 2008-04-22 |
| | First Named Inventor | Robert K. Yang |
| | Art Unit | 1794 |
| | Examiner Name | |
| | Attorney Docket Number | 1199-26 DIV |

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|---|---|---|---|
| 12/107,389 | 04/22/2008 | Robert K. Yang | 1199-26 DIV |

**CONFIRMATION NO. 9641**

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

**PUBLICATION NOTICE**

*OC000000032748386*

**Title:**POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

**Publication No.**US-2008-0260809-A1
**Publication Date:**10/23/2008

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| Application Number | 12107389 |
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| First Named Inventor | Robert K. Yang |
| Art Unit | 1794 |
| Examiner Name | |
| Attorney Docket Number | 1199-26 DIV |

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| | Art Unit | 1794 |
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| **International Application Number:** | |
| **Confirmation Number:** | 9641 |
| **Title of Invention:** | POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM |
| **First Named Inventor/Applicant Name:** | Robert K. Yang |
| **Customer Number:** | 23869 |
| **Filer:** | Irene Ann Lippa/Barbara Thomas |
| **Filer Authorized By:** | Irene Ann Lippa |
| **Attorney Docket Number:** | 1199-26 DIV |
| **Receipt Date:** | 18-SEP-2008 |
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| **Time Stamp:** | 15:44:59 |
| **Application Type:** | Utility under 35 USC 111(a) |

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| | 1 | 6264981 | B1 | 2001-07-24 | Zhang et al. | |

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|---|---|---|
| | Application Number | 12107389 |
| | Filing Date | 2008-04-22 |
| | First Named Inventor | Robert K. Yang |
| | Art Unit | 1794 |
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| Signature | /Jon A. CHIODO, Reg. No. 52,739// | Date (YYYY-MM-DD) | 2008-08-15 |
|---|---|---|---|
| Name/Print | Jon A. Chiodo | Registration Number | 52739 |

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| **EFS ID:** | 3788310 |
| **Application Number:** | 12107389 |
| **International Application Number:** | |
| **Confirmation Number:** | 9641 |
| **Title of Invention:** | POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM |
| **First Named Inventor/Applicant Name:** | Robert K. Yang |
| **Customer Number:** | 23869 |
| **Filer:** | Jon Anthony Chiodo/Marcy Mancuso |
| **Filer Authorized By:** | Jon Anthony Chiodo |
| **Attorney Docket Number:** | 1199-26 DIV |
| **Receipt Date:** | 15-AUG-2008 |
| **Filing Date:** | 22-APR-2008 |
| **Time Stamp:** | 14:06:39 |
| **Application Type:** | Utility under 35 USC 111(a) |

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| Document Number | Document Description | File Name | File Size(Bytes) /Message Digest | Multi Part /.zip | Pages (if appl.) |
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| 1 | Information Disclosure Statement (IDS) Filed (SB/08) | US_IDS_Form_SB_08a.pdf | 867754<br>9a62a3b960eee2b706bbf7a551e18542d97010fb | no | 4 |

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**( Not for submission under 37 CFR 1.99)**

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| Application Number | 12107389 |
| Filing Date | 2008-04-22 |
| First Named Inventor | Robert K. Yang |
| Art Unit | 1794 |
| Examiner Name | |
| Attorney Docket Number | 1199-26 DIV |

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| | 1 | 0307537 | | 1884-11-04 | Foulks | |
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| | 9 | 3444858 | | 1969-05-20 | Russell | |
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|---|---|---|---|---|---|---|
| | 42 | 4438258 | | 1984-03-20 | Graham | |
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| | 44 | 4466973 | | 1984-08-21 | Rennie | |
| | 45 | 4503070 | | 1985-03-05 | Eby, III | |

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| | 1 | 20010022964 | A1 | 2001-09-20 | Leung et al | |
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| | 1 | 19646392 | DE | A1 | 1998-05-14 | LTS Lohmann Therapie-Systeme GmbH | | ☐ |

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| | 6 | 1110546 | EP | A1 | 2001-06-27 | Johnson & Johnson Consumer Companies, Inc. | | ☐ |
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|---|---|---|---|
| | 1 | XP-002298105; Polyethylenglykole; Internet: www.roempp.com; 09/20/2004 | ☐ |
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| | 3 | Repka et al.; Bioadhesive properties of hydroxypropylcellulose topical films produced by hot-melt extrusion; Journal of Controlled Release; Vol. 70; pp 341-351; 2001 | ☐ |

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(51) Int. Cl.[6]:
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A 61 K 7/16
A 61 K 9/70
A 61 L 15/62

(21) Aktenzeichen: 196 46 392.0
(22) Anmeldetag: 11. 11. 96
(43) Offenlegungstag: 14. 5. 98

DE 196 46 392 A 1

(71) Anmelder:
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(74) Vertreter:
Flaccus, R., Dipl.-Chem. Dr.rer.nat., Pat.-Anw., 50389 Wesseling

(72) Erfinder:
Zerbe, Horst Georg, Dr., Green Pond, N.J., US; Guo, Jian-Hwa, Dr., Sparta, N.J., US

(56) Entgegenhaltungen:

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EP 02 19 762 A1
CA 12 63 312
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**Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen**

Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Zubereitung zur Anwendung in der Mundhöhle mit einer an der Schleimhaut haftklebenden, Pharmazeutika oder Kosmetika zur dosierten Abgabe enthaltenden Schicht

(57) Eine Zubereitung zur Anwendung in der Mundhöhle mit einer an der Schleimhaut haftklebenden Schicht ist dadurch gekennzeichnet, daß die haftklebende Schicht eine homogene Mischung enthält, bestehend aus einem wasserlöslichen Polymer, einer Mischung nichtionischer oberflächenaktiver Stoffe, einem Polyalkohol, einem kosmetischen oder pharmazeutischen Wirkstoff, und einem Geschmacks- oder Aromastoff.

DE 196 46 392 A 1

## Beschreibung

Zubereitung zur Anwendung in der Mundhöhle mit einer an der Schleimhaut haftklebenden, Pharmazeutika oder Kosmetika zur dosierten Abgabe enthaltenden Schicht.

Derartige an der Mundschleimhaut haftklebende Dosiersysteme zur Anwendung in der Mundhöhle sind bekannt. Die US 5,047,244 beschreibt einen an der Mundschleimhaut haftklebenden Träger zur kontrollierten Abgabe eines therapeutischen Wirkstoffs durch das Schleimhautgewebe, der eine wasserfreie, aber hydratisierbare Polymermatrix und amorphes Siliciumdioxid enthält.

Fakultativ kann ein wasserunlöslicher Film beigefügt werden, um die Oberfläche nichtadhäsiv zu gestalten. Die WO 91/06270 des gleichen Erfinders offenbart einen dreischichtigen Film zur verlängerten Abgabe eines aktiven Wirkstoffs in der Mundhöhle.

In gleicher Weise offenbart US 4,876,092 eine flächenförmige, adhäsive Zubereitung, umfassend eine adhäsive Schicht, welche bestimmte wasserlösliche und wasserunlösliche Polymere und einen wasserunlöslichen Träger enthält, welcher an der Mundschleimhaut haftet und dabei einen aktiven Wirkstoff an die Mundhöhle abgibt.

Alle diese vorgenannten Vorrichtungen sind nicht vollständig wasserlöslich und verbleiben in der Mundhöhle, selbst nach Erreichen des therapeutischen Ziels, und bereiten dem Patienten ein gewisses Unbehagen im Mund, das hauptsächlich durch die Trägerschicht verursacht wird, welche einen unlöslichen Rückstand im Mund zurückläßt.

Eine Reihe von Versuchen wurde unternommen, um das ungute Gefühl in der Mundhöhle zu verringern, welches durch die Starrheit und mangelnde Flexibilität der Trägerschicht verursacht wurde, indem man weiche Filmträger einführte. Die Dokumente EP 0 200 508 und EP 0 381 194 schlagen die Verwendung von Polyethylenfilmen, Polyvinylacetat, Ethylen-Vinylacetat-Copolymeren, Metallfolien, Stofflaminaten, Papier- oder Plastikfilm und ähnlichen Materialien als weiche Träger vor, wobei synthetische Harze wie Polyethylen, Vinylacetat-Homopolymere und Ethylen-Vinyl-Acetat bevorzugte Materialien sind. In gleicher Weise offenbart CA-PS 1 263 312 die Verwendung von Polyolefinen wie Polyethylen, Polypropylen, Polyester, PVC, sowie Vliesstoffen als weiche Trägermaterialien. Dennoch hinterlassen diese beim Patienten eine beträchtliche Menge von Rückständen des wasserunlöslichen Trägerfilms und verursachen dabei immer noch ein unbehagliches Gefühl. Eine naheliegende Lösung zur Überwindung dieses Problems war die Entwicklung schleimhauthaftender Filme, welche vollständig zerfallen oder sich im Speichel auflösen.

Fuchs und Hilmann (DE 24 49 865.5) stellten homogene, wasserlösliche Filme für buccale Zuführung von Hormonen her. Sie schlugen die Verwendung von wasserlöslichen Cellulosederivaten wie Hydroxyethylcellulose, Hydroxypropylcellulose oder Methylhydroxypropylcellulose als Filmbildner vor.

Die beiden Patentschriften DE 36 30 603 und EP 0 219 762 offenbaren die Verwendung von quellbaren Polymeren wie Gelatine oder Maisstärke als Filmbildner, welche nach Applikation in der Mundhöhle langsam zerfallen, wobei sie einen aktiven Wirkstoff freisetzen, der im Film enthalten ist. Die gleichen Polymere können ebenfalls verwendet werden, um Filme herzustellen, die zur Zahnpflege dienen sollen, entsprechend der Beschreibung in EP 0 452 446. Aber auch diese Zubereitungen rufen ebenfalls ein ungutes Gefühl im Mund hervor, insbesondere verursacht durch ihre anfängliche Starrheit und verzögerte Erweichung. Hieraus resultiert ein Bedarf für eine Komposition zur Verwendung in der Mundhöhle, die dem Erfordernis



eines Wohlgefühls im Mund Rechnung trägt.

Der vorliegenden Erfindung liegt daher die Aufgabe zugrunde, eine Zubereitung anzugeben, die geeignet ist, ein angenehmes Gefühl im Mund zu erzeugen, indem sie einen Film zur Applikation an der Mundschleimhaut vorsieht, der eine sofortige Benetzbarkeit aufweist und eine haftklebende Befestigung in der Mundhöhle unter Abgabe pharmazeutischer oder kosmetischer Wirkstoffe, ermöglicht, die sich rasch auflöst bzw. zerfällt.

Die Lösung der Aufgabe gelingt bei einer Zubereitung der im Oberbegriff von Anspruch 1 genannten Art mit der Erfindung dadurch, daß die haftklebende Schicht eine homogene Mischung enthält, bestehend aus einem wasserlöslichen Polymer, einer Mischung nichtionischer oberflächenaktiver Stoffe, einem Polyalkohol, einem kosmetischen oder pharmazeutischen Wirkstoff, und einem Geschmacksstoff.

Mit großem Vorteil ist der daraus resultierende Film charakterisiert durch eine sofortige Benetzbarkeit, welche den Film unverzüglich nach Applikation am Schleimhautgewebe erweichen läßt und beim Patienten ein unangenehmes Gefühl im Mund verhindert.

Der Film ist unter Verwendung konventioneller Beschichtungs- und Trocknungstechniken herstellbar, in Form und Größe nach Anforderungen spezieller Applikation vereinzelbar und in geeignete Packungen verpackbar.

Eine Ausgestaltung der Erfindung sieht vor, daß das wasserlösliche Polymer der Zubereitung Hydroxypropylmethylcellulose, Hydroxy-ethylcellulose, Hydroxypropylcellulose, Polyvinylpyrrolidon, Carboxymethylcellulose, Polyvinylalkohol, Natriumalginat, Polyethylenglycol, Xanthanharz, Traganth, Guarharz, Akazienharz, Gummiarabicum, Polyacrylsäure, Methylmethacrylatcopolymer, Carboxyvinylcopolymere oder deren Mischungen umfaßt.

Dabei ist vorgesehen, daß die Konzentration des wasserlöslichen Polymers in der Trockenmasse der Filmschicht zwischen 20 und 60 Gew.-% beträgt. Eine bevorzugte Konzentration beträgt zwischen 30 und 50 Gew.-%.

Weiterhin ist mit der Erfindung vorgesehen, daß die Mischung der oberflächenaktiven Stoffe vorzugsweise aus zwei Komponenten besteht. Dabei ist die erste Komponente ein Polyethoxysorbitan-fettsäureester oder ein α-hydro-ω-hydroxypoly(ethoxy)-poly-(propoxy)-poly(ethoxy)-Blockcopolymer.

Die zweite Komponente ist ein Polyethoxy-alkylether oder ein Polyethoxy-rizinusölderivat.

Bevorzugt soll der HLB-Wert der Polyethoxysorbitanfettsäurester zwischen 10 und 20 betragen, wobei ein Bereich zwischen 13 und 17 besonders bevorzugt ist. Das αhydro-ω-hydroxypoly(ethoxy)-poly(propoxy)-poly(ethoxy)-Blockcopolymer soll mindestens 35 Propoxy-Einheiten, bevorzugt mindestens 50 Propoxy-Einheiten enthalten.

Der Polyethoxyalkylether sollte einen HLB-Wert zwischen 10 und 20 besitzen, bevorzugt nicht weniger als 15. Das Polyethoxy-rizinusölderivat soll einen HLB-Wert zwischen 14 und 16 besitzen.

Um die erwünschte, sofortige Benetzbarkeit zu erreichen, soll das Verhältnis zwischen der ersten und der zweiten Komponente einer binären oberflächenaktiven Mischung zwischen 1 : 10 und 1 : 1 gehalten werden, bevorzugt zwischen 1 : 5 und 1 : 3.

Die Gesamtkonzentration der oberflächenaktiven Stoffe im Film hängt ab von den Eigenschaften der anderen Ingredienzien, soll jedoch üblicherweise zwischen 1 und 5 Gew.-% betragen.

Der Polyalkohol wird benötigt, um den erwünschten Weichheitsgrad des Filmes zu erreichen. Beispiele von Polyalkoholen umfassen Glycerin, Polyethylenglycol, Propylenglycol, Glycerinmonoester mit Fettsäuren, oder sonstige

pharmazeutisch verwendete Polyalkohole. Die Konzentration von Polyalkohol in der Trockenmasse des Filmes beträgt üblicherweise 4 bis 25 Gew.-%.

Der Film ist besonders gut geeignet zur Abgabe eines weiten Bereiches pharmazeutisch aktiver Wirkstoffe durch die Schleimhautmembranen eines Patienten, insbesondere durch die buccalen Schleimhäute.

Therapeutische Wirkstoffe, die Absorptionsprobleme infolge begrenzter Löslichkeit, Abbau im Gastrointestinaltrakt oder extensiven Metabolismus haben, sind besonders gut geeignet. Als Beispiele der einsetzbaren therapeutischen Wirkstoffe sind zu nennen: Hypnotica, Sedativa, Antiepileptica, Weckamine, Psychoneurotropica, Neuro-Muskelblokker, Antispasmodica, Antihistaminica, Antiallergica, Cardiotonica, Antiarrhythmica, Diuretica, Hypotensiva, Vasopressoren, Antitussiva, Expectorantia, Thyroidhormone, Sexualhormone, Antidiabetica, Antitumor-Wirkstoffe, Antibiotica sowie Chemotherapeutica und Narcotica. Die im Film einzulagernde Menge von Wirkstoff hängt von dessen Art ab und beträgt üblicherweise zwischen 0,01 und 20 Gew.-%.

Kosmetische Wirkstoffe umfassen Atemerfrischer wie Menthol, andere Geschmacks-, Aroma- oder Duftstoffe, wie sie üblicherweise für Mundhygiene oder Zahnpflege verwendet werden, beispielsweise quartäre Ammoniumbasen. Die Wirkung von Geschmacks- und Aromastoffen kann durch Geschmacksverstärker wie Weinsäure, Zitronensäure, Vanillin oder dergleichen verstärkt werden.

Farbstoffe, welche wahlweise dem Film beigemischt werden, müssen hinsichtlich Toxizität sicher sein und sollten zur Verwendung in Kosmetika durch die zuständigen Behörden zugelassen sein.

Der erfindungsgemäße mucoadhäsive Film kann folgendermaßen hergestellt werden:
Wirkstoff, oberflächenaktive Stoffe, Polyalkohol und andere mögliche Bestandteile außer dem wasserdispersiblen Polymer werden mit einer genügenden Menge eines kompatiblen Lösungsmittels gelöst. Beispiele eines kompatiblen Lösungsmittels umfassen Wasser, Alkohole oder deren Mischungen. Nach Bildung einer klaren Lösung wird das wasserdispersible Polymer oder die Mischung wasserdispersibler Polymere langsam unter Rühren zugegeben, bis eine klare und homogene Lösung gebildet ist. Diese wird auf einen Träger aufgetragen und zu einem Film getrocknet. Das Trägermaterial muß eine Oberflächenspannung haben, die es ermöglicht, die Polymerlösung gleichmäßig über die vorgesehene Beschichtungsbreite zu verteilen. Beispiele für geeignete Materialien umfassen nichtsilikonisierte Polyethylen-Terephthalat-Filme, nichtsiliconisiertes Kraftpapier, oder nichtsiliconisierten Polyethylenfilm. Der Auftrag der Lösung auf das Trägermaterial kann mit jeder geeigneten Vorrichtung ausgeführt werden. Eine speziell bevorzugte Auftragstechnik betrifft eine Walzenrakel-Streichmaschine.

Die Dicke der resultierenden Filmschicht hängt von der Konzentration der Feststoffe in der Beschichtungslösung sowie von der Spaltbreite der Beschichtungsmaschine ab und kann zwischen 5 und 200 µm variieren. Die Trocknung des Films wird in einem Heißluftbad unter Verwendung eines Trockenofens, Trockentunnels, Vakuumtrockners oder anderer geeigneter Trockenvorrichtungen vorgenommen. Um ein unangenehmes Gefühl im Mund zuverlässig zu vermeiden, soll die Filmdicke 70 µm nicht überschreiten. Zur besseren Gebrauchserleichterung kann der Film in Stücke von geeigneter Größe und Form geschnitten und verpackt werden.

Die Erfindung wird anhand nachfolgender Beispiele veranschaulicht.

Beispiel 1

15 g Sorbit, 6 g Glycerin, 0,5 g Polysorbat 80 (Tween 80), 2 g Brij 35, 25 g Zitronenminzearoma, 3 g Aspartam, 15 g l-Menthol und 3 g Zitronensäure werden bei 60°C in einer Mixtur von 250 g Wasser und 250 g Ethanol solange gerührt, bis sich eine klare Lösung gebildet hat. Zu der Lösung werden 30 g Hydroxypropylmethylcellulose langsam unter Rühren zugegeben, bis eine klare und homogene Lösung gebildet ist. Die resultierende Lösung wird dann bis auf Raumtemperatur abkühlen gelassen und unter Verwendung einer üblichen Beschichtungsvorrichtung auf ein geeignetes Trägermaterial aufgestrichen, beispielsweise nichtsiliconisiertes polyethylenbeschichtetes Kraftpapier.

Beschichtungsspalt und Bahngeschwindigkeit müssen so geregelt werden, daß eine Trockenfilmdicke zwischen 20 und 50 µm erreicht wird. Die Trockentemperatur hängt von der Länge des Trockenofens und der Materialgeschwindigkeit ab und soll so eingestellt werden, daß die Lösungsmittel vollständig, oder zumindest weitgehend vollständig vom Film entfernt werden. Der resultierende Film wird vom Träger abgelöst und zum Gebrauch in Stücke von geeigneter Größe und Form zerteilt.

Beispiel 2

3 g Sorbit, 1,5 g Kollidon 30 (Lieferant: BASF), 5 g Glycerin, 5 g Propylenglycol, 5 g Polyethylenglycol, 4 g Polysorbat 80 (Tween 80), 8 g Brij 35, 12 g Pfefferminzaroma, 0,8 g Aspartam werden in einer Mischung von 400 g Wasser und 400 g Ethanol bei 60°C unter Rühren aufgelöst. Zu der klaren Lösung werden 28 g Hydroxypropylmethylcellulose unter Rühren langsam zugegeben. Nach völliger Auflösung des Polymers wird die Lösung auf Raumtemperatur abgekühlt und auf einen Träger unter den gleichen Bedingungen wie in Beispiel 1 aufgestrichen. Der trockene Film wird wieder in Stücke von geeigneter Größe und Form zerteilt.

Beispiel 3

15 g Sorbit, 22,5 g Glycerin, 2,5 Propylenglycol, 2,5 g Brij 35, 2,5 g Poloxamer 407, 3,5 g Cremophor RH 40, 9 g Kräuterminzearoma, 0,5 g Aspartam werden unter ständigem Rühren bei 60°C in einer Mischung von 250 g Wasser und 250 g Ethanol gelöst. Zu der klaren Lösung werden 75 g Hydroxypropylcellulose unter ständigem Rühren langsam zugegeben. Mit der klaren Lösung wird wiederum beschichtet und unter den beschriebenen Bedingungen getrocknet, wie in Beispiel 1; der trockene Film wird in Stücke von geeigneter Größe und Form zerteilt.

Patentansprüche

1. Zubereitung zur Anwendung in der Mundhöhle mit einer an der Schleimhaut haftklebenden Schicht, **dadurch gekennzeichnet**, daß die haftklebende Schicht eine homogene Mischung enthält, bestehend aus einem wasserlöslichen Polymer, einer Mischung nichtionischer oberflächenaktiver Stoffe, einem Polyalkohol, einem kosmetischen oder pharmazeutischen Wirkstoff, und einem Geschmacks- oder Aromastoff.

2. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß das wasserlösliche Polymer Hydroxypropylmethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose, Polyvinylpyrrolidon, Carboxylmethylcellulose, Polyvinylalkohol, Natriumalginat, Polyethylenglycol, Xanthanharz, Traganth, Guarharz, Akazienharz, Gummiarabicum, Polyacrylsäure, Methylme-

thacrylatcopolymer, Carboxyvinylcopolymere oder deren Mischungen umfaßt.

3. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß die Konzentration des wasserlöslichen Polymers in der Trockenmasse der Filmschicht zwischen 20 und 60 Gew.-% beträgt.

4. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß die Mischung der oberflächenaktiven Stoffe aus zwei Komponenten besteht.

5. Zubereitung nach Anspruch 4, dadurch gekennzeichnet daß die erste Komponente des oberflächenaktiven Stoffs ein Polyethoxysorbitan-fettsäureester oder ein α-hydroωhydroxypoly(ethoxy)-poly(propoxy)-poly(ethoxy)-Blockcopolymer ist.

6. Zubereitung nach Anspruch 4, dadurch gekennzeichnet, daß die zweite Komponente des oberflächenaktiven Stoffs ein Polyethoxy-alkylether oder ein Polyethoxyrizinusölderivat ist.

7. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß der Polyalkohol ausgewählt ist aus Glycerin, Polyethylenglycol, Propylenglycol oder Glycerinmonoestern mit Fettsäuren.

8. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß der therapeutische Wirkstoff ausgewählt ist aus der Gruppe von Hypnotica, Sedativa, Antiepileptica, Weckaminen, Psychoneurotropica, Neuro-Muskelblockern, Antispasmodica, Antihistaminica, Antiallergica, Cardiotonica, Antiarrhythmica, Diuretica, Hypotensiva, Vasopressoren, Antitussiva, Expectorantia, Thyroidhormonen, Sexualhormonen, Antidiabetica, Antitumor-Wirkstoffen, Antibiotica sowie Chemotherapeutica oder Narcotica.

9. Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß der kosmetische Wirkstoff Atemerfrischer wie Menthol, Geschmacks-, Aroma- oder Duftstoffe, wie sie üblicherweise für Mundhygiene verwendet werden, und/oder Wirkstoffe zur Zahn- oder Mundpflege umfaßt, wie quartäre Ammoniumbasen.

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(54) Title: FAST DISSOLVING ORALLY CONSUMABLE FILMS CONTAINING AN ION EXCHANGE RESIN AS A TASTE MASKING AGENT

(57) Abstract: Physiologically acceptable films, including edible films, are disclosed. The films include a water soluble film-forming polymer, such as pullulan, and a taste masked pharmaceutically active agent, such as dextromethorphan. The taste masking agent is preferably a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene, such as AMBERLITE. Methods for producing the films are also disclosed.

# FAST DISSOLVING ORALLY CONSUMABLE FILMS CONTAINING AN ION EXCHANGE RESIN AS A TASTE MASKING AGENT

## SPECIFICATION

## FIELD OF THE INVENTION

This invention relates to fast dissolving orally consumable films containing an agent to mask the taste of a pharmaceutically active agent therein, and more specifically to such films containing an ion exchange resin as the taste masking agent.

## BACKGROUND OF THE INVENTION

It has been known to administer pharmaceutically active agents in an edible film vehicle.

For example, WO 99/17753 discloses rapidly dissolving films for delivery of drugs to be adsorbed in the digestive tract.

WO 98/26780 discloses a flat, foil, paper or wafer type presentation for the application and release of active substances in the buccal cavity. The specific active ingredient disclosed in WO 98/26780 is buprenorphine.

WO 98/20862 discloses a film for use in the oral cavity that can contain a cosmetic or pharmaceutical active substance.

WO 98/26763 discloses a flat, foil, paper or wafer like presentation for release of active substances into the buccal cavity. The particular active disclosed is apomorphine.

U.S. Patent Application No. 09/395,104 also discloses the delivery of pharmaceutical agents in a edible film vehicle.

U.S. Patent No. 5,411,945 to Ozaki et al. discloses a pullulan binder and products produced therewith, including edible films (Example B-2). The products can include a variety of ingredients in addition to pullulan, such as other polysaccharides, antibacterial agents, flavor-imparting agents and pharmaceutically active substances (column 4, lines 5-15).

U.S. Patent No. 3,784,390 Hijiya et al. discloses pullulan films and their use in coating and packing materials for foods, pharmaceuticals and other oxygen sensitive materials. All of the examples in this patent teach mixing pullulan in hot water.

It has also been known to combine ion exchange resins with pharmaceutically active agents to provide sustained release formulations.

For example, U.S. Patent No. 6,001,392 to Wen et al. discloses a controlled-release syrup suspension for oral administration containing dextromethorphan adsorbed to a polystyrene sulfonate ion exchange resin. Pharmaceutical films are not disclosed.

U.S. Patent No. 5,980,882 to Eichman discloses a method for improving the stability of a pharmaceutical composition that contains a drug-resin complex, comprising adding a chelating agent in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex. Although Eichman teaches that complexing a drug with an ion exchange resin can mask the taste of the drug. Pharmaceutical films are not disclosed.

The inventors are not aware of any suggestion in the published art that ion exchange resins can act as taste masking agents in a fast dissolving orally consumable film. Accordingly, an object of this invention is to provide fast dissolving orally consumable films containing an ion exchange resin to mask the taste of a pharmaceutically active agent therein.

All references cited herein are incorporated herein by reference in their entireties.

## SUMMARY OF THE INVENTION

The invention provides a consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein the film comprises at least one water soluble polymer, at least one pharmaceutically active agent and at least one taste masking agent.

Also provided is a method for preparing the consumable film of the invention, comprising:

dissolving water-soluble ingredients in water to provide an aqueous solution;

mixing at least one water soluble film former and at least one stabilizing agent to provide a film-forming mixture;

combining the film-forming mixture and the aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

adding the oil mixture to the hydrated polymer gel and mixing to provide a uniform gel;

casting the uniform gel on a substrate; and

drying the cast gel to provide the film.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention provides a physiologically acceptable film that is particularly well adapted to adhere to and dissolve in a mouth of a consumer to deliver a pharmaceutically active agent. Preferred films according to the invention comprise a pharmaceutically active agent, an ion exchange resin, a film-forming agent, and at least one of the following additional ingredients: water, antimicrobial agents, plasticizing agents, flavoring agents, saliva stimulating agents, cooling agents, surfactants, stabilizing agents, emulsifying agents, thickening agents, binding agents, coloring agents, sweeteners, fragrances, triglycerides, preservatives, polyethylene oxides, propylene glycol, and the like.

The expression "physiologically acceptable" as used herein is intended to encompass compounds, which upon administration to a patient, are adequately tolerated without causing undue negative side effects. The expression encompasses edible compounds.

The expression "pharmaceutically active agents" as used herein is intended to encompass agents other than foods, which promote a structural and/or functional change in and/or on bodies to which they have been administered. These agents are not particularly limited; however, they should be physiologically acceptable and compatible with the film. Suitable pharmaceutically active agents include, but are not limited to:

A. antimicrobial agents, such as triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA, and the like;

B. non-steroidal anti-inflammatory drugs, such as aspirin, acetaminophen, ibuprofen, ketoprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and the like;

C. anti-tussives, such as benzonatate, caramiphen edisylate, menthol, dextromethorphan hydrobromide, chlophedianol hydrochloride, and the like;

D. decongestants, such as pseudoephedrine hydrochloride, phenylepherine, phenylpropanolamine, pseudoephedrine sulfate, and the like;

E. anti-histamines, such as brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenylpyraline hydrochloride, azatadine meleate, diphenhydramine citrate, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride, acrivastine, loratadine, brompheniramine, dexbrompheniramine, and the like;

F. expectorants, such as guaifenesin, ipecac, potassium iodide, terpin hydrate, and the like;

G. anti-diarrheals, such a loperamide, and the like;

H. $H_2$-antagonists, such as famotidine, ranitidine, and the like;

I. proton pump inhibitors, such as omeprazole, lansoprazole, and the like;

J. general nonselective CNS depressants, such as aliphatic alcohols, barbiturates and the like;

K. general nonselective CNS stimulants such as caffeine, nicotine, strychnine, picrotoxin, pentylenetetrazol and the like;

L. drugs that selectively modify CNS function, such as phenyhydantoin, phenobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phensuximide, trimethadione, diazepam, benzodiazepines, phenacemide, pheneturide, acetazolamide, sulthiame, bromide, and the like;

M. antiparkinsonism drugs such as levodopa, amantadine and the like;

N. narcotic-analgesics such as morphine, heroin, hydromorphone, metopon, oxymorphone, levorphanol, codeine, hydrocodone, xycodone, nalorphine, naloxone, naltrexone and the like;

O. analgesic-antipyretics such as salycilates, phenylbutazone, indomethacin, phenacetin and the like; and

P. psychopharmacological drugs such as chlorpromazine, methotrimeprazine, haloperidol, clozapine, reserpine, imipramine, tranylcypromine, phenelzine, lithium and the like.

The amount of pharmaceutically active agent that can be used in the rapidly dissolving films, according to the present invention, is dependent upon the dose needed to provide an effective amount of the pharmaceutically active agent. Examples of doses for specific pharmaceutically active agents that can be delivered per one strip of rapidly dissolving oral film are reviewed in Table A.

TABLE A

| PHARMACEUTICALLY ACTIVE AGENT | PREFERRED DOSE |
|---|---|
| Chlorpheniramine Maleate | 4 mg. |
| Brompheniramine Maleate | 4 mg. |
| Dexchlorpheniramine | 2 mg. |
| Dexbrompheniramine | 2 mg. |
| Triprolidine Hydrochloride | 2.5 mg. |
| Acrivastine | 8 mg. |
| Azatadine Maleate | 1 mg. |
| Loratidine | 10 mg. |
| Phenylephrine Hydrochloride | 10 mg. |
| Dextromethorphan Hydrobromide | 10-30 mg. |
| Ketoprofen | 12.5-25 mg. |
| Sumatriptan Succinate | 35 - 70 mg. |
| Zolmitriptan | 2.5 mg. |
| Loperamide | 2 mg. |
| Famotidine | 10 mg. |
| Nicotine | 2 mg. |
| Diphenhydramine Hydrochloride | 12.5-25 mg. |
| Pseudoephedrine Hydrochloride | 30 mg. |

Ion exchange resins preferred for use in the films of the invention are water-insoluble and consist of a pharmacologically inert organic or inorganic matrix containing covalently bound functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene), or partially synthetic (e.g., modified cellulose and dextrans). The inorganic matrix can also be, e.g., silica gel modified by the addition of ionic groups. The covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., quaternary ammonium), weakly basic (e.g., primary amine), or a combination of acidic and basic groups. In general, those types of ion exchangers suitable for use in ion exchange chromatography and for such applications as deionization of water are suitable for use in these

controlled release drug preparations. Such ion exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp. 312-343). The ion exchange resins useful in the present invention have exchange capacities below about 6 milliequivalents per gram (meq/g) and preferably below about 5.5 meq/g.

The resin is crosslinked with a crosslinking agent selected from difunctional compounds capable of crosslinking polystyrenes; these are commonly known in the art. Preferably, the crosslinking agent is a divinyl or polyvinyl compound. Most preferably the crosslinking agent is divinylbenzene. The resin is crosslinked to an extent of about 3 to about 20%, preferably about 4 to about 16%, more preferably about 6 to about 10%, and most preferably about 8% by weight based on the total resin. The resin is crosslinked with the crosslinking agent by means well known in the art.

The size of the ion exchange resins should preferably fall within the range of about 20 to about 200 micrometers. Particle sizes substantially below the lower limit are difficult to handle in all steps of the processing. Particle sizes substantially above the upper limit, e.g., commercially available ion exchange resins having a spherical shape and diameters up to about 1000 micrometers, are gritty in liquid dosage forms and have a greater tendency to fracture when subjected to drying-hydrating cycles.

Representative resins useful in this invention include AMBERLITE IRP-69 (obtained from Rohm and Haas) and Dow XYS-40010.00 (obtained from The Dow Chemical Company). Both are sulfonated polymers composed of polystyrene cross-linked with 8% of divinylbenzene, with an ion exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H+-form). Their essential difference is in physical form. AMBERLITE IRP-69 comprises irregularly-shaped particles with a size range of 47 to 149 micrometers, produced by milling the parent, large-sized spheres of AMBERLITE IRP-120. The Dow XYS-40010.00 product comprises spherical particles with a size

range of 45 to 150 micrometers. Another useful exchange resin, Dow XYS-40013.00, is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group; its exchange capacity is normally within the range of approximately 3 to 4 meq/g of dry resin.

The most preferred resin is AMBERLITE IRP-69. However, in less preferred embodiments, the taste masking agent need not be an ion exchange resin. In these embodiments, the taste masking agent can be, e.g., magnesium trisilicate. See, e.g., U.S. Patents Nos. 4,650,663 and 4,581,232 to Peters et al. Taste can also be masked by polymers, such as EUDRAGIT E (Rohm and Haas), and/or cellulosics, such as ethylcellulose, and the like.

The film-forming agent used in the films according to the present invention can be selected from the group consisting of pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof. A preferred film former is pullulan, in amounts ranging from about 0.01 to about 99 wt%, preferably about 30 to about 80 wt%, more preferably from about 45 to about 70 wt% of the film and even more preferably from about 60 to about 65 wt% of the film.

Unless specified otherwise, the term "wt%" as used herein with reference to the final product (i.e., the film, as opposed to the formulation used to create it), denotes the percentage of the total dry weight contributed by the subject ingredient. This theoretical value can differ from the experimental

value, because in practice, the film typically retains some of the water and/or ethanol used in preparation.

In embodiments containing relatively high oil content, it is preferable to avoid substantial amounts of humectant in the film (and more preferable to have no humectant in the film), so as to avoid producing an overly moist, self-adhering film. In particular, it is preferred to formulate high oil content films with a plasticizing agent other than glycerin, which is also a humectant, and with a sweetener other than sorbitol, which is a mild humectant.

Saliva stimulating agents can also be added to the films according to the present invention. Useful saliva stimulating agents are those disclosed in U.S. Patent No. 4,820,506. Saliva stimulating agents include food acids such as citric, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acids. Preferred food acids are citric, malic and ascorbic acids. The amount of saliva stimulating agents in the film is from about 0.01 to about 12 wt%, preferably about 1 wt% to about 10 wt%, even more preferably about 2.5 wt% to about 6 wt%.

Preferred plasticizing agents include triacetin in amounts ranging from about 0 to about 20 wt%, preferably about 0 to about 2 wt%. Other suitable plasticizing agents include monoacetin and diacetin.

Preferred cooling agents include monomenthyl succinate, in amounts ranging from about 0.001 to about 2.0 wt%, preferably about 0.2 to about 0.4 wt%. A monomenthyl succinate containing cooling agent is available from Mane, Inc. Other suitable cooling agents include WS3, WS23, Ultracool II and the like.

Preferred surfactants include mono and diglycerides of fatty acids and polyoxyethylene sorbitol esters, such as, Atmos 300 and Polysorbate 80. The surfactant can be added in amounts ranging from about 0.5 to about 15 wt%, preferably about 1 to about 5 wt% of the film. Other suitable surfactants

include pluronic acid, sodium lauryl sulfate, and the like.

Preferred stabilizing agents include xanthan gum, locust bean gum and carrageenan, in amounts ranging from about 0 to about 10 wt%, preferably about 0.1 to about 2 wt% of the film. Other suitable stabilizing agents include guar gum and the like.

Preferred emulsifying agents include triethanolamine stearate, quaternary ammonium compounds, acacia, gelatin, lecithin, bentonite, veegum, and the like, in amounts ranging from about 0 to about 5 wt%, preferably about 0.01 to about 0.7 wt% of the film.

Preferred thickening agents include methylcellulose, carboxyl methylcellulose, and the like, in amounts ranging from about 0 to about 20 wt%, preferably about 0.01 to about 5 wt%.

Preferred binding agents include starch, in amounts ranging from about 0 to about 10 wt%, preferably about 0.01 to about 2 wt% of the film.

Suitable sweeteners that can be included are those well known in the art, including both natural and artificial sweeteners. Suitable sweeteners include, e.g.:

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

B. water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2, 2-dioxide, the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (acesulfame-K), the free acid form of saccharin,

and the like;

C. dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame) and materials described in U.S. Pat. No. 3,492,131, L- alpha-aspartyl-N-(2,2,4,4--tetramethyl-3-thietanyl)-D-alaninamide hydrate, methyl esters of L-aspartyl-L-phenylglycerin and L-aspartyl-L-2,5,dihydrophenyl-glycine, L-aspartyl-2,5-dihydro- L-phenylalanine, L-aspartyl-L-(1-cyclohexyen)-alanine, and the like;

D. water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as a chlorinated derivative of ordinary sugar (sucrose), known, for example, under the product description of sucralose; and

E. protein based sweeteners such as thaumatoccous danielli (Thaumatin I and II).

In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with the sweetener selected. This amount will normally be 0.01 % to about 10 % by weight of the composition when using an easily extractable sweetener. The water-soluble sweeteners described in category A above, are usually used in amounts of about 0.01 to about 10 wt%, and preferably in amounts of about 2 to about 5 wt%. Some of the sweeteners in category A (e.g., glycyrrhizin) can be used in amounts set forth for categories B-E below due to the sweeteners' known sweetening ability. In contrast, the sweeteners described in categories B-E are generally used in amounts of about 0.01 to about 10 wt%, with about 2 to about 8 wt% being preferred and about 3 to about 6 wt% being most preferred. These amounts may be used to achieve a desired level of sweetness independent from the flavor level achieved from any optional flavor oils used. Of course, sweeteners need not be added to films intended for non-oral administration.

The flavorings that can be used include those known to the skilled artisan, such as natural and artificial flavors. These flavorings may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Representative flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also useful are artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. These flavorings can be used individually or in admixture. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in admixture. Flavorings such as aldehydes and esters including cinnamyl acetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and so forth may also be used. Generally, any flavoring or food additive, such as those described in Chemicals Used in Food Processing, publication 1274 by the National Academy of Sciences, pages 63-258, may be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamic aldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral, i.e. beta citral (lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream); heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter, cheese); valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal (citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits); aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla);

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

The amount of flavoring employed is normally a matter of preference subject to such factors as flavor type, individual flavor, and strength desired. Thus, the amount may be varied in order to obtain the result desired in the final product. Such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In general, amounts of about 0.1 to about 30 wt% are useable with amounts of about 2 to about 25 wt% being preferred and amounts from about 8 to about 10 wt% are more preferred.

The compositions of this invention can also contain coloring agents or colorants. The coloring agents are used in amounts effective to produce the desired color. The coloring agents useful in the present invention, include pigments such as titanium dioxide, which may be incorporated in amounts of up to about 5 wt%, and preferably less than about 1 wt%. Colorants can also include natural food colors and dyes suitable for food, drug and cosmetic applications. These colorants are known as FD&C dyes and lakes. The materials acceptable for the foregoing spectrum of use are preferably water-soluble, and include FD&C Blue No. 2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye known as Green No. 3 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-N-ethyl-p-sulfobenzylamino) diphenyl-methylene]-[1-N-ethyl-N-p-sulfonium benzyl)-2,5-cyclo-hexadienimine]. A full recitation of all FD&C and D&C dyes and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, Volume 5, Pages 857-884, which text is accordingly incorporated herein by reference.

The films can also include a triglyceride. Examples of triglycerides include vegetable oils such as corn oil, sunflower oil, peanut oil, olive oil,

canola oil, soybean oil and mixtures thereof. A preferred triglyceride is olive oil. The triglyceride is added to the film in amounts from about 0.1 wt% to about 12 wt%, preferably in a range from about 0.5 wt% to about 9 wt%, of the film.

The films can include a preservative in amounts from about 0.001 wt% to about 5 wt%, preferably from about 0.01 wt% to about 1 wt% of the film. Preferred preservatives include sodium benzoate and potassium sorbate. Other suitable preservatives include, but are not limited to, salts of edetate (also known as salts of ethylenediaminetetraacetic acid, or EDTA, such as disodium EDTA) and parabens (e.g., methyl, ethyl, propyl or butyl-hydroxybenzoates, etc.) or sorbic acid. The preservatives listed above are exemplary, but each preservative must be evaluated on an empirical basis, in each formulation, to assure the compatibility and efficacy of the preservative. Methods for evaluating the efficacy of preservatives in pharmaceutical formulations are known to those skilled in the art.

The films can also include a polyethylene oxide compound. The molecular weight of the polyethylene oxide compound ranges from about 50,000 to about 6,000,000. A preferred polyethylene oxide compound is N-10 available from Union Carbide Corporation. The polyethylene oxide compound is added in amounts from about 0.1 wt% to about 5 wt%, preferably from about 0.2 wt% to about 4.0 wt% of the film.

The films can also include propylene glycol. The propylene glycol is added in amounts from about 1 wt% to about 20 wt%, preferably from about 5 wt% to about 15 wt% of the film.

Methods for preparing films according to the invention are capable of encapsulating the oil ingredients within the film-forming matrix and maintaining the integrity of the film, even when the film contains oils in amounts of 10 wt% or more.

In certain methods for preparing films according to the invention, the film-forming ingredients are mixed and hydrated with water separately from the water-soluble ingredients, which are mixed in aqueous solution separately from the organic ingredients and surfactants. In these methods, the final formulation is preferably produced by mixing the film-forming phase with the aqueous phase, then mixing in the organic phase, which includes surfactants, such as Polysorbate 80 and Atmos 300. This mass is mixed until emulsified. In other embodiments, the aqueous and film forming phases are combined into a single phase by dissolving the water soluble ingredients in the water and then adding the gums to hydrate. The organic phase is then added to this single aqueous phase.

The resulting formulation is cast on a suitable substrate and dried to form a film. The film is preferably air-dried or dried under warm air and cut to a desired dimension, packaged and stored. The film can contain from about 0.1% to about 10 wt% moisture, preferably from about 3 % to about 8 wt% moisture, even more preferably from about 4 to about 7 wt% moisture.

The film-forming phase can include pullulan and stabilizing agents such as xanthan gum, locust bean gum and carrageenan. These ingredients are mixed and then hydrated in water for about 30 to about 48 hours to form a gel. The water is preferably heated to a temperature of about 25 to about 45°C to promote hydration. The amount of water is about 40 to 80% of the gel. The resulting hydrated gel is then chilled to a temperature of about 20 to about 30°C for about 1 to about 48 hours. The water is preferably deionized.

In preferred embodiments, the aqueous phase includes water heated to a temperature of about 60 to 90°C, preferably 70 to 80°C, and ingredients such as the pharmaceutically active agent, ion exchange resin (or other masking agent), coloring agent, preservative and sweetener. The water is preferably deionized and the amount of water used is about 5 to about 80 wt% of the final gel

mixture.

The pharmaceutically active agent is sorbed to the ion exchange resin (or other masking agent) without separating ion exchanged pharmaceutically active agent from unexchanged agent and counter ion salts.

Adsorption of the pharmaceutically active agent onto the ion exchange resin particles to form the pharmaceutically active agent/resin complex is a well known technique as shown in U.S. Pat. Nos. 2,990,332 and 4,221,778. In general, the pharmaceutically active agent is mixed with an aqueous suspension of the resin, and in less preferred embodiments, the complex is then washed and dried. Adsorption of pharmaceutically active agent onto the resin may be detected by measuring a change in the pH of the reaction medium, or by measuring a change in concentration of sodium or pharmaceutically active agent.

Binding of pharmaceutically active agent to resin can be accomplished according to four general reactions. In the case of a basic pharmaceutically active agent, these are: (a) resin (Na-form) plus pharmaceutically active agent (salt form); (b) resin (Na-form) plus pharmaceutically active agent (as free base); (c) resin (H-form) plus pharmaceutically active agent (salt form); and (d) resin (H-form) plus pharmaceutically active agent (as free base). All of these reactions except (d) have cationic byproducts, by competing with the cationic pharmaceutically active agent for binding sites on the resin, reduce the amount of pharmaceutically active agent bound at equilibrium. For basic pharmaceutically active agents, stoichiometric binding of pharmaceutically active agent to resin is accomplished only through reaction (d).

Four analogous binding reactions can be carried out for binding an acidic pharmaceutically active agent to an anion exchange resin. These are: (a) resin (Cl--form) plus pharmaceutically active agent (salt form); (b) resin (Cl--form) plus pharmaceutically active agent (as free acid); (c) resin

(OH--form) plus pharmaceutically active agent (salt form); and (d) resin (OH--form) plus pharmaceutically active agent (as free acid). All of these reactions except (d) have ionic by-products and the anions generated when the reactions occur compete with the anionic pharmaceutically active agent for binding sites on the resin with the result that reduced levels of pharmaceutically active agent are bound at equilibrium. For acidic pharmaceutically active agents, stoichiometric binding of pharmaceutically active agent to resin is accomplished only through reaction (d). The binding may be performed, for example, as a batch or column process, as is known in the art.

In less preferred embodiments, the adsorption complex, including pharmaceutically active agent and resin, is collected and washed with ethanol and/or water to insure removal of any unadsorbed pharmaceutically active agent. The complexes are usually air-dried in trays at room or elevated temperature.

The ratio of the pharmaceutically active agent adsorbate to ion exchange resin adsorbent in the adsorption complex is about 1:3 to about 3:1, preferably about 1:2 to about 2:1, most preferably about 1:1. The only limit to using ratios in excess of 1:3 is an economic and aesthetic one.

The amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 25 to about 75% by weight of the pharmaceutically active agent/resin adsorption complex (hereinafter referred to as the "pharmaceutically active agent/resin complex" or "complex"). More preferably, the amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 33 to about 77% by weight of the pharmaceutically active agent/resin complex. Most preferably, the amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 40 to about 60% by weight of the pharmaceutically active agent/resin complex.

The amount of pharmaceutically active agent/resin complex in the formulation is adjusted to deliver a predetermined dose of the pharmaceutically active agent over a predetermined period of time.

For example, a preferred antitussive film of the invention is administered at one dose every 12 hours to deliver a pharmaceutically effective amount of dextromethorphan over a period of approximately 12 hours to a patient in need of such administration. A typical adult dose of a film of the invention measuring 1" x 1.25" (2.54 cm x 3.18 cm) weighs about 60 to about 190 mg and contains about 20 to about 130 mg of pharmaceutically active agent/resin complex to deliver about 5 to about 65 mg of pharmaceutically active agent (e.g., dextromethorphan hydrobromide) when the average pharmaceutically active agent:ion exchange resin ratio is about 1:1.

In a particularly preferred embodiment of the invention, pullulan is present in the film in an amount of about 2 to about 6 mg/cm$^2$, dextromethorphan is present in the film in an amount of about 1.4 to about 3 mg/cm$^2$, and sulfonated polymer ion exchange resin is present in said film in an amount of about 1.4 to about 2 mg/cm$^2$.

The antitussive pharmaceutically active agents that are suitable for use in these preparations are acidic, amphoteric or most often basic antitussives. Examples of basic pharmaceutically active agents useful in the present invention include, but are not limited to dextromethorphan, diphenhydramine, caramiphen, carbapentane, ethylmorphine, noscapine and codeine. In addition, the antitussive embodiments of the invention can further comprise additional agents that are therapeutically effective to treat conditions other than coughing. That is, more than one type of pharmaceutically active agent can be included in a film of the invention. For example, in the case of a film containing an antitussive agent, the film can further comprise an antihistamine, sympathomimetic pharmaceutically active agent (nasal decongestant,

bronchodilator), analgesic, antiinflammatory, cough suppressant and/or expectorant. Compounds which are antihistamines, sympathomimetic pharmaceutically active agents (nasal decongestant, bronchodilator), analgesic, antiinflammatory, cough suppressants and/or expectorants are well known to those of skill in the art and need not be discussed in detail herein.

In embodiments, a certain percentage of the films disclosed herein will contain non-coated pharmaceutically active agent/resin complexes. The remaining pharmaceutically active agent/resin complexes are further characterized by the presence of a coating. In the preferred embodiment of the present invention, about 20 to about 80% of the pharmaceutically active agent/resin complexes in the sustained-release compositions are coated, most preferably about 40 to about 60% of the pharmaceutically active agent/resin complexes. The coating is a water-permeable, diffusion barrier coating material. The presence of a coating allows one to selectively modify the dissolution profile as desired of a pharmaceutical composition comprising the pharmaceutically active agent/resin complexes of the present invention.

The coating materials can in general be any of a large number of conventional natural or synthetic film-forming materials used singly, in admixture with each other, and in admixture with plasticizers, pigments, etc. with diffusion barrier properties and with no inherent pharmacological or toxic properties. In general, the major components of the coating should be insoluble in water, and permeable to water and pharmaceutically active agent. However, it might be desirable to incorporate a water-soluble substance, such as methyl cellulose, to alter the permeability of the coating, or to incorporate an acid-insoluble, base-soluble substance to act as an enteric coating. The coating materials may be applied as a suspension in an aqueous fluid or as a solution in organic solvents. Suitable examples of such coating materials are described by R. C. Rowe in Materials used in Pharmaceutical Formulation. (A. T. Florence,

editor), Blackwell Scientific Publications, Oxford, 1-36(1984), incorporated by reference herein. Preferably the water-permeable diffusion barrier is selected from the group consisting of ethyl cellulose, methyl cellulose and mixtures thereof Most preferably, the coating material is SURELEASE, manufactured by Colorcon which is water based ethyl cellulose latex, plasticized with dibutyl sebacate or with vegetable oils. Other non-limiting coating materials included within the scope of the present invention are AQUACOAT, manufactured by FMC Corporation of Philadelphia, which is ethylcellulose pseudolatex; solvent based ethylcellulose; shellac; zein; rosin esters; cellulose acetate; EUDRAGITS, manufactured by Rohm and Haas of Philadelphia, which are acrylic resins; silicone elastomers; poly(vinyl chloride) methyl cellulose; and hydroxypropylmethyl cellulose.

Conventional coating solvents and coating procedures (such as fluid bed coating and spray coating) can be employed to coat the particles. Techniques of fluid bed coating are taught, for example, in U.S. Patents Nos. 3,089,824, 3,117,027, and 3,253,944. The coating is normally applied to the pharmaceutically active agent/resin complex, but alternatively can be applied to the resin before complexing with the pharmaceutically active agent. Non-limiting examples of coating solvents include ethanol, a methylene chloride/acetone mixture, coating emulsions, methyl acetone, tetrahydrofuran, carbonetetrachloride, methyl ethyl ketone, ethylene dichloride, trichloroethylene, hexane, methyl alcohol, isopropyl alcohol, methyl isobutyl ketone, toluene, 2-nitropropane, xylene, isobutyl alcohol, n-butyl acetate.

It is preferred that the coated pharmaceutically active agent/resin complexes are coated in the range from about 40 to about 70% w/w pharmaceutically active agent/resin complex. More preferably, the pharmaceutically active agent/resin complex is coated in the range from about 45 to about 55% w/w pharmaceutically active agent/resin complex. Most

preferably, the pharmaceutically active agent/resin complex is coated about 50% w/w pharmaceutically active agent/resin complex. Variation in the amount of coating and/or the use of coated/uncoated complex mixtures can be employed to selectively modify the dissolution profile as desired.

The average particle sizes of the non-hydrated coated and uncoated pharmaceutically active agent/resin complexes is about 60 to about 200 and about 60 to about 250 micrometers, respectively. More preferably, average particle sizes of the coated pharmaceutically active agent/resin complexes is between about 70 and about 190 micrometers, and most preferably about 70 to about 180 micrometers. More preferably, average particle sizes of the uncoated pharmaceutically active agent/resin complexes is between about 55 and about 160 micrometers, and most preferably about 60 to about 150 micrometers. It is desirable that about 85%, preferably about 95%, and most preferably about 98% of the resin particles have sizes within the ranges set forth above. Adjustments within these ranges can be made to accommodate desired aesthetic qualities of the final formulation product. It is more preferable that the resin dextromethorphan complex have particle sizes within these ranges as well.

In embodiments, it is possible to hydrate the film-forming ingredients and combine all of the ingredients without heating. This method comprises dissolving the water-soluble ingredients in water to form an aqueous mixture; mixing the film-forming ingredients in powder form to form a powder mixture; adding the powder mixture to the aqueous mixture to form a hydrated polymer gel; stirring the hydrated polymer at room temperature for about 30 minutes to about 48 hours; mixing the cooling agent, menthol and any other oils to form an oil mixture; adding the oil mixture to the hydrated polymer gel and mixing until uniform; deaerating the film until air bubbles are removed, casting the uniform mixture on a suitable substrate; and drying the cast mixture to form a

film. This method hydrates the film-forming ingredients without heating the water, which can reduce energy costs in the manufacturing process and undesirable losses of volatile ingredients to evaporation. Further, mixing the oils in two steps minimizes the amount of flavor lost.

While not wishing to be bound by any theories, it is believed that the film-forming ingredients can be hydrated and mixed without heating due to an ionic effect known as the Donnan equilibrium. Hydrating the film-forming agents in the presence of electrolytes in solution effectively lowers the viscosity of the polymer gel being formed, thus increasing the efficiency of the hydrating process. The water-soluble ingredients of the formulation provide the electrolytes, which are dissolved in the hydration solution prior to addition of the film-forming ingredients. High-shear mixing also accelerates hydration, which delumps the powders, providing greater surface area for water contact. In addition, local heating effects, generated in the shear regions, provide energy for hydration without substantially raising the temperature of the mass.

Examples

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

Example 1

The ingredients listed in Table 1 were combined to provide a comparative example of an antitussive film in accordance with the following procedure:

A. The water was heated to 50°C. The potassium sorbate and sweeteners were dissolved in the water with mixing. The titanium dioxide was then added with further mixing to form Preparation A.

B. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) were mixed in a separate container to form

Preparation B.

C. Preparation B was slowly added to Preparation A with rapid mixing, followed by overnight mixing at a reduced rate to provide Preparation C.

D. The glycerin and olive oil were combined in a separate container and then the menthol and monoammonium glycyrrhizinate (MAG) were dissolved therein by heating to 45°C to form Preparation D.

E. Preparation D was added to Preparation C with thorough mixing and then the flavor agents were added with continued mixing to provide Preparation E.

F. Dextromethorphan coated with ethyl cellulose was then added to Preparation E with mixing. The pH was adjusted as necessary to 6.0 using 10% citric acid solution to provide Preparation F (Examples 1-3 only).

Preparation F was poured on a mold and cast to form a film of a desired thickness at room temperature. The film was dried under warm air and cut to a desired dimension (dictated by, e.g., dosage and mouthfeel) for taste testing. The film was segmented into 1" x 1.25" (2.54 cm x 3.18 cm) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 70±3 mg.

A placebo film was also prepared in accordance with the foregoing to facilitate evaluation of, e.g., the taste and appearance of the active film.

Table 1

| Material | % w/w in batch | g/batch | %w/w* | mg/dose* | %w/w* active film | % w/w actual batch |
|---|---|---|---|---|---|---|
| Coated Dextromethorphan (55% DM) | | 103.6291 | | 27.3000 | 29.5775 | 9.3899 |
| Xanthan Gum | 0.0600 | 0.6000 | 0.2432 | 0.1581 | 0.1713 | 0.0544 |
| Locust Bean Gum | 0.0700 | 0.7000 | 0.2837 | 0.1844 | 0.1998 | 0.0634 |
| Carrageenan | 0.3000 | 3.0000 | 1.2159 | 0.7903 | 0.8563 | 0.2718 |
| Pullulan | 16.0000 | 160.0000 | 64.8466 | 42.1503 | 45.6666 | 14.4976 |
| Potassium Sorbate | 0.0600 | 0.6000 | 0.2432 | 0.1581 | 0.1713 | 0.0544 |
| Acesulfame Potassium Salt | 0.5000 | 5.0000 | 2.0265 | 1.3172 | 1.4271 | 0.4531 |
| Aspartame NF | 1.4000 | 14.0000 | 5.6741 | 3.6882 | 3.9958 | 1.2685 |
| Purified Water | 75.3264 | 753.2640 | | | | 68.2534 |
| Physcool | 0.1000 | 1.0000 | 0.4053 | 0.2634 | 0.2854 | 0.0906 |
| Menthol | 1.0000 | 10.0000 | 4.0529 | 2.6344 | 2.8542 | 0.9061 |
| Citric Acid | 0.0710 | 0.7100 | 0.2878 | 0.1870 | 0.2026 | 0.0643 |
| Cherry Flavor (Givudan) | 0.1500 | 1.5000 | 0.6079 | 0.3952 | 0.4281 | 0.1359 |
| Peppermint Flavor | 0.5000 | 5.0000 | 2.0265 | 1.3172 | 1.4271 | 0.4531 |
| Mono ammonium glycyrrhizinate (MAG) | 0.0100 | 0.1000 | 0.0405 | 0.0263 | 0.0285 | 0.0091 |
| Polysorbate 80 NF | 0.3500 | 3.5000 | 1.4185 | 0.9220 | 0.9990 | 0.3171 |
| Atmos 300 | 0.3500 | 3.5000 | 1.4185 | 0.9220 | 0.9990 | 0.3171 |
| Glycerine | 3.0000 | 30.0000 | 12.1587 | 7.9032 | 8.5625 | 2.7183 |
| Olive Oil | 0.5000 | 5.0000 | 2.0265 | 1.3172 | 1.4271 | 0.4531 |
| FD&C green #3 | 0.0026 | 0.0260 | 0.0105 | 0.0068 | 0.0074 | 0.0024 |
| Titanium Dioxide | 0.2500 | 2.5000 | 1.0132 | 0.6586 | 0.7135 | 0.2265 |
| | | | | | | |
| Total w/o active | | 0.0000 | 100.0000 | 65.0000 | | |
| Total with active | 100.0000 | 1103.6291 | | 92.3000 | 100.0000 | 100.0000 |
| * assuming that all water is evaporated | | | | | | |

The active film was gritty and bitter.

Example 2

Comparative films having the ingredients listed in Table 2 were prepared in accordance with the method of Example 1.

Table 2

| Material | %w/w in batch | g/batch | %w/w* placebo film | mg/dose* | %w/w* active film | % w/w actual batch |
|---|---|---|---|---|---|---|
| Coated Dextromethorphan (53.5% DM) | | 106.4239 | | 28.0374 | 30.1356 | 9.6187 |
| Xanthan Gum | 0.0600 | 0.6000 | 0.2432 | 0.1581 | 0.1699 | 0.0542 |
| Locust Bean Gum | 0.0700 | 0.7000 | 0.2837 | 0.1844 | 0.1982 | 0.0633 |
| Carrageenan | 0.3000 | 3.0000 | 1.2159 | 0.7904 | 0.8495 | 0.2711 |
| Pullulan | 16.0000 | 160.0000 | 64.8493 | 42.1520 | 45.3065 | 14.4610 |
| Potassium Sorbate | 0.0600 | 0.6000 | 0.2432 | 0.1581 | 0.1699 | 0.0542 |
| Acesulfame Potassium Salt | 0.5000 | 5.0000 | 2.0265 | 1.3173 | 1.4158 | 0.4519 |
| Aspartame NF | 1.4000 | 14.0000 | 5.6743 | 3.6883 | 3.9643 | 1.2653 |
| Purified Water | 75.3274 | 753.2740 | | | | 68.0819 |
| Physcool | 0.1000 | 1.0000 | 0.4053 | 0.2635 | 0.2832 | 0.0904 |
| Menthol | 1.0000 | 10.0000 | 4.0531 | 2.6345 | 2.8317 | 0.9038 |
| Citric Acid (used to adjust pH to 6.0) | 0.0700 | 0.7000 | 0.2837 | 0.1844 | 0.1982 | 0.0633 |
| Cherry Flavor (Givudan) | 0.1500 | 1.5000 | 0.6080 | 0.3952 | 0.4247 | 0.1356 |
| Peppermint Flavor | 0.5000 | 5.0000 | 2.0265 | 1.3173 | 1.4158 | 0.4519 |
| Mono ammonium glycyrrhizinate (MAG) | 0.0100 | 0.1000 | 0.0405 | 0.0263 | 0.0283 | 0.0090 |
| Polysorbate 80 NF | 0.3500 | 3.5000 | 1.4186 | 0.9221 | 0.9911 | 0.3163 |
| Atmos 300 | 0.3500 | 3.5000 | 1.4186 | 0.9221 | 0.9911 | 0.3163 |
| Glycerine | 3.0000 | 30.0000 | 12.1592 | 7.9035 | 8.4950 | 2.7114 |
| Olive Oil | 0.5000 | 5.0000 | 2.0265 | 1.3173 | 1.4158 | 0.4519 |
| FD&C Green #3 | 0.0026 | 0.0260 | 0.0105 | 0.0069 | 0.0074 | 0.0024 |
| Titanium Dioxide | 0.2500 | 2.5000 | 1.0133 | 0.6586 | 0.7079 | 0.2260 |
| | | | | | | |
| Total w/o active | | 0.0000 | 100.0000 | 65.0000 | | |
| Total with active | 100.0000 | 1106.4239 | | 93.0374 | 100.0000 | 100.0000 |
| * assuming that all water is evaporated | | | | | | |

The active film was gritty and bitter.

Example 3

Comparative films having the ingredients listed in Table 3 were prepared in accordance with the method of Example 1.

Table 3

| Material | %w/w in batch | g/batch | %w/w* placebo film | mg/dose* | %w/w* active film | % w/w actual batch |
|---|---|---|---|---|---|---|
| Coated Dextromethorphan (60% DM) | | 94.7292 | | 25.0000 | 27.7778 | 8.6532 |
| Xanthan Gum | 0.0600 | 0.6000 | 0.2436 | 0.1583 | 0.1759 | 0.0548 |
| Locust Bean Gum | 0.0700 | 0.7000 | 0.2842 | 0.1847 | 0.2053 | 0.0639 |
| Carrageenan | 0.3000 | 3.0000 | 1.2180 | 0.7917 | 0.8797 | 0.2740 |
| Pullulan | 16.0000 | 160.0000 | 64.9625 | 42.2256 | 46.9174 | 14.6155 |
| Potassium Sorbate | 0.0600 | 0.6000 | 0.2436 | 0.1583 | 0.1759 | 0.0548 |
| Acesulfame Potassium Salt | 0.5000 | 5.0000 | 2.0301 | 1.3196 | 1.4662 | 0.4567 |
| Aspartame NF | 1.4000 | 14.0000 | 5.6842 | 3.6947 | 4.1053 | 1.2789 |
| Purified Water | 75.3704 | 753.7040 | | | | 68.8484 |
| Physcool | 0.1000 | 1.0000 | 0.4060 | 0.2639 | 0.2932 | 0.0913 |
| Menthol | 1.0000 | 10.0000 | 4.0602 | 2.6391 | 2.9323 | 0.9135 |
| Citric Acid | 0.0270 | 0.2700 | 0.1096 | 0.0713 | 0.0792 | 0.0247 |
| Cherry Flavor (Givudan) | 0.1500 | 1.5000 | 0.6090 | 0.3959 | 0.4399 | 0.1370 |
| Peppermint Flavor | 0.5000 | 5.0000 | 2.0301 | 1.3196 | 1.4662 | 0.4567 |
| Mono ammonium glycyrrhizinate (MAG) | 0.0100 | 0.1000 | 0.0406 | 0.0264 | 0.0293 | 0.0091 |
| Polysorbate 80 NF | 0.3500 | 3.5000 | 1.4211 | 0.9237 | 1.0263 | 0.3197 |
| Atmos 300 | 0.3500 | 3.5000 | 1.4211 | 0.9237 | 1.0263 | 0.3197 |
| Glycerine | 3.0000 | 30.0000 | 12.1805 | 7.9173 | 8.7970 | 2.7404 |
| Olive Oil | 0.5000 | 5.0000 | 2.0301 | 1.3196 | 1.4662 | 0.4567 |
| FD&C green #3 | 0.0026 | 0.0260 | 0.0106 | 0.0069 | 0.0076 | 0.0024 |
| Titanium Dioxide | 0.2500 | 2.5000 | 1.0150 | 0.6598 | 0.7331 | 0.2284 |
| | | | | | | |
| Total w/o active | | 0.0000 | 100.0000 | 65.0000 | | |
| Total with active | 100.0000 | 1094.7292 | | 90.0000 | 100.0000 | 100.0000 |
| * assuming that all water is evaporated | | | | | | |

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The active film was very thin, blue and gritty. Sensations of bitterness and numbness were minimal, but the flavor was not entirely agreeable.

Example 4

Films of the invention having the ingredients listed in Table 4 were prepared in accordance with the method of Example 1, except that Step F comprised adding uncoated dextromethorphan hydrobromide and AMBERLITE resin to Preparation E as separate ingredients.

Table 4

| Material | %w/w in batch | g/batch | %w/w* placebo film | mg/dose* | %w/w* active film | % w/w actual batch |
|---|---|---|---|---|---|---|
| Dextromethorphan | | 17.0326 | | 15.0000 | 15.7563 | 5.0951 |
| Amberlite IRP69 | | 17.2597 | | 15.2000 | 15.9664 | 5.1630 |
| Xanthan Gum | 0.0600 | 0.1800 | 0.2439 | 0.1585 | 0.1665 | 0.0538 |
| Locust Bean Gum | 0.0700 | 0.2100 | 0.2845 | 0.1849 | 0.1943 | 0.0628 |
| Carrageenan | 0.3000 | 0.9000 | 1.2194 | 0.7926 | 0.8326 | 0.2692 |
| Pullulan | 16.0000 | 48.0000 | 65.0338 | 42.2720 | 44.4033 | 14.3587 |
| Potassium Sorbate | 0.0600 | 0.1800 | 0.2439 | 0.1585 | 0.1665 | 0.0538 |
| Acesulfame Potassium Salt | 0.5000 | 1.5000 | 2.0323 | 1.3210 | 1.3876 | 0.4487 |
| Aspartame NF | 1.4000 | 4.2000 | 5.6905 | 3.6988 | 3.8853 | 1.2564 |
| Purified Water | 75.3974 | 226.1922 | | | | 67.6630 |
| Physcool | 0.1000 | 0.3000 | 0.4065 | 0.2642 | 0.2775 | 0.0897 |
| Menthol | 1.0000 | 3.0000 | 4.0646 | 2.6420 | 2.7752 | 0.8974 |
| Citric Acid | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Cherry Flavor (Givudan) | 0.1500 | 0.4500 | 0.6097 | 0.3963 | 0.4163 | 0.1346 |
| Peppermint Flavor | 0.5000 | 1.5000 | 2.0323 | 1.3210 | 1.3876 | 0.4487 |
| Mono ammonium glycyrrhizinate (MAG) | 0.0100 | 0.0300 | 0.0406 | 0.0264 | 0.0278 | 0.0090 |
| Polysorbate 80 NF | 0.3500 | 1.0500 | 1.4226 | 0.9247 | 0.9713 | 0.3141 |
| Atmos 300 | 0.3500 | 1.0500 | 1.4226 | 0.9247 | 0.9713 | 0.3141 |
| Glycerine | 3.0000 | 9.0000 | 12.1938 | 7.9260 | 8.3256 | 2.6923 |
| Olive Oil | 0.5000 | 1.5000 | 2.0323 | 1.3210 | 1.3876 | 0.4487 |
| FD&C green #3 | 0.0026 | 0.0078 | 0.0106 | 0.0069 | 0.0072 | 0.0023 |
| Titanium Dioxide | 0.2500 | 0.7500 | 1.0162 | 0.6605 | 0.6938 | 0.2244 |
| | | | | | | |
| Total w/o active | | 300.0000 | 100.0000 | 65.0000 | | |
| Total with active | 100.0000 | 334.2922 | | 95.2000 | 100.0000 | 100.0000 |
| * assuming that all water is evaporated | | | | | | |

The active film had a pleasing appearance and taste.

Example 5

The ingredients listed in Table 5 were combined to provide an example of an antitussive film of the invention in accordance with the following procedure:

A. The water was heated to 75°C. Uncoated dextromethorphan hydrobromide was dissolved with mixing in the water, while maintaining the temperature at 75°C. AMBERLITE resin was then mixed into the water with heating for 4 to 5 hours at 70-80°C. Heating was stopped, water lost to evaporation was replaced, and the potassium sorbate and sweeteners were then added to the composition with mixing to form Preparation A.

B. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) were mixed in a separate container to form Preparation B.

C. Preparation B was slowly added to Preparation A with rapid mixing, followed by overnight mixing at a reduced rate to provide Preparation C.

D. The menthol was dissolved with mixing in the alcohol in a separate container. The Physcool was then dissolved with mixing therein. The MAG, Polysorbate 80, Atmos 300 and flavors were then added to the mixture and mixed to enhanced uniformity to form Preparation D.

E. Preparation D, glycerine and mannitol were added to Preparation C with thorough mixing to provide Preparation E.

Preparation E was poured on a mold and cast to form a film of a desired thickness at room temperature. The film was dried under warm air and cut to a desired dimension (dictated by, e.g., dosage and mouthfeel) for taste testing. The film was segmented into 1.5 $in^2$ (9.7 $cm^2$) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 70±3 mg.

A placebo film was also prepared in accordance with the foregoing to facilitate evaluation of, e.g., the taste and appearance of the active film.

Table 5

| Material | %w/w in batch | g/batch | mg/dose* | %w/w* film | % w/w actual batch |
|---|---|---|---|---|---|
| Dextromethorphan HBr | | 11.4615 | 15.0000 | 21.4286 | 9.2666 |
| Amberlite IRP69 | | 12.2256 | 16.0000 | 22.8571 | 9.8843 |
| Xanthan Gum | 0.0600 | 0.0600 | 0.0944 | 0.1348 | 0.0485 |
| Locust Bean Gum | 0.0700 | 0.0700 | 0.1101 | 0.1573 | 0.0566 |
| Carrageenan | 0.3000 | 0.3000 | 0.4718 | 0.6740 | 0.2425 |
| Pullulan | 16.0000 | 16.0000 | 25.1613 | 35.9447 | 12.9359 |
| Potassium Sorbate | 0.0600 | 0.0600 | 0.0944 | 0.1348 | 0.0485 |
| Acesulfame Potassium Salt | 0.5000 | 0.5000 | 0.7863 | 1.1233 | 0.4042 |
| Aspartame NF | 1.4000 | 1.4000 | 2.2016 | 3.1452 | 1.1319 |
| Purified Water | 70.2000 | 70.2000 | | | 56.7561 |
| Alcohol USP | 5.0000 | 5.0000 | | | 4.0425 |
| Physcool | 0.1000 | 0.1000 | 0.1573 | 0.2247 | 0.0808 |
| Menthol | 1.5000 | 1.5000 | 2.3589 | 3.3698 | 1.2127 |
| Peppermint Flavor | 0.1000 | 0.1000 | 0.1573 | 0.2247 | 0.0808 |
| Raspberry Flavor (Givudan) | 0.5000 | 0.5000 | 0.7863 | 1.1233 | 0.4042 |
| Mono ammonium glycyrrhizinate (MAG) | 0.0100 | 0.0100 | 0.0157 | 0.0225 | 0.0081 |
| Polysorbate 80 NF | 0.3500 | 0.3500 | 0.5504 | 0.7863 | 0.2830 |
| Atmos 300 | 0.3500 | 0.3500 | 0.5504 | 0.7863 | 0.2830 |
| Glycerine | 1.5000 | 1.5000 | 2.3589 | 3.3698 | 1.2127 |
| Mannitol USP | 2.0000 | 2.0000 | 3.1452 | 4.4931 | 1.6170 |
| | | | | | |
| Total w/o active | | 100.0000 | 39.0000 | | |

The active film had a pleasing appearance and taste.

Example 6

Films of the invention having the ingredients listed in Table 6 were prepared in accordance with the method of Example 5.

Table 6

| Material | %w/w in batch | g/batch | mg/dose* | %w/w* | %w/w |
|---|---|---|---|---|---|
| Dextromethorphan HBr | | 11.6538 | 15.0000 | 21.4286 | 9.3919 |
| Amberlite IRP69 | | 12.4308 | 16.0000 | 22.8571 | 10.0180 |
| Xanthan Gum | 0.0600 | 0.0600 | 0.0925 | 0.1321 | 0.0484 |
| Locust Bean Gum | 0.0700 | 0.0700 | 0.1079 | 0.1542 | 0.0564 |
| Carrageenan | 0.3000 | 0.3000 | 0.4625 | 0.6606 | 0.2418 |
| Pullulan | 16.0000 | 16.0000 | 24.6640 | 35.2343 | 12.8944 |
| Potassium Sorbate | 0.0600 | 0.0600 | 0.0925 | 0.1321 | 0.0484 |
| Acesulfame Potassium Salt | 0.5000 | 0.5000 | 0.7708 | 1.1011 | 0.4030 |
| Aspartame NF | 1.4000 | 1.4000 | 2.1581 | 3.0830 | 1.1283 |
| Purified Water | 69.7000 | 69.7000 | | | 56.1713 |
| Alcohol USP | 5.0000 | 5.0000 | | | 4.0295 |
| Physcool | 0.1000 | 0.1000 | 0.1542 | 0.2202 | 0.0806 |
| Menthol | 2.0000 | 2.0000 | 3.0830 | 4.4043 | 1.6118 |
| Peppermint Flavor | 0.1000 | 0.1000 | 0.1542 | 0.2202 | 0.0806 |
| Raspberry Flavor (Givudan) | 0.5000 | 0.5000 | 0.7708 | 1.1011 | 0.4030 |
| Mono ammonium glycyrrhizinate (MAG) | 0.0100 | 0.0100 | 0.0154 | 0.0220 | 0.0081 |
| Polysorbate 80 NF | 0.3500 | 0.3500 | 0.5395 | 0.7708 | 0.2821 |
| Atmos 300 | 0.3500 | 0.3500 | 0.5395 | 0.7708 | 0.2821 |
| Glycerine | 1.5000 | 1.5000 | 2.3123 | 3.3032 | 1.2089 |
| Mannitol USP | 2.0000 | 2.0000 | 3.0830 | 4.4043 | 1.6118 |
| | | | | | |
| Total w/o active | | 0.0000 | 39.0000 | | |
| Total with active | 100.0000 | 124.0846 | 70.0000 | 100.0000 | 100.0000 |
| * assuming that all water and alcohol is evaporated | | | | | |

The active film had a pleasing appearance and taste.

Example 7

A film of the invention having the ingredients listed in Table 7 were

prepared in accordance with the method of Example 5. The film was segmented into 1" x 1.25" (2.54 cm x 3.18 cm) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 63.6±3 mg.

Table 7

| Material | %w/w in batch | kg/batch | mg/dose* | %w/w* | %w/w |
|---|---|---|---|---|---|
| Dextromethorphan HBr | | 1.3567 | 15.0000 | 23.5981 | 9.3918 |
| Amberlite IRP69 | | 1.4472 | 16.0000 | 25.1713 | 10.0180 |
| Xanthan Gum | 0.0600 | 0.0070 | 0.0772 | 0.1215 | 0.0484 |
| Locust Bean Gum | 0.0700 | 0.0081 | 0.0901 | 0.1417 | 0.0564 |
| Carrageenan | 0.3000 | 0.0349 | 0.3661 | 0.6075 | 0.2418 |
| Pullulan | 16.0000 | 1.8627 | 20.5941 | 32.3988 | 12.8944 |
| Potassium Sorbate | 0.0600 | 0.0070 | 0.0772 | 0.1215 | 0.0484 |
| Acesulfame Potassium Salt | 0.5000 | 0.0582 | 0.6436 | 1.0125 | 0.4030 |
| Aspartame NF | 1.4000 | 0.1630 | 1.8020 | 2.8349 | 1.1283 |
| Purified Water | 69.7000 | 8.1145 | | | 56.1714 |
| Alcohol USP | 5.0000 | 0.5821 | | | 4.0295 |
| Physcool | 0.1000 | 0.0116 | 0.1287 | 0.2025 | 0.0806 |
| Menthol | 2.0000 | 0.2328 | 2.5743 | 4.0498 | 1.6118 |
| Peppermint Flavor | 0.1000 | 0.0116 | 0.1287 | 0.2025 | 0.0806 |
| Raspberry Flavor (Givudan) | 0.5000 | 0.0582 | 0.6436 | 1.0125 | 0.4030 |
| Mono ammonium glycyrrhizinate (MAG) | 0.0100 | 0.0012 | 0.0129 | 0.0202 | 0.0081 |
| Polysorbate 80 NF | 0.3500 | 0.0407 | 0.4505 | 0.7087 | 0.2821 |
| Atmos 300 | 0.3500 | 0.0407 | 0.4505 | 0.7087 | 0.2821 |
| Glycerine | 1.5000 | 0.1746 | 1.9307 | 3.0374 | 1.2089 |
| Mannitol USP | 2.0000 | 0.2328 | 2.5743 | 4.0498 | 1.6118 |
| | | | | | |
| Total w/o active + resin | | 11.6420 | 32.5644 | | |
| Total with active + resin | 100.0000 | 14.4459 | 63.5644 | 100.0000 | 100.0000 |
| * assuming that all water and alcohol is evaporated | | | | | |

The active film had a pleasing appearance and taste.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

# CLAIMS

WHAT IS CLAIMED IS:

1. A consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein said film comprises at least one water soluble polymer, at least one pharmaceutically active agent and at least one taste masking agent.

2. The consumable film according to claim 1, wherein said at least one water soluble polymer is a member selected from the group consisting of pullulan, hydroxyproplymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof.

3. The consumable film according to claim 2, wherein said at least one water soluble polymer is pullulan.

4. The consumable film according to claim 1, wherein said at least one pharmaceutically active agent is a member selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory agents, antitussives, decongestants, anti-histamines, expectorants, anti-diaherrals, $H_2$-antagonists, proton pump inhibitors, central nervous system agents, analgesics and mixtures thereof.

5. The consumable film according to claim 4, wherein the antimicrobial agent is a member selected from the group consisting of triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA and mixtures thereof.

6. The consumable film according to claim 4, wherein the non-steroidal anti-inflammatory agent is a member selected from the group consisting of aspirin, acetaminophen, ibuprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and mixtures thereof.

7. The consumable film according to claim 4, wherein the antitussive is a member selected from the group consisting of benzonatate, caramiphen edisylate, dextromethorphan, chlophedianol, diphenhydramine, salts thereof and mixtures thereof.

8. The consumable film according to claim 4, wherein the decongestant is selected from the group consisting of pseudoephedrine, phenylepherine, phenylpropanolamine, salts thereof and mixtures thereof.

9. The consumable film according to claim 4, wherein the anti-histamine is selected from the group consisting of brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenhydramine citrate, diphenylpyraline hydrochloride, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride and mixtures thereof.

10. The consumable film according to claim 4, wherein the expectorant is selected from the group consisting of guaifenesin, ipecac, potassium iodide, terpin hydrate and mixtures thereof.

11. The consumable film according to claim 4, wherein the anti-diarrheal is loperamide.

12. The consumable film according to claim 4, wherein the $H_2$-antagonist is selected from the group consisting of famotidine, ranitidine and mixtures thereof.

13. The consumable film according to claim 4, wherein the proton pump inhibitor is selected from the group consisting of omeprazole,

lansoprazole, and mixtures thereof.

14. The consumable film according to claim 1, wherein the at least one taste masking agent is an ion exchange resin.

15. The consumable film according to claim 14, wherein the ion exchange resin is a sulfonated polymer comprising polystyrene cross-linked with divinylbenzene.

16. The consumable film according to claim 14, wherein the ion exchange resin is a sulfonated polymer comprising polystyrene cross-linked with 8% of divinylbenzene, with an ion exchange capacity of about 4.5 to 5.5 meq/g of dry resin ($H^+$-form).

17. The consumable film according to claim 16, wherein the ion exchange resin has irregularly-shaped particles ranging in size from about 47 to about 149 micrometers.

18. The consumable film according to claim 16, wherein the ion exchange resin has spherical particles ranging in size from about 45 to about 150 micrometers.

19. The consumable film according to claim 14, wherein the ion exchange resin is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group, and wherein an exchange capacity of said ion exchange resin is normally within a range of about 3 to about 4 meq/g of dry ion exchange resin.

20. The consumable film according to claim 1, wherein the at least one taste masking agent is magnesium trisilicate.

21. The consumable film according to claim 1, wherein said at least one water soluble polymer is pullulan, said at least one pharmaceutically active agent is dextromethorphan, and said at least one taste masking agent is a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene.

22. The consumable film according to claim 21, wherein said pullulan is present in an amount of about 40 to about 80 wt% of said film, said dextromethorphan is present in an amount of about 5 to about 40 wt% of said film, said sulfonated polymer ion exchange resin is present in an amount of about 5 to about 40 wt% of said film, and a ratio of said dextromethorphan to said sulfonated polymer ion exchange resin is 1:3 to 3:1.

23. The consumable film according to claim 22, wherein said pullulan is present in said film in an amount of about 2 to about 6 $mg/cm^2$, said dextromethorphan is present in said film in an amount of about 1.4 to about 2 $mg/cm^2$, and said sulfonated polymer ion exchange resin is present in said film in an amount of about 1.4 to about 2 $mg/cm^2$.

24. The consumable film according to claim 22, further comprising:

about 0.01 to about 5 wt% of at least one stabilizing agent;

about 0.001 to about 0.1 wt% of at least one of at least one coloring agent;

about 0.1 to about 70 wt% of water;

about 0.1 to about 15 wt% of at least one sweetening agent;

about 0.1 to about 15 wt% of at least one flavoring agent;

about 0.1 to about 4 wt% of at least one cooling agent;

about 0.1 to about 5 wt% of at least one surfactant;

about 0.1 to about 12 wt% of a triglyceride;

about 0.001 to about 5 wt% of a preservative;

about 0.1 to about 5 wt% of a polyethylene oxide compound; and

about 1 to about 20 wt% of propylene glycol.

25. A method for preparing the consumable film of claim 1, said method comprising:

dissolving water-soluble ingredients in water to provide an aqueous solution;

mixing at least one water soluble film former and at least one stabilizing agent to provide a film-forming mixture;

combining said film-forming mixture and said aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

adding said oil mixture to said hydrated polymer gel and mixing to provide a uniform gel;

casting the uniform gel on a substrate; and

drying the cast gel to provide said film.

26. The method of claim 25, wherein said at least one pharmaceutically active agent and said at least one taste masking agent are incorporated into said aqueous solution or into said uniform gel.

27. The method of claim 25, wherein said at least one taste masking agent is an ion exchange resin, and said at least one pharmaceutically active agent is sorbed to said ion exchange resin without separating ion exchanged pharmaceutically active agent from unexchanged agent and counter ion salts.

# INTERNATIONAL SEARCH REPORT

Inter. ›nal Application No
PCT/US 01/02192

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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☐ Further documents are listed in the continuation of box C.

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(54) Title: DELIVERY SYSTEM FOR LOCALIZED ADMINISTRATION OF MEDICAMENTS TO THE UPPER RESPIRATORY TRACT

(57) Abstract

The present invention pertains to delivery systems for the localized administration of a medicament to the upper respiratory tract. The delivery system comprises: (a) a save and effective amount of a medicament useful for treating the upper respiratory tract; (b) an ionic polysaccharide; and (c) a cross-linking agent. The present invention provides for the controlled, *in situ* formation of a thin, bioadhesive film which may bind to the buccal epithelial cells which form the surface of said upper respiratory tract. Said film formation occurs when the delivery system of the present invention comprising a medicament, an ionic polysaccharide and a cross-linking agent, in a pharmaceutically acceptable carrier, is slowly ingested by dissolution through salivation of the pharmaceutically acceptable carrier. By a series of cross-linking reactions, the cross-linking agent polymerizes the ionic polysaccharide to a film in the form of aggregates, which bind to the buccal epithelial cells in the upper respiratory tract. During the *in situ* cross-linking reaction, the medicament becomes entrapped in the bioadhesive polymer aggregate and thereafter is gradually released, i.e., becomes available through dissolution.

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# DELIVERY SYSTEM FOR LOCALIZED ADMINISTRATION OF MEDICAMENTS TO THE UPPER RESPIRATORY TRACT

## Background Of The Invention

### Field Of The Invention

The present invention pertains to delivery systems for the localized administration of a medicament to the upper respiratory tract and medicated compositions containing the delivery systems. The system comprises (a) a safe and effective amount of a medicament useful for treating the upper respiratory tract; (b) an ionic polysaccharide; and, (c) a cross-linking agent. This invention also relates to methods for preparing and using the delivery systems and compositions.

### Description of the Background

Pharyngitis, the acute inflammation of the pharynx, is characterized, inter alia, by sore throat and painful swallowing. Painful swallowing is also often associated with laryngitis, the inflammation of the larynx. Patients suffering from sore throat and painful swallowing seek medication which can provide rapid onset of relief as well as sustained local action. Present therapeutic lozenge formulations do not provide sustained local therapeutic effects because of salivary dilution and rapid swallowing. Moreover, anesthetic-type lozenges tend to have a numbing effect on the entire mouth and tongue area and are not targeted to the oral pharyngeal area.

Various materials and techniques have been used to trap active ingredients and control their release. United States patent no. 4,695,463 discloses a particulate delivery system comprising an insolubilized active ingredient selected from the group consisting of flavoring agents, drugs, coloring agents, sweetening agents, perfumes, and bulking agents, entrapped in a cross-linked alginate or carrageenate matrix.

United States patent no. 5,330,761 discloses a controlled release, solid tablet comprising a bioadhesive mixture of a heterodisperse gum matrix and a bioadhesive agent selected from the group consisting of carbomer, polycarbophil and polyethylene oxide combined with an inert diluent and an active ingredient.

United States patent no. 5,147,648 discloses the improved adherence of gels to the mucous membranes by the separate application to the same area two components capable of forming a gel such as a metallic salt and a polysaccharide. One of the two components is used as a carrier for medicaments.

United States patent no. 4,843,098 discloses an ingestible substantially anhydrous aggregate comprising a pre-swelled hydrocolloid which partially entraps and binds a drug substrate. The hydrocolloid is selected from the group consisting of carboxymethyl cellulose, methyl cellulose, karaya gum, acacia gum, sodium alginate, calcium alginate, and hydroxypropyl methyl cellulose. The substrate is selected from the group consisting of potassium chloride, calcium carbonate, magnesium oxide, cholestyramine, and N-acetyl procainamide.

United States patent no. 4,857,331 discloses a sugarless ingestible gel confectionery delivery system comprising by weight of the final delivery system (a) a pectin gel component in an amount from about 1% to about 5%, (b) an algin gel component in an amount from about 0.2% to about 1.5%, (c) a polymer network gel component in an amount of up to about 5%, and (d) an edible insoluble solid in an amount sufficient to strengthen the internal gel network such that the gel retains its structural integrity during mold removal.

United States patent no. 4,981,698 discloses a sweetener delivery system comprising (a) a first solid natural or artificial high intensity sweetener; (b) a first inner coating selected from

hydrophobic and hydrophobic coating materials, wherein the inner coating and first sweetener are mixed and prepared to form a core; and (c) a second outer coating of a hydrophobic polymer containing a second sweetener. The second outer coating is selected from the group consisting of gum arabic, tragacanth, karaya, ghatti, agar, alginates, carrageenans, furcellaran, and psyllium.

United States patent no. 5,004,595 discloses a free-flowing particulate delivery system comprising (a) a core comprising a flavor in particulate form; and (b) an encapsulating matrix for the core, wherein the matrix comprises an outer coating of a hydrophobic polymer containing an intense sweetener. The outer coating is selected from the group consisting of gum arabic, tragacanth, karaya, ghatti, agar, alginates, carrageenans, furcellaran, and psyllium.

While the above compositions provide various means for controlling the release of ingredients, none of the above compositions are entirely satisfactory for the targeted localized administration of a medicament to the upper respiratory tract.

## Summary Of The Invention

The present invention pertains to delivery systems for the localized administration of a medicament to the upper respiratory tract. The delivery system comprises:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide, and,

(c) a cross-linking agent.

This invention also pertains to the medicated compositions containing the targeted delivery system in a pharmaceutically acceptable carrier. This invention further pertains to methods for preparing and using the delivery systems and medicated compositions.

## Detailed Description Of The Invention

As used herein, the term "upper respiratory tract" refers to the larynx, throat and oral pharyngeal area. The present invention provides for the controlled, in situ formation of a thin, bioadhesive film which may bind to the buccal epithelial cells which form the surface of said upper respiratory tract. Said film formation occurs when the delivery system of the present invention comprising a medicament, an ionic polysaccharide and a cross-linking agent, in a pharmaceutically acceptable carrier, is slowly ingested by dissolution through salivation of the pharmaceutically acceptable carrier. By a series of cross-linking reactions, the cross-linking agent polymerizes the ionic polysaccharide to a film in the form of aggregates, which bind to the buccal epithelial cells in the upper respiratory tract. During the in situ cross-linking reaction, the medicament becomes entrapped in the bioadhesive polymer aggregate and thereafter is gradually released, i.e., becomes available through dissolution. The timing of the cross-linking reaction can be controlled through selection of (a) the ionic polysaccharide, (b) the cross-linking agent, and further, through selection of (c) the pharmaceutically acceptable carrier.

Because the film binds to buccal epithelial cells, the novel delivery system provides both targeted and sustained effects to the upper respiratory tract. Because the delivery systems are targeted delivery systems, compositions containing anesthetic-type agents will minimally affect the mouth and the tongue.

The delivery system may be employed to administer a wide variety of medicaments to the upper respiratory tract. The term "medicament" as used herein refers to drugs and pharmaceuticals useful for treating the upper respiratory tract and may be selected from a wide variety of water-soluble and water-insoluble medicaments. Nonlimiting illustrative categories of such medicaments include analgesics, topical anesthetics, antitussives, topical antimicrobials, antihistamines, decongestants, expectorants, cell and tissue healing agents, bronchodilators, steroidal anti-inflammatory agents, and mixtures thereof.

Nonlimiting illustrative specific examples of topical anesthetic agents include dyclonine, promazine, phenol, hexyl resorcinol, lidocaine, benzocaine, benzyl alcohol, butacaine and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of analgesic agents include acetylsalicylic acid, salicylic acid, acetaminophen, ibuprofen, phenacetin, phenylbutazone, salicylamide, meclofenamic acid, naproxen, sulindac, diflunisal, piroxicam, indomethacin, etodolac, fenoproben, ketoprofen, mefenamic acid, nabumetone, ketorolac tromethamine, diclofenac, evening primrose oil (containing about 72% linoleic acid and about 9% *gamma*-linolenic acid), mesalamine, salsalate, diflunisal, salicylsalicylic acid, choline magnesium trisalicylate and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of antitussive agents include menthol, camphor, dextromethorphan, dextromethorphan, noscapine, carbetapentane, chlophedianol, codeine, carmiphen and diphenhydramine, hydrocodone, hydromorphone, fominoben, noscapine and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of topical antimicrobial agents include cetylpyridinium chloride, quaternary ammonium salts, chlorhexidine, essential oils such as thymol, menthol and eucalyptol, methyl salicylate, hexetidine, triclosan, stannous fluoride, sanguinarine, zinc salts, sodium lauryl sulfate and the like.

Nonlimiting illustrative specific examples of antihistamine agents include chlorpheniramine, brompheniramine, phenindamine, pyrilamine, methapyrilene, doxylamine, pheniramine, diphenhydramine, dexbrompheniramine, azatadine, cyproheptadine, hydroxyzine, clemastine, bromdiphenhydramine, chlorcyclizine, thonzylamine, prilamine, dexchlorpheniramine, triprolidine, acrivastine, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, terfenadine and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of decongestant agents include phenylephrine, phenylpropanolamine, pseudoephedrine, ephedrine, propylhexedrine, xylometazoline, naphazoline, oxymetazoline and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of expectorant agents include guaifenesin, glyceryl guaiacolate, N-acetyl cysteine, terpin hydrate, bromhexine, ambroxol, ammonium chloride and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of cell and tissue healing agents include natural products such as aloe, primrose oil, fatty acids, Vitamin E, herbal extracts, botanicals and the like.

Nonlimiting illustrative specific examples of steroidal anti-inflammatory agents include flunisolide, triamcinoline, triamcinoline acetonide, beclomethasone diproprionate, betamethasone diproprionate, hydrocortisone, cortisone, dexamethasone, prednisone, methyl prednisolone, and prednisolone and their pharmaceutically acceptable salts.

Nonlimiting illustrative specific examples of bronchodilator agents include ephedrine, epinephrine, racepinephrine, terbutalin, atropine, aminophylline, isoprenaline, metaproterenol, bitoterol, theophylline and their pharmaceutically acceptable salts.

The delivery system may be used to deliver other medicaments. Nonlimiting illustrative categories of such medicaments include antiasmatic agents, antibacterial agents, antifungal agents, antinauseant agents, antipyretic agents, antiviral agents, immunostimulating agents, nutritional supplements, and various alkaloid agents such as caffeine and codeine.

Preferably, the medicament is selected from the group consisting of anesthetics, analgesics and antitussives. More preferably the medicament is dyclonine, menthol, phenol, hexyl resorcinol or benzocaine.

The medicament of the present invention may be used in many distinct physical forms well known in the pharmaceutical art to provide an initial dosage of the medicament and/or a further time-release form of the medicament. Without being limited thereto, such physical forms include free forms and encapsulated forms, and mixtures thereof.

As used herein the term "safe and effective amount" means an amount of a medicament high enough when administered orally to significantly positively modify the condition to be treated, but low enough to avoid serious side effects. The amount of medicament used in the present invention may vary depending upon the recommended or permitted therapeutic dosage for the particular active agent. Such dosages are known to the skilled practitioner in the medical arts and are not a part of the present invention. In general, the amount of medicament in the medicated composition of the present invention may vary from 0.001% to 12% by weight of the total medicated composition.

The ionic polysaccharides of the present invention are bioadhesive agents which have the ability to entrap a medicament useful for treating the upper respiratory tract. As used herein the term "ionic polysaccharide" refers to polysaccharides comprised of saccharide monomers having an acidic nature, e.g., saccharide monomers having -COOH or -$SO_4H$ groups. Ionic polysaccharides belong to a group of substances generally known as hydrocolloids. These substances are strongly hydrophilic macromolecular materials that dissolve or disperse in water, producing a thickening or viscosity effect. Hydrocolloids are both natural and synthetic materials. Natural hydrocolloids are derived from both plant and animal sources. Ionic polysaccharides which may be used in the practice of the present invention may be selected from natural hydrocolloids. Preferred for use in the present invention are algin, carrageenan and pectin with the use of algin especially preferred. Algin and pectin have several carboxylic acid groups along their polymer chains while carrageenan contains sulfuric acid groups. It is preferred to use a monocationic salt of the acid, especially the sodium salt, for solubility considerations, i.e., the salt being more soluble in the aqueous environment of the oral cavity. These ionic polysaccharides swell when hydrated and change from a water-soluble solid to a gel in the presence of multivalent cations such as calcium or magnesium. The multivalent cation forms stable bridges between neighboring molecules resulting in the gel formation. If a suitable amount of the multivalent cation is used precipitation of the film can occur. Where the monovalent cationic salt is used this can occur during a chemical exchange of a multivalent ion for a monovalent ion.

Algin is a generic designation of the derivatives of alginic acid. Alginic acid is a mixed polymer of ß-(1-4)-D-mannosyluronic acid and I-(1-4)-L-gulosyluronic acid, the relative

proportions of which vary with the botanical source and state of maturation of the giant kelp plant Macrocystis pyrifera from which algin is derived. The magnitude and kinetics of the cross-linking reaction of the algin can be controlled by varying the L-guluronic acid and D-mannurinic acid content (also known as G and M blocks). G blocks, having a more buckled, ribbon-like structure will gel quicker. Alginic acid higher in D blocks will be more delayed.

Carrageenan is extracted from Irish moss Chondrus crispus. It consists of alternating copolymers of J-(1-3)-D-galactose and (1-4)-3,6-anhydro-D- or L-galactose. Family members differ in the amount of sulfate ester and/or other substituent groups they carry. They are identified as R-, S- and Q-carrageenan. Kappa and iota form gels, kappa forming stronger gels than iota. Kappa-carrageenan contains only one sulfate group in each disaccharide repeating unit. Iota-carrageenan is the most highly sulfated member of the family.

Pectin is a generic name for a range of products derived from the cell walls of plant tissue classified as pectinic acids. Pectin substances are polymers of 1-4 linked I-galacturonic acid that exist in varying degrees of esterification or neutralization. They are coiled molecules rather than straight. The best gel formation is obtained with pectins wherein the methoxyl level has been reduced.

The amount of ionic polysaccharide in the delivery systems of the present invention may vary depending upon the type of polysaccharide and the type of medicament in the delivery system, as well as the particular result desired. The desirable amount of ionic polysaccharide present will also depend on the pharmaceutical carrier. The ionic polysaccharide may be added to the formulation in a proportion of from 10:1 to 1:10 by weight to the medicament although a ratio of 5:1 to 1:5 by weight would be preferred. It is not a requirement of the present invention that all of the medicament be trapped by the bioadhesive film. Wherein an upper amount of 12% medicament is present in the medicated composition and 1% ionic polysaccharide it is possible that not all of the medicament may be trapped by the film. In general, the ionic polysaccharide will be from about 0.001% to about 1.0%, more preferably from about 0.01% to about 0.6%, by weight of the total medicated composition. For pharmaceutical carriers such as a cooked candy mass wherein processing adversely affects ionic polysaccharides, a lower amount of polysaccharide is desirable.

The cross-linking agents of the present invention are cationic salts that react with the ionic polysaccharide to form a cross-linked polymeric film which adheres to the upper respiratory tract. The rate of gel formation as well as the quality and texture of the resultant gel can be controlled by the solubility and availability of the cation source. Nonlimiting illustrative categories of such cross-linking agents are the salts of multivalent cations such as aluminum, calcium, copper, iron, magnesium, manganese, zinc, and the like, and mixtures thereof. Nonlimiting examples of useful cross-linking compounds are the chloride, sulfate, acetate, and carboxylate salts of calcium, magnesium, copper, zinc, manganese, aluminum, iron, and the like. The preferred multivalent cations are bivalent, and the preferred bivalent cation is calcium. Preferably, the cross-linking agent may be selected from the group consisting of calcium carbonate, stearate, lactate, tartrate, sulfate, chloride, monocalcium phosphate, tricalcium phosphate, dicalcium phosphate dihydrate and mixtures thereof. More preferably, the cross-linking agent is calcium lactate.

The amount of cross-linking agent in the delivery systems of the present invention may depend upon the type of ionic polysaccharide employed as well as the particular result desired, more specifically, the degree of film formation to be achieved. The cross-linking agent may be added to the formulation in amounts sufficient to substantially polymerize the ionic polysaccharide present. Preferably for monocationic salts an excess of multivalent cations are added to insure substantial replacement of the monovalent cation with the multivalent cation.

In general, the amount of cross-linking agent in the delivery system will be from about 0.001% to about 1.2%, more preferably from about 0.01% to about 0.8%, by weight of the total medicated composition.

In another embodiment, the cross-linking agent is premixed with a sequestering agent to further control the timing of the cross-linking reaction. Sequestering agents are compounds that prevent ions from exhibiting their usual properties because of close combination with the sequestering agent. In the present invention, a sequestering agent can form a coordination complex with the metallic ions of the cross-linking agent to delay precipitation of the bioadhesive agent. Nonlimiting examples of useful sequestering agents may be selected from

the group consisting of sodium citrate, tetrasodium phosphate, sodium hexametaphosphate, ethylene diamine tetraacetic acid and the like.

It is preferred to use a sequestering agent in a non-solid application such as in a medicated liquid center wherein the sequestering agent delays an otherwise too rapid polymerization of the ionic polysaccharide. The amount of sequestering agent in the delivery system of the present invention may vary depending upon the cross-linking agent employed and the particular result desired. In general, the amount of sequestering agent in the delivery system will be from about 0.001% to about 1.2%, more preferably from about 0.01% to about 0.8% by weight of the total medicated composition.

Although the sequestering agent may be used per se in the delivery system, it is preferred to use a pharmaceutically acceptable acid in conjunction with the sequestering agent. The pharmaceutically acceptable acids of the present invention are slow-dissolving compounds that react with the sequestered cross-linking agents to release the agent so that the later can react with the monovalent cation salts to form a polymeric film. The timing of the cross-linking reaction can be controlled through selection of the appropriate slow-dissolving pharmaceutically acceptable acid. Nonlimiting examples of useful pharmaceutically acceptable acid are citric, fumaric, malic. tartaric, lactic, adipic, phosphoric, benzoic, glutamic, sorbic, propionic, erythorbic, tannic, succinic, aconitic, and ascorbic. Preferably, the pharmaceutically acceptable acid is selected from the group consisting of citric, fumaric, malic, tartaric, lactic, adipic, and phosphoric. More preferably, the pharmaceutically acceptable acid is citric acid.

The amount of the pharmaceutically acceptable acid in the delivery systems of the present invention may vary depending upon the type of cross-linking agent employed as well as the particular result desired. In general, the amount of pharmaceutically acceptable acid in the delivery system will be from about 0.001% to about 1.2%, more preferably from about 0.01% to about 0.8% by weight of the total medicated composition.

In yet another embodiment, the release of a soluble medicament can be delayed by premixing the medicament with a pharmaceutically acceptable oil and an emulsifier, wherein the emulsifier has a hydrophilic-lipophilic balance in the range from about 1 to about 10.

Nonlimiting examples of useful pharmaceutically acceptable oils may be selected from the group consisting of animal, vegetable, and marine oils, fats, and waxes (such as sunflower oil or shark liver oil), and synthetic oils, fats, and waxes. More preferably, the pharmaceutically acceptable oils are selected from the group consisting of vegetable oils and the like. Most preferably, the pharmaceutically acceptable oil is a vegetable oil. In general, the amount of pharmaceutically acceptable oil in the delivery system will be from about 0.001% to about 1%, more preferably from about 0.01% to about 0.2%, by weight of the total medicated composition.

Nonlimiting examples of useful emulsifiers having a hydrophilic-lipophilic balance in the range from about 1 to about 10 may be selected from the group consisting of decaglycerol decaoleate, lecithin and sorbitan fatty acid esters. Preferably, the emulsifier is decaglycerol decaoleate. In general, the amount of emulsifier in the delivery system will be from about 0.001% to about 1%, more preferably from about 0.01% to about 0.6% by weight of the total medicated composition.

The present invention also concerns medicated compositions comprising the targeted delivery systems. These medicated compositions comprise

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide,

(c) a cross-linking agent, and,

(d) a pharmaceutically acceptable carrier suitable for administering of a medicament to the upper respiratory tract.

By "pharmaceutically acceptable carrier" is meant one or more filler or encapsulating or carrier materials which are suitable for oral administration to a human. Pharmaceutically acceptable carrier materials suitable for the preparation of dosage forms for oral administration are well-known in the art. The delivery systems useful for the localized administration of a medicament to the upper respiratory tract may be utilized in a wide variety of pharmaceutically acceptable carriers. Various oral dosage forms can be used including but not limited to such solid forms as lozenges, tablets, capsules, granules, and bulk powders and liquid centers such as syrups and suspensions.

The pharmaceutically acceptable carrier of the present invention may contain conventional excipients and additives which function to facilitate processing or storage. Thus coloring agents, flavoring agents, perfumes, sweetening agents, surface active agents, lubricants, softeners, glidants, stabilizing agents, and the like, and mixtures thereof, may be present in the medicated composition. The pharmaceutically acceptable carrier material including optional additives is present in a quantity sufficient to bring the total amount of the medicated composition to 100%.

The present invention is also directed to methods for preparing the medicated compositions. In a specific embodiment, the present invention is directed at a method for preparing a medicated composition useful for the localized administration of medicaments to the upper respiratory tract which comprises the steps of:

(1) providing the following ingredients:

(a) a medicament useful for treating the upper respiratory tract;

(b) an ionic polysaccharide;

(c) a cross-linking agent; and,

(d) a pharmaceutically acceptable carrier suitable for administering of a medicament to the upper respiratory tract;

(2) admixing the ingredients from step (1) to form the composition.

The present invention is also directed to a method for treating the upper respiratory tract. In a specific embodiment the present invention is directed at the local administration of a medicament to the upper respiratory tract which method comprises orally administering to a patient a medicated composition which comprises:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide,

(c) a cross-linking agent, and,

(d) a pharmaceutically acceptable carrier suitable for administration of a medicament to the upper respiratory tract.

An important aspect of the present invention includes a hard or soft confectionery composition incorporating the inventive delivery systems and a method for preparing the hard or soft confections. In this form of the invention, the medicated compositions includes the delivery system and a pharmaceutically acceptable carrier such as a confectionery bulking agent, and various additives. The confectionery may be in the form of a lozenge, tablet, toffee, nougat, suspension, chewy candy, and the like. The pharmaceutically acceptable carriers may be prepared from a wide range of materials. Without being limited thereto, such materials include diluents, binders and adhesives, lubricants, disintegrants, coloring agents, bulking agents, flavoring agents, sweetening agents and miscellaneous materials such as buffers and adsorbents in order to prepare a particular medicated confection.

The preparation of confectionery formulations is historically well known and has changed little through the years. Confectionery items have been classified as either "hard" confectionery or "soft" confectionery. The medicated compositions of the present invention can be incorporated into confectionery compositions by admixing the inventive compositions into conventional hard and soft confections.

As used herein, the term confectionery material means a product containing a bulking agent selected from a wide variety of materials such as sugar, corn syrup, and the like, and in the case of sugarless bulking agents, sugar alcohols such as sorbitol and mannitol and the like, and mixtures thereof. Confectionery material may include such exemplary substances as lozenges, tablets, toffee, nougat, suspensions, chewy candy, chewing gum and the like. The bulking agent is present in a quantity sufficient to bring the total amount of confectionery composition to 100%.

Lozenges are flavored medicated dosage forms intended to be sucked and held in the mouth. Lozenges may be in the form of various shapes such as flat, circular, octagonal and biconvex forms. The lozenge bases are generally in two forms: hard, boiled candy lozenges and compressed tablet lozenges.

Hard boiled candy lozenges may be processed and formulated by conventional means. In general, a hard boiled candy lozenge has a base composed of a mixture of sugar and other

carbohydrate bulking agents kept in an amorphous or glassy condition. This amorphous or glassy form is considered a solid syrup of sugars generally having from about 0.5% to about 3% moisture. Such materials normally contain up to about 92% sugar, up to about 55% corn syrup and from about 0.1% to about 5% water, by weight of the final composition. The syrup component is generally prepared from corn syrups, but may include other materials. Further ingredients such as flavoring agents, sweetening agents, acidulants, coloring agents and the like may also be added.

Boiled candy lozenges may also be prepared from non-fermentable sugars such as sorbitol, mannitol, isomalt, and hydrogenated starch hydrolysates. Typical hydrogenated starch hydrolysates are LYCASINÔ, a commercially available product manufactured by Roquette Corporation, and HYSTARÔ, a commercially available product manufactured by Lonza, Inc. The candy lozenges may contain up to about 95% sorbitol, a mixture of sorbitol and mannitol in a ratio from about 9.5:0.5 up to about 7.5:2.5, and hydrogenated starch hydrolysates to about 55%, by weight of the solid syrup component.

Boiled candy lozenges may be routinely prepared by conventional methods such as those involving fire cookers, vacuum cookers, and scraped-surface cookers also referred to as high speed atmospheric cookers.

Fire cookers involve the traditional method of making a boiled candy lozenge base. In this method, the desired quantity of carbohydrate bulking agent is dissolved in water by heating the agent in a kettle until the bulking agent dissolves. Additional bulking agent may then be added and the cooking continued until a final temperature of 1450 C to 1560 C is achieved. The batch is then cooled and worked as a plastic-like mass to incorporate additives such as flavoring agents, coloring agents and the like.

A high-speed atmospheric cooker uses a heat-exchanger surface which involves spreading a film of candy on a heat exchange surface, the candy is heated to 1650 C to 1700 C in a few seconds. The candy is then rapidly cooled to 1000 C to 1200 C and worked as a plastic-like mass enabling incorporation of the additives, such as flavor agents, coloring agents and the like.

In vacuum cookers, the carbohydrate bulking agent is boiled at a temperature from about 1250 C to about 1320 C, vacuum is applied and additional water is boiled off without extra heating. When cooking is complete, the mass is a semi-solid and has a plastic-like consistency. At this point, flavoring agents, coloring agents, and other additives are admixed in the mass by routine mechanical mixing operations.

The optimum mixing required to uniformly mix the flavoring agents, coloring agents and other additives during conventional manufacturing of boiled candy lozenges is determined by the time needed to obtain a uniform distribution of the materials. Normally, mixing times of from about 4 to about 10 minutes have been found to be acceptable.

Once the boiled candy lozenge has been properly tempered, it may be cut into workable portions or formed into desired shapes. A variety of forming techniques may be utilized depending upon the shape and size of the final product desired. A general discussion of the composition and preparation of hard confections may be found in H.A. Lieberman, Pharmaceutical Dosage Forms, Volume 1: Tablets (1989), Marcel Dekker, Inc., New York, N.Y. at Medicated Confections, pages 419-582, which disclosure is incorporated herein by reference.

In contrast, compressed tablet confections contain particulate materials and are formed into structures under pressure. These confections generally contain sugars in amounts up to about 95%, by weight of the composition, and typical tablet excipients such as binders and lubricants as well as flavoring agents, coloring agents and the like.

In addition to hard confectionery materials, the lozenges of the present invention may be made of soft confectionery materials such as those contained in nougat. The preparation of soft confections, such as nougat, involves conventional methods, such as the combination of two primary components, namely (1) a high boiling syrup such as a corn syrup, hydrogenated starch hydrolysate or the like, and (2) a relatively light textured frappe, generally prepared from egg albumin, gelatin, vegetable proteins, such as soy derived compounds, sugarless milk derived

compounds such as milk proteins, and mixtures thereof. The frappe is generally relatively light, and may, for example, range in density from about 0.5 to about 0.7 grams/cc.

The high boiling syrup, or "bob syrup" of the soft confectionery is relatively viscous and has a higher density than the frappe component, and frequently contains a substantial amount of a bulking agent such as a sugar, corn syrup, or a hydrogenated starch hydrolysate. Conventionally, the final nougat composition is prepared by the addition of the "bob syrup" to the frappe under agitation, to form the basic nougat mixture. Further ingredients such as flavoring agents, additional carbohydrate bulking agents, coloring agents, preservatives, medicaments, mixtures thereof and the like may be added thereafter also under agitation. A general discussion of the composition and preparation of nougat confections may be found in B.W. Minifie, Chocolate, Cocoa and Confectionery: Science and Technology, 2nd edition, AVI Publishing Co., Inc., Westport, Conn. (1980), at pages 424-425, which disclosure is incorporated herein by reference.

The procedure for preparing the soft confectionery involves known procedures. In general, the frappe component is prepared first and thereafter the syrup component is slowly added under agitation at a temperature of at least about 650 C, and preferably at least about 1000 C. The mixture of components is continued to be mixed to form a uniform mixture, after which the mixture is cooled to a temperature below 800 C, at which point, the flavoring agent may be added. The mixture is further mixed for an additional period until it is ready to be removed and formed into suitable confectionery shapes.

The novel medicated compositions may also be in the form of a pharmaceutical suspension. Pharmaceutical suspensions of this invention may be prepared by conventional methods long established in the art of pharmaceutical compounding.

Medicated candy is prepared by procedures similar to those used to make soft confectionery. In a typical procedure, a boiled sugar-corn syrup blend is formed to which is added a frappe mixture. The boiled sugar-corn syrup blend may be prepared from sugar and corn syrup blended in parts by weight ratio of about 90:10 to about 10:90. The sugar-corn syrup blend is heated to temperatures above about 1200 C to remove water and to form a

molten mass. The frappe is generally prepared from gelatin, egg albumin, milk proteins such as casein, and vegetable proteins such as soy protein, and the like, which is added to a gelatin solution and rapidly mixed at ambient temperature to form an aerated sponge like mass. The frappe is then added to the molten candy mass and mixed until homogeneous at temperatures between about 650 C and about 1200 C.

The delivery systems of the present invention can then be added to the homogeneous mixture as the temperature is lowered to about 650 C-950 C whereupon additional ingredients can then be added such as flavoring agents and coloring agents. The formulation is further cooled and formed into pieces of desired dimensions.

A general discussion of the lozenge and tablet forms of confectionery may be found in H.A. Lieberman, Pharmaceutical Dosage Forms, Volume 1: Tablets (1989), Marcel Dekker, Inc., New York, N.Y. at Medicated Confections, pages 419-582, which disclosure is incorporated herein by reference.

Throughout this application, various publications have been referenced. The disclosures in these publications are incorporated herein by reference in order to more fully describe the state of the art.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

The present invention is further illustrated by the following examples which are not intended to limit the effective scope of the claims. All parts and percentages in the examples and throughout the specification and claims are by weight of the final composition unless otherwise specified.

## Examples

Examples 1 and 2:

Examples 1 and 2 provide a comparison of a medicated cough drop containing the delivery system with a control confectionery. Menthol was used as the active agent. Table 1 below sets out the components in the drops.

**Table 1**

**Medicated Drops**

| Examples | | |
|---|---|---|
| Formula % | 1[a] | 2[b] |
| sucrose | 54.39 | 54.45 |
| corn syrup | 55.40 | 44.55 |
| water | 1.00 | 1.00 |
| sodium alginate[c] | 0.103 | --- |
| Candy Base Portion Total | 97.338 | 97.35 |
| calcium lactate | 0.012 | --- |
| menthol | 0.230 | 0.230 |
| eucalyptus oil | 0.200 | 0.200 |
| citric acid | 0.220 | 0.220 |
| salvage | 2.000 | 2.000 |
| Portion Total | 2.662 | 2.65 |
| Total | 100 | 100 |

a: delivery system
b: control
c: added as a 4% solution

For example 1 the sucrose, corn syrup (80% dry solids), water and sodium alginate were heated in a cooking pot to approximately 1450C. The menthol, eucalyptus oil, citric acid, calcium lactate (premixed 1:1 with water) were mixed with the salvage portion and then mixed into the mass. The candy was formed by in a drop roller press sized at 2.2g per piece. Each piece contained approximately 5mg menthol.

A test panel evaluated the two comparative samples for degree (intensity) of cooling effects on the nasal passages, the mouth and the throat. The results of the evaluation are set out in Table 2.

**Table 2**

**Test Panel**

| Examples | | |
|---|---|---|
| | 1[a] | 2[b] |
| Nasal | 4.62 | 5.0 |
| Mouth | 5.75 | 5.62 |
| Throat | 6.12 | 5.25 |

a: delivery system
b: control

Scale:
On a scale of 1-9 with 1 being very little and 9 being very much

The control was found to have more diffuse vapor action having greater cooling effects in the nasal passages. The inventive sample provided cooling more directly to the throat area, i.e., the inventive sample had less cooling in the nasal passages and more cooling in the throat area, the targeted area.

Examples 3-6:

Examples 3-6 provide a comparison of a medicated anesthetic-type lozenge containing the delivery system (3) with a control confectionery (5), a system containing a polymer added per se (4), and a commercial product (6). The components in the prepared confectionery compositions, Examples 3-5, are set out in Table 3.

**Table 3**

**Anesthetic-Type Lozenge**

| Examples | | | |
|---|---|---|---|
| Formula % | 3[a] | 4[b] | 5[c] |
| Sucrose | 54.39 | 54.44 | 49.49 |
| Corn Syrup | 44.50 | 44.55 | 49.49 |
| Coloring Agent | 0.01 | 0.01 | 0.01 |
| Sodium Alginate | 0.10 | --- | --- |
| Residual Moisture | 1.00 | 1.00 | 1.00 |
| Candy Base Portion Total | 96.05 | 97.37 | 97.41 |
| Menthol | 0.01 | 0.01 | 0.01 |
| Flavoring Agent | 0.29 | 0.29 | 0.29 |
| Citric Acid | 0.15 | 0.15 | 0.15 |
| Salvage-portion 1 | 2.00 | 2.00 | 2.00 |
| Dyclonine Hydrochloride | 0.14 | 0.14 | 0.14 |
| Decaglycerol Decaoleate | 0.14 | --- | --- |
| Vegetable Oil | 0.14 | --- | --- |
| Salvage-portion 2 | 1.00 | --- | --- |
| Calcium Lactate.$5H_2O$ | 0.08 | --- | --- |
| Carbomer | --- | 0.04 | --- |
| Portion Total | 3.95 | 2.63 | 2.59 |
| Total | 100.00 | 100.00 | 100.00 |

a: delivery system

b: polymer

c: control

For example 3, the candy base was prepared by adding the sucrose, corn syrup (80% dry solids), coloring agent (as a 1% aqueous solution), and sodium alginate (as a 4% aqueous solution) to a cooking pot with sufficient wetting water and cooking the mixture up to a temperature of about 1450 C to 1500 C. The menthol, flavoring agent and citric acid were then admixed with the salvage-portion 1 (sugar and corn syrup). The dyclonine and decaglycerol decaoleate were then mixed, the vegetable oil then admixed with this mixture, and this admixture then mixed with the salvage-portion 2. The menthol-salvage admixture, dyclonine-salvage admixture, and calcium lactate hydrate (premix 1:1 with water) were then folded into the candy. The flavored candy mass was pressed through a candy drop roller and formed into candy pieces. The candy pieces were cooled and shaken and stored in a closed container with dehydrating packets.

For examples 4 and 5, the candy base was prepared by adding the sucrose, corn syrup (80% dry solids), and coloring agent (as a 1% aqueous solution) to a cooking pot with sufficient wetting water and cooking the mixture up to a temperature of about 1450 C to 1500 C. The menthol, flavoring agent, citric acid, and dyclonine, and carbomer when present, were then admixed with salvage-portion 1 and this admixture was then folded into the candy. The flavored candy mass was pressed through a candy drop roller and formed into candy pieces. The candy pieces were cooled and shaken and stored in a closed container with dehydrating packets.

A consumer taste panel evaluated the throat numbing action of the confectionery compositions set out in Table 3, and also a commercial lozenge containing 0.14% dyclonine hydrochloride, for taste and efficacy in random order and the findings were pooled and averaged. The results from the taste panel are set out below in Table 4.

Table 4

Consumer Study

| Examples | | | | |
|---|---|---|---|---|
| | 3[a] | 4[b] | 5[c] | 6[d] |
| Overall Liking | 6.2 | 6.0 | 5.4 | 4.9 |
| Perceived Efficacy | 5.8 | 5.5 | 5.1 | 5.5 |
| Intensity of Throat Numbing | 4.9 | 4.2 | 4.6 | 4.2 |
| Intensity of Mouth Numbing | 5.5 | 5.7 | 5.5 | 4.8 |

a: delivery system
b: polymer
c: control
d: commercial product containing 0.14% dyclonine hydrochloride

Scale:
Overall Liking; on a scale of 1-9, 1 being extremely disliked and 9 being extremely liked.
Perceived Efficacy: on a scale of 1-9, 1 being ineffective and 9 being effective.
Intensity of Throat Numbing: on a scale of 1-9, 1 being very little, 5 being just right, and 9 being too much.
Intensity of Mouth Numbing: on a scale of 1-9, 1 being very little and 9 being very much.

The greatest significance of these findings is that the delivery system (3) provided strongest throat numbing and overall preference. It was especially preferred over the commercial product which was more non-localized in its effect. The test also showed that consumers believed that (3) was more efficacious.

The test further showed that merely adding a polymer (4) does not provide the same result as provided by the delivery system (3) of the present invention.

We claim:

1. A delivery system for the localized administration of a medicament to the upper respiratory tract which comprises:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide, and,

(c) a cross-linking agent.

2. The delivery system according to claim 1, wherein the medicament useful for treating the upper respiratory tract is selected from the group consisting of analgesics, topical anesthetics, antitussives, topical antimicrobials, antihistamines, decongestants, expectorants, cell and tissue healing agents, bronchodilators, steroidal anti-inflammatory agents, and mixtures thereof.

3. The delivery system according to claim 2 wherein the medicament is an analgesic, topical anesthetic or antitussive.

4. The delivery system according to claim 3 wherein the medicament is an antitussive.

5. The delivery system according to claim 4 wherein the medicament is menthol.

6. The delivery system according to claim 3, wherein the medicament is a topical anesthetic agent.

7. The delivery system according to claim 6, wherein the medicament is dyclonine hydrochloride.

8. The delivery system according to claim 1, wherein the ionic polysaccharide selected from the group consisting of algin, carrageenan and pectin.

9. The delivery system according to claim 8 wherein the ionic polysaccharide is a monocationic salt.

10. The delivery system according to claim 9 wherein the salt is sodium.

11. The delivery system according to claim 1, wherein the ratio of the ionic polysaccharide to medicament is from 10:1 to 1: 10 by weight.

12. The delivery system according to claim 1, wherein the cross-linking agent contains a multivalent ion selected from the group consisting of aluminum, calcium, copper, iron, magnesium, manganese, zinc, and mixtures thereof.

13. The delivery system according to claim 12, wherein the cross-linking agent is selected from the group consisting of calcium stearate, calcium lactate, calcium tartrate, calcium sulfate, monocalcium phosphate, tricalcium phosphate, dicalcium phosphate dihydrate and mixtures thereof.

14. The delivery system according to claim 13, wherein the cross-linking agent is calcium lactate.

15. The delivery system according to claim 1, wherein the cross-linking agent is premixed with a sequestering agent.

16. The delivery system according to claim 15, wherein the sequestering agent is selected from the group consisting of sodium citrate, tetrasodium phosphate, sodium hexametaphosphate, ethylene diamine tetraacetic acid.

17. The delivery system according to claim 15, wherein the delivery system further comprises a pharmaceutically acceptable acid selected from the group consisting of citric acid, fumaric acid, malic acid, tartaric acid, lactic acid, adipic acid, phosphoric acid, benzoic acid, glutamic acid, sorbic acid, propionic acid, erythorbic acid, tannic acid, succinic acid, aconitic acid, ascorbic acid, and mixtures thereof

18. The delivery system according to claim 17, wherein the pharmaceutically acceptable acid is selected from the group consisting of citric acid, fumaric acid, malic acid, tartaric acid, lactic acid, adipic acid, phosphoric acid, and mixtures thereof.

19. The delivery system according to claim 18, wherein the pharmaceutically acceptable acid is citric acid.

20. The delivery system according to claim 1, wherein the medicament is premixed with a pharmaceutically acceptable oil and an emulsifier having a hydrophilic-lipophilic balance in the range from about 1 to about 10.

21. The delivery system according to claim 20, wherein the pharmaceutically acceptable oil is selected from the group consisting of animal, vegetable, marine, and synthetic oils, fats, and waxes.

22. The delivery system according to claim 20, wherein the emulsifier having a hydrophilic-lipophilic balance in the range from about 1 to about 10 is selected from the group consisting of decaglycerol decaoleate, lecithin and sorbitan fatty acid esters.

23. The delivery system according to claim 21, wherein the pharmaceutically acceptable oil is vegetable oil and the emulsifier is decaglycerol decaoleate.

24. A medicated composition which comprises:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide,

(c) a cross-linking agent, and,

(d) a pharmaceutically acceptable carrier suitable for administration of a medicament to the upper respiratory tract.

25. The medicated composition according to claim 24, wherein the medicament useful for treating the upper respiratory tract is selected from the group consisting of analgesics, topical anesthetics, antitussives, topical antimicrobials, antihistamines, decongestants, expectorants, cell and tissue healing agents, bronchodilators, steroidal anti-inflammatory agents, and mixtures thereof.

26. The medicated composition according to claim 25 wherein the medicament is an analgesic, topical anesthetic or antitussive.

27. The medicated composition according to claim 26 wherein the medicament is an antitussive.

28. The medicated composition according to claim 27 wherein the medicament is menthol.

29. The medicated composition according to claim 26, wherein the medicament is a topical anesthetic agent.

30. The medicated composition according to claim 29, wherein the medicament is dyclonine hydrochloride.

31. The medicated composition according to claim 24, wherein the ionic polysaccharide selected from the group consisting of algin, carrageenan and pectin.

32. The medicated composition according to claim 31 wherein the ionic polysaccharide is a monocationic salt.

33. The medicated composition according to claim 32 wherein the salt is sodium.

34. The medicated composition according to claim 24, wherein the cross-linking agent contains a multivalent ion selected from the group consisting of aluminum, calcium, copper, iron, magnesium, manganese, zinc, and mixtures thereof.

35. The medicated composition according to claim 34, wherein the cross-linking agent is selected from the group consisting of calcium stearate, calcium lactate, calcium tartrate, calcium sulfate, monocalcium phosphate, tricalcium phosphate, dicalcium phosphate dihydrate and mixtures thereof.

36. The medicated composition according to claim 35, wherein the cross-linking agent is calcium lactate.

37. The medicated composition according to claim 24, wherein the medicament useful for treating the upper respiratory tract is present in an amount from about 0.001% to about 12%, by weight of the delivery system.

38. The medicated composition according to claim 24, wherein the ionic polysaccharide is present in an amount from about 0.001% to about 1%, by weight of the composition.

39. The medicated composition according to claim 24, wherein the cross-linking agent is present in an amount from about 0.001% to about 1.2%, by weight of the composition.

40. The medicated composition according to claim 24, wherein the cross-linking agent is premixed with a sequestering agent.

41. The medicated composition according to claim 40, wherein the sequestering agent is selected from the group consisting of sodium citrate, tetrasodium phosphate, sodium hexametaphosphate, ethylene diamine tetraacetic acid.

42. The medicated composition according to claim 24, wherein the delivery system further comprises a pharmaceutically acceptable acid selected from the group consisting of citric acid, fumaric acid, malic acid, tartaric acid, lactic acid, adipic acid, phosphoric acid, benzoic acid, glutamic acid, sorbic acid, propionic acid, erythorbic acid, tannic acid, succinic acid, aconitic acid, ascorbic acid, and mixtures thereof

43. The medicated composition according to claim 42, wherein the pharmaceutically acceptable acid is selected from the group consisting of citric acid, fumaric acid, malic acid, tartaric acid, lactic acid, adipic acid, phosphoric acid, and mixtures thereof.

44. The medicated composition according to claim 43 wherein the pharmaceutically acceptable acid is citric acid.

45. The medicated composition according to claim 24, wherein the pharmaceutically acceptable acid is present in an amount from about 0.001% to about 1.2%, by weight of the delivery system.

46. The medicated composition according to claim 24, wherein the medicament is premixed with a pharmaceutically acceptable oil and an emulsifier having a hydrophilic-lipophilic balance in the range from about 1 to about 10.

47. The medicated composition according to claim 46, wherein the pharmaceutically acceptable oil is selected from the group consisting of animal, vegetable, marine, and synthetic oils, fats, and waxes.

48. The medicated composition according to claim 46, wherein the emulsifier having a hydrophilic-lipophilic balance in the range from about 1 to about 10 is selected from the group consisting of decaglycerol decaoleate, lecithin and sorbitan fatty acid esters.

49. The medicated composition according to claim 46, wherein the pharmaceutically acceptable oil is vegetable oil and the emulsifier is decaglycerol decaoleate.

50. A method for preparing a medicated composition useful for the localized administration of medicaments to the upper respiratory tract which comprises the steps of:

(1) providing the following ingredients:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide,

(c) a cross-linking agent, and,

(d) a pharmaceutically acceptable carrier suitable for administration of a medicament to the upper respiratory tract;

(2) admixing the ingredients from step (1) to form the medicated composition.

51. A method for the local administration of a medicament to the upper respiratory tract of a patient which comprises orally administering a medicated composition which comprises:

(a) a safe and effective amount of a medicament useful for treating the upper respiratory tract,

(b) an ionic polysaccharide,

(c) a cross-linking agent, and,

(d) a pharmaceutically acceptable carrier suitable for administration of a medicament to the upper respiratory tract.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/00252

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/36 A61K47/02 A61K31/045 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 92 03124 A (ORAMED INC) 5 March 1992<br>* see in particular example 5, page 8 line 20 - page 9, line 8, and page 30 lines 6 - 15 *<br>--- | 1-3,6, 8-12, 24-26, 29, 31-34, 37-39, 50,51 |
| A | EP 0 221 850 A (WARNER LAMBERT CO) 13 May 1987<br>* see in particular example 1 *<br>---<br>-/-- | 1-51 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 9 April 1997 | 06.05.1997 |

| Name and mailing address of the ISA | Authorized officer |
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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: ( + 31-70) 340-3016 | Isert, B |

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/00252

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 5 147 648 A (BANNERT CHRISTIAN) 15 September 1992<br>cited in the application<br>* see in particular example 2 *<br>----- | 1-51 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/00252

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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(54) **Title:** Pharmaceutical compositions for acute glucocorticoid therapy

(57) **Abstract:** The present invention relates to glucocorticoid-containing pharmaceutical compositions or kits for use in acute emergency situations where acute glucocorticoid therapy is required. Notably, the invention relates to pharmaceutical compositions and kits that are designed to be administered by non-medically trained persons outside a hospital or another medical or clinical setting. The invention also relates to a method for treating a disorder requiring acute glucocorticoid therapy by providing a fast onset of action of a glucocorticoid

# Pharmaceutical compositions for acute glucocorticoid therapy

## Field of the invention

The present invention relates to glucocorticoid-containing pharmaceutical compositions or kits for use in acute emergency situations where acute glucocorticoid therapy is required. Notably, the invention relates to pharmaceutical compositions and kits that are designed to be administered by non-medically trained persons outside a hospital or another medical or clinical setting. The invention also relates to a method for treating a disorder requiring acute glucocorticoid therapy by providing a fast onset of action of a glucocorticoid.

## Background of the invention

Glucocorticoids are important steroids for intermediary metabolism, immune function, musculoskeletal and connective tissue as well as the brain. The importance of the glucocorticoids is best understood in patients with glucocorticoid deficiency. In such patients, the one-year survival rate was only 20% in the 1950s before the availability of glucocorticoid replacement therapy. The major use of glucocorticoids in clinical practice began, however, with their use in the treatment of rheumatoid arthritis in the 1940s. Both natural and synthetic glucocorticoids have been employed in the management of a wide variety of conditions and they play a crucial part of many emergency treatments involving allergic and inflammatory disorders.

The endogenous glucocorticoids are steroids predominantly produced in the adrenal cortex. The main glucocorticoid in the body is cortisol. The production and secretion of cortisol is governed by a complex and highly efficient system that includes the hypothalamus, pituitary and the adrenal glands i.e. hypothalamic-pituitary-adrenal axis (HPA). Cortisol secretion has a circadian release rhythm with peak values in early morning and trough values at midnight. The HPA axis is also activated by several physical and psychological stressors. Thus, under stress conditions, such as physical activity, fever, surgery or mental stress, the serum cortisol concentration is increased.

Adrenocortical deficiency results in a number of complex symptoms that results from deficiency of adrenocortical hormone activity. It may be of a primary type as a result of a disease in the adrenal cortex, a secondary (central) type due to the specific pathology in the hypothalamus and/or the pituitary gland, or a tertiary type due to a suppressed HPA axis after long-term high dose glucocorticoid treatment.

The onset of adrenocortical insufficiency may vary from insidious to an acute life-threatening situation with severe salt and water deficit, which leads to shock and death if not treated fast and adequately.

Therapy of e.g. acute adrenal crisis requires that the one or more glucocorticoids quickly enter (are absorbed) into the systemic circulation at a therapeutically effective concentration interval (therapeutic window). Although a number of various glucocorticoid-containing pharmaceutical compositions already are on the market, most of these are not suitable for the treatment of a disorder requiring acute glucocorticoid therapy as they either result in a too slow appearance in the systemic circulation (e.g. conventional tablets) or in a too low, if any, glucocorticoid serum level (many glucocorticoid-containing pharmaceutical compositions are intended for local treatment e.g. in the nose or on the skin).

There are today two ways of administering glucocorticoids in medical emergencies. One is the parenteral route where an intravenous (IV ) infusion has to be set up or a deep intramuscular (IM) injection has to be given. However, one disadvantage of this administration is that an IV route can be challenging to establish particularly in patients with compromised peripheral circulation. Furthermore, parenteral administration requires qualified personnel and is therefore limited to well-crewed ambulances and in-hospital settings.

The other administration route is traditionally by oral administration using a dissolvable betamethasone tablet in water. This route is mainly used in outpatient clinics and for patient self-medication. However, the disadvantages are the considerable lag-time when preparing the solution and the time from intake until a significant serum level of the drug is obtained. The maximum plasma concentration ($C_{max}$) is usually reached within 1 to 3 hours after administration ($T_{max}$) It is also well known that the onset of intestinal absorption cannot be earlier than 0.5 hour for these oral immediate release products of a rapidly dissolved and rapidly absorbed drug (a class I drug according to the FDA's Biopharmaceutics Classification System), the gastric emptying being very variable both in the fasted and fed state. Furthermore, it is mandatory that the patient is conscious and has unaffected ability to swallow the solution since a weak gastrointestinal motility results in a further delay in gastric emptying and reduced intestinal absorption (both rate and extent).

Examples of such cumbersome oral administrations are obtained in patients with acute laryngitis, patients with severe distress due to breathlessness, children with croup or severe angiooedema, and in patients with gastroenteritis where gastrointestinal absorption is uncertain.

Accordingly, it would be of great therapeutic advantage to develop pharmaceutical compositions that enable self-administration by patients and administration to patients by non-medically trained persons outside of a hospital, clinic, ambulance, paramedical or similar medical settings and at the same time result in a sufficient treatment of a disorder requiring acute glucocorticoid therapy (e.g. acute adrenal crises) by providing a fast onset of action after administration. Moreover, there is also a need for pharmaceutical compositions that can be administered to a patient who e.g. is unconscious or otherwise unable to swallow a composition (e.g. a tablet or solution) and that does not require medically trained personnel or need be done in a medical setting.

**Detailed disclosure of the invention**

The present invention meets the above-described needs by providing a pharmaceutical composition comprising one or more glucocorticoids for substantially immediate release, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 30 min after start of an in vitro dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and a suitable dissolution medium such as, e.g., water, simulated saliva or simulated intestinal fluid without enzymes, and wherein a glucocorticoid serum level of a subject of at least 20% of $C_{max}$ is reached within 20 min after administration of the composition via a mucosa of the subject.

The dissolution medium can be chosen depending on the type of composition in question. Accordingly, water or simulated saliva can be used for compositions intended for administration to the oral cavity. A person skilled in the art will know how to chose the right dissolution medium depending on the formulation in question. Normally a dissolution medium based on water and adjusted to a pH in the range of from pH 4.5 to about 8 is suitable irrespective of whether the compositions are intended for administration via nasal, rectal, vaginal mucosa.

In the present context the term "substantially immediate release" is intended to include all types of release which differ from the release obtained from plain tables and provide a release, which is faster than that obtained from plain tablets. In particular, the term is related to a rapid release of the one or more glucocorticoids in an *in vitro* dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and simulated intestinal fluid without enzymes as dissolution medium.

The term "$C_{max}$" denotes the average maximum serum//plasma/blood concentration or serum//plasma/blood level obtained after administration of the composition to at least six normal healthy human subjects.

The term "via a mucosa" indicates that the one or more glucocorticoids must enter into the systemic circulation in order to obtain the desired effect and that the administration route is different from that of topical, intravenous and intramuscular administration.

In another aspect, the invention relates to a kit for treating a subject suffering from a disorder requiring acute glucocorticoid therapy comprising one or more containers for housing a pharmaceutical composition according to the invention and instructions for use thereof. In a specific embodiment, the one or more containers are in the form of blisters or blister packs.

In a further aspect, the invention relates to a method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of $C_{max}$ within 20 min after administration.

In a still further aspect, the invention relates to the use of an amount of one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined herein for the treatment of a disorder requiring acute glucocorticoid therapy by providing a fast rise in the glucocorticoid serum level to at least 20% of $C_{max}$ within 20 min after administration via a mucosa.

As mentioned above, in order to obtain a fast onset of action it is required that a fast rise of glucocorticoid serum level is obtained after administration of a composition of the invention. Accordingly, in specific embodiments least 40% of $C_{max}$ is reached within

30 min and/or at least 75% of $C_{max}$ is reached within 45 min after administration of the composition via a mucosa of the subject.

Normally, $T_{max}$ (i.e. the time it takes to obtain the maximum serum/plasma/blood concentration in the serum/plasma/blood concentration time profile) is reached within 60 min after administration of the composition via a mucosa of the subject. $T_{max}$ is typically within a range of from about 30 to about 75 min such as in a range of from about 45 to about 60 min.

As mentioned above, the pharmaceutical compositions and kits of the present invention are suitable for use in the treatment of a disorder requiring acute glucocorticoid therapy. Examples of such disorders are acute adrenal crises relating to a primary, secondary or tertiary adrenal insufficiency, an anaphylactic reaction, an Addison crisis, a status asthmaticus, a blood transfusion reaction, a brain edema, acute kidney transplant rejection, systemic lupus erythematosus or a severe allergic reaction. Other examples include inflammatory disorders, autoimmune disorders, or medical disorders in which a glucocorticoid forms a part of the first line emergency medical treatment or intense short-time medical treatment. Specific examples of disorders that can be treated according to the present invention are given in the following.

*Active substance, dosage and administration routes*

In the present context, the term "glucocorticoid" or "glucocorticosteroid" is intended to denote a therapeutically, prophylactically and/or diagnostically active glucocorticoid or a glucocorticoid that has physiologic effect. The term is intended to include the glucocorticoid in any suitable form such as e.g. a pharmaceutically acceptable salt, complex, solvate, ester, active metabolites or prodrug thereof of in any physical form such as, e.g., in the form of crystals, amorphous or a polymorphous form or, if relevant, in any stereoisomer form including any enantiomeric or racemic form, or a combination of any of the above. The glucocorticoid may be a synthetic glucocorticoid.

The one or more glucocorticoids used according to the invention are selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone including pharmaceutically acceptable esters, salts, complexes and mixtures thereof. In a preferred embodiment of the invention, the glucocorticoid is betamethasone.

Specific examples of pharmaceutically acceptable salt suitable for use according to the invention are phosphates, succinates, lysinates, acetates, cypionates, valerates, hemisuccinates, butyrates and trometamole salts.

As the glucocorticoid is intended for immediate release, the release and/or absorption into the systemic circulation takes place already in the oral cavity in the case the composition is administered orally. In such cases, the glucocorticoid of choice for the first part may be any other than hydrocortisone (as such) or cortisone as these two active substances have a bitter taste. However, these substances may be employed provided that a sufficient taste masking is obtained. In the paragraph relating to "Pharmaceutically acceptable excipients" taste-masking is discussed in more detail. Accordingly, the one or more glucocorticoids of the first part may have an acceptable taste, may be tasteless or it may be effectively taste-masked.

Furthermore, in specific embodiments of the invention, the glucocorticoid used may be a readily water-soluble glucocorticoid (e.g. a water-soluble salt of the glucocorticoid) in order to ensure a fast dissolution of the glucocorticoid from the composition.

In a preferred embodiment of the invention the glucocorticoid is hydrocortisone trometamole (or succinate) due to its high solubility in water, which in turn leads to a rapid absorption into the systemic circulation.

*Dosage*

In general, the dosage of the glucocorticoids present in a composition according to the invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

The term "hydrocortisone equivalents" is used herein to define the amount in mg of a specific glucocorticoid that corresponds to 1 mg of hydrocortisone for the purpose of glucocorticoid therapy as generally understood by medical practitioners. The term is based on the fact that the individual glucocorticoids have different potency and in order to achieve a desired therapeutic effect different doses of the individual glucocorticoids are required. Equivalent doses of the glucocorticoids can be calculated based on the following table.

| Glucocorticoid | Equivalent amount (mg) | Hydrocortisone equivalent (1 mg of the glucocorticoid corresponds to the listed amount in mg of hydrocortisone) |
|---|---|---|
| Cortisone acetate | 25 | 0.8 |
| Hydrocortisone | 20 | 1 |
| Prednisolone | 5 | 4 |
| Prednisone | 5 | 4 |
| Methylprednisolone | 4 | 5 |
| Triamcinolone | 4 | 5 |
| Paramethasone | 2 | 10 |
| Betamethasone | 0.75 | 26.66 |
| Dexamethasone | 0.75 | 26.66 |
| Fludrocortisone | 0.05 | 400 |

In general, a pharmaceutical composition according to the invention contains a total amount of the one or more glucocorticoids expressed as hydrocortisone of from about 1 to about 200 mg. In specific embodiments, the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 100, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1 to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

More specifically, normal dose ranges are given below for acute glucocorticoid therapy

| | |
|---|---|
| Hydrocortisone | 1-200 mg; in acute adrenal crises about 100 mg |
| Cortisone | 1-200 mg such as about 100 mg |
| Betamethasone | 1-20 mg; in increased intracranial pressure e.g. brain oedema about 4 mg daily<br>In chemotherapy or radiation induced nausea 4-8 mg |
| Prednisolon | 1-100 mg; such as from 1 to 30 mg daily; in severe cases 50-60 mg/day |

| | |
|---|---|
| Dexamethasone | 0.1-6 mg such as 0.5-2 mg or 1.5-3 mg; in severe cases up to 6 mg/day |
| Fludrocortisone | 0.05-5 mg; in Addison disease to correct inadequate electrolyte balance 0-05-0.2 mg daily; Cortical adrenal hyperplasia ("salt losing adrenogental syndrome") 0.1-0.2 mg |
| Prednisone | 10-100 mg such as 50 mg |
| Methylprednisolone | 2-40 mg such as 2-20 mg |

In the following are given suitable doses of the individual glucocorticoids in various treatment regimens.

Acute asthma – adults

| | |
|---|---|
| betamethasone | 4-8 mg |
| prednisolone | 30-60mg |
| methylprednisolone | 40 mg |

Acute anaphylaxia - adults

| | |
|---|---|
| betamethasone | 5 mg up to 20 mg |
| hydrocortisone | 200 mg |
| dexamethasone | 4-20mg –80mg |

Acute anaphylaxia - children

| | |
|---|---|
| hydrocortisone | 100-200 mg |

Septic shock - adults

| | |
|---|---|
| hydrocortisone | 200-300 mg/day |
| methylprednisone | 30 mg/kg |

Acute bacterial meningitis

| | |
|---|---|
| dexamethasone | 0.3 mg/kg/dose (max 10 mg) x 4 times daily for 2-4 days |
| betamethasone | 8 mg x 4 times daily |

Acute RSV (respiratory syncytial virus) infection with bronchiolitis in children

betamethasone 4-6 mg

Acute croup-children
betamethasone 4-6 mg

Mononucleosis with complications (airway obstruction, thrombocytopenia or haemolytical anaemia)
betamethasone 5-6 mg

Tonsillitis/peritonsillitis – children with airway obstruction
betamethasone 4-6 mg

A composition according to the invention is designed to provide a fast onset of action and upon administration a fast rise in glucocorticoid serum/plasma/blood level is obtained. In the case hydrocortisone is used as the glucocorticoid a serum level of at least about 200 nmol/l is obtained within 20 min after administration. In the case that another glucocorticoid than hydrocortisone is used, a person skilled in the art will know how to determine suitable equivalent serum/plasma/blood concentrations.

For example, hydrocortisone can be rapidly released from a composition during a time period of from about 0 to abut 30 minutes after administration and 5-10 mg of hydrocortisone can be rapidly administered as an extra dose in conjunction with fever etc in patients with adrenal insufficiency. Likewise, 5-20 mg of betamethasone can be rapidly released for most indications in which a rapid glucocorticoid effect is of value.

*Administration routes*

As mentioned above, the one or more glucocorticoids used according to the invention are administered to the subject (preferably a human) via a mucosa into the systemic circulation. In particular, in specific embodiments of the invention, the mucosa is the mucosa in the oral cavity, the nose, the rectum or in the vagina or via pulmonary, bronchial or respiratory mucosa and ephithelia. Preferably, the mucosa is the oral mucosa.

Figures 11 and 12 show sites of oral mucosal administration suitable for use. Four well-defined sites may be used, namely

"buccal" administration that includes the term "labial" administration and is used for administration of a pharmaceutical composition to a mucosa between the gums (gingiva) and the inside of the cheeks;
"sublingual" administration that refers to administration of a pharmaceutical composition under the tongue;
"palatal" administration that refers to administration of a pharmaceutical composition to the hard and/or soft palate; and
"gingival" administration that refers to administration of a pharmaceutical composition to the upper and/or lower gingiva.

All the above-mentioned sites are suitable for use to obtain a very fast onset of action due to a rapid absorption (transport of active drug) into the systemic circulation. In specific embodiments of the invention the buccal administration route is preferred, i.e. administration of a composition to the oral mucosa between the gums and the inside of the cheeks and thus enabling the absorption to take place from two sites, namely the gingival mucosa and the buccal mucosa.

*Pharmaceutical compositions*

In the following is given a description of pharmaceutical compositions according to the invention.

*Release of the one or more glucocorticoids*

A rapid release of the one or more glucocorticoids is necessary in order to obtain a fast onset of action after administration via a mucosa where the glucocorticoid is rapidly absorbed (transported) into the systemic circulation. Accordingly a general requirement is that at least 60% of the one or more glucocorticoids contained in the composition must be released within 30 min when tested in an *in vitro* dissolution test as defined herein. Specific embodiments of the composition fulfil one or more of the requirements given in the following table. In general, it is preferred that the requirement stated within 30 min after start of the dissolution test is fulfilled. In preferred embodiments, at least 70% or at least 80% of the one or more glucocorticoids contained in the composition are released within the first 20 min of the dissolution test.

| time after start of the dissolution test | % hydrocortisone equivalents released (based on the content in the |
|---|---|

| | composition) |
|---|---|
| within 30 min | at least about 60% such as, e.g., at least about 70%, preferably at least about 80% or more preferably at least about 90% |
| within 20 min | at least about 60%, preferably at least about 70%, at least about 80% or even more preferred at least about 90% |
| within 15 min | at least about 60% such as, e.g., at least about 70%, preferably at least about 80%or at least about 90% |
| within 10 min | at least about 60% such as, e.g., at least about 70%, preferably at least about 80% or at least about 90% |
| within 5 min | at least about 60% |

In specific embodiments (cf. the examples herein) more than 50 % of the one or more glucocorticoids can be released within 2 min, between 50 and 90 % can be released within 5-8 min, and more than 90 % of the dose can be released within 15 min.

.

A pharmaceutical composition according to the invention is designed for systemic administration via a mucosa. In a preferred embodiment the mucosa is the mucosa in the oral cavity.

The pharmaceutical composition may be in any suitable form including liquid, semi-solid or solid form.

In a preferred aspect of the invention the pharmaceutical composition is in the form of a dosage form such as a unit dosage form.

Examples of compositions according to the invention suitable for administration via the oral mucosa into the systemic circulation are typically solid or semi-solid dosage forms. The solid dosage form is typically selected from the group consisting of granules, beads, pellets and powders and - when presented in unit dosage form - it may be in the form of a tablet including a chewable tablet, a suckable tablet, an effervescent tablet, a sublingual tablet, a rapid-burst tablet, an immediate release tablet, a rapidly dissolvable tablet, melt tablets, lozenges, pastilles or it may be presented in a more candy-like form, or the like.

A pharmaceutical composition for administration via the oral mucosa into the systemic circulation may also be in the form of a spray, a wafer, a film, a gel, a hydrogel, a patch, a gingival patch, a bioadhesive patch, a sachet, a solution, an inhaler or the like.

Examples of compositions according to the invention suitable for administration via the mucosa in the nose into the systemic circulation are typically in the form of nasal sprays, nasal aerosols, nasal solutions including nasal drops and the like.

Examples of compositions according to the invention suitable for administration via the pulmonary, bronchial and respiratory mucosa and epithelia into the systemic circulation are inhalers including powder inhalers.

Examples of compositions according to the invention suitable for administration via the mucosa in the rectum or the vagina into the systemic circulation include suppositories, vagitories, clysmas etc.

A pharmaceutical composition according to the invention may also have bio/mucoadhesive properties. The absorption of drugs into the systemic circulation from a mucosal drug delivery system is significantly improved if a mucosal bioadhesive component is added in the formulation. It will prevent both swallowing and create a high local concentration of the glucocorticoid adjacent to the absorption site. The mucoadhesive component will be mixed in an appropriate way together with the glucocorticoid and other ingredients in the dosage form. The term "bio/mucoadhesive is used to denote that the composition is able to reversible adhere to a biological mucosa. In some cases a bio/mucoadhesion promoting agent is included in the composition to promote adherence to the mucosa.

In the term bio/mucoadhesion promoting agent mucoadhesion and bioadhesion are used interchangeable even if bioadhesion may have a wider definition meaning that an adhesion to any biological feature available at the mucosa takes place. If present, the bio/mucoadhesion promoting agent may be a polymeric substance, preferable a substance having an average molecular weight above 5 kD. The hydration property is crucial for the bio/mucoadhesion forces and therefore a rapid swelling of the polymer will initiate the bio/mucoadhesion process. A swelling factor by volume when brought into contact with the saliva fluid should be between 10 and 20.

A pharmaceutical composition according to the invention typically contains one or more pharmaceutically acceptable excipients. A general description of pharmaceutically acceptable excipients suitable for use in a composition according to the present invention is given in the paragraph under the heading "Pharmaceutically acceptable excipients". Depending on the specific kind of dosage form a person skilled in the art will know which kinds of excipients to choose, if necessary guided by the teaching in handbooks like Remington's Pharmaceutical Science and Handbook of Pharmaceutical Excipients. In the following is given a description of specific kinds of excipients suitable for use in the formulation of compositions in the form of film or patches especially for administration to the oral cavity.

When the pharmaceutical composition is in the form of a film, patch, wafer, gel, sachet, gingival patch or the like it may contain a pharmaceutically acceptable excipient selected from the group consisting of an acrylic polymer including a derivative thereof, a cellulose derivative, modified starch, polyethylene oxide, chitosan, gelatin, sodium alginate, pectin, scleroglucan, xanthan gum, guar gum, or poly-co-(methyl vinyl ether-maleic anhydride), alone or in combinations thereof. The cellulose derivative may be selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, modified cellulose gum, or crosscaramellose.

A pharmaceutical composition according to the invention may also contain the one or more bio/mucoadhesion promoting agents. Normally such bio/mucoadhesion promoting agents are present in concentration of from about 0.1 to about 25% w/w. Examples of bio/mucoadhesion promoting agents include polymers including synthetic polymers, natural polymers and derivatives thereof, and mixtures thereof. The polymer

may be selected from a carbomer, a polyethylene oxide, a poly co-(methylvinyl ether/maleic anhydride, and mixtures thereof; or it may be a polysaccharide. The polysaccharide may be selected from the group consisting of gelatin, sodium alginate, pectin, scleroglucan, xanthan gum; guar gum, microcrystalline cellulose, crosscaramellose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, moderately cross-linked starch, and chitosan.

A pharmaceutical composition according to the invention may also containg a dissolution promoting agent. If present, a dissolution promoting agent is present in a concentration of from about 0.05 to about 5% w/w of the total weight of the composition. The dissolution promoting agent may be selected from the group consisting of sodium lauryl sulphate, a polysorbate, a bile acid, a bile salt, a salt of cholic acid or cholanic acid, isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and a sorbitan ester.

In specific embodiment the one or more glucocorticoids in a composition of the invention are present as microparticles or nanoparticles. In general, he mean particle size of such particles is 10 μm or less. Furthermore, the micro- or nanoparticles may be encapsulated such as coated with a coating comprising a lechitin or a lechitin based compound.

When the glucocorticoid is present in the form of micro- or nanoparticles, a pharmaceutical composition according to the invention may also comprise a disintegrating agent. Such agents promote the dispersion of microparticles of the glucucorticoid over the administration site in for example the labial and gingival mucosa. Examples of pharmaceutically acceptable disintegrating agents are cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, and cellulose gum. If present, it is normally used in a concentration of from 0.5 to 10 w/w based on the total weigh of the composition Different pharmaceutical excipients, such as mannitol and lactose, have been found to be particularly suitable as excipients.

As mentioned above, the pharmaceutical composition according to the invention may further comprise a taste-masking agent. Examples of a taste-masking agent are e.g. menthol, peppermint, vanillin, a terpene based compound, or an artificial sweetener. In a specific embodiment, the one or more glucocorticoids are taste masked by incorporation into an inclusion complex by means of alpha-, beta-, or gamma-cyclodextrins, preferably by beta-cyclodextrins.

In general, the composition of the invention contains from 0.05 up to 50 weight percent such as, e.g., from 0.05 up to 40 weight percent, 0.05 up to 30 weight percent or from about 0.05 up to 20 weight percent of glucocorticoid. More preferably, the compositions contains from 0.05 to 10 weight per cent of glucocorticoid, and especially from 0.1 to 5 weight per cent. The contents can also be expressed as the amount of glucocorticoid in a dose unit of the composition, such as a tablet. In this connection a dose refers to the therapeutically amount of the at least one glucocorticoid, or its derivative, which is to be administered at one time. When the glucocorticoid is used in the form of a pharmaceutically acceptable salt, these percentages and amounts should be recalculated accordingly.

*Pharmaceutically acceptable excipients*

In the present context the terms "pharmaceutically acceptable excipients" are intended to denote any material, which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. Such an excipient may be added with the purpose of making it possible to obtain a pharmaceutical, which have acceptable technical properties.

Examples of suitable excipients for use in a solid dosage form according to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixture thereof. As the individual parts of a composition or kit according to the invention are used for different purposes (e.g. immediate and extended release), the choice of excipients is normally made taken such different uses into considerations. A person skilled in the art will know which kinds of pharmaceutically acceptable excipients that are suitable choices depending on the specific dosage form in question. Other pharmaceutically acceptable excipients for suitable use are e.g. acidifying agents, alkalising agents, preservatives, antioxidants, buffering agents, chelating agents, colouring agents, complexing agents, emulsifying and/or solubilizing agents, flavours and perfumes, humectants, sweetening agents, wetting agents etc.

Examples of suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K, Metolose SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60 SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrins, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

Specific examples of diluents are e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, sugar etc.

Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

Specific examples of binders are e.g. acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

Glidants and lubricants may also be included in the composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica,

hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

Other excipients which may be included in a composition of the invention are e.g. flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

The composition or kit components according to the invention may also be coated with a film coating, a protective coating, an anti-adhesive coating etc.

A composition according to the invention may also be coated in order to obtain suitable properties e.g. with respect to taste-masking of the one or more glucocorticoids. The coating may also be applied as a readily soluble film. The coating may be applied on single unit dosage forms (e.g. tablets) or it may be applied on a multiple-unit dosage form or on its individual units.

Suitable coating materials are e.g. methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, glyceryl monostearate, zein.

Plasticizers and other ingredients may be added in the coating material. The same or different active substance may also be added in the coating material.

*Taste masking*

In general, it is difficult in most cases to prepare a formulation for oral mucosa or nasal administration with satisfactory safety and stability from a drug having irritating properties or capable of forming molecular aggregates, although it depends on the kind of the drug used. In the case of hydrocortisone, the base has a distinctively bitter taste and a formulation has to be taste masked in order to be applicable for repeated use.

The taste masking agent can be a menthol, a peppermint, a vanillin, or a terpene based compound. In addition, the taste masking agent can be an artificial sweetener, e.g. sorbitol, xylitol or aspartame. Taste masking can also be achieved by microencapsulation of the glucocorticoid as particles. This is for example accomplished with lecithin based compounds. The taste masking agent is carefully mixed with the active drug in order to be present both at the surface and within the administration formulation. Taste masking can also be achieved by formation of inclusion complexes with cyclodextrins.

Typical examples of the cyclodextrin compound are alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrin, hydroxypropyl .beta.-cyclodextrin, dimethyl .beta.-cyclodextrin, maltosyl .beta.-cyclodextrin and .beta.-cyclodextrin sulfate. Particularly preferred are .alpha.-cyclodextrin, .beta.-cyclodextrin and .gamma.-cyclodextrin. These cyclodextrin compounds may be used alone or in combination.

The amount of cyclodextrin compound to be used may vary with its solubility and the concentration of hydrocortisone. It is, however, desirable that the amount of cyclodextrin compound is 0.5 to 4.0 moles, preferably 2.0 to 4.0 moles, as much as the mole of hydrocortisone.

*Method aspect*

A pharmaceutical composition or a kit according to the invention is suitable for use in the treatment of a subject such as a mammal including a human suffering from a disorder requiring acute glucocorticoid therapy.

Accordingly, in a separate aspect the invention relates to a method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of $C_{max}$ within 20 min after administration.

Normally, it is preferred that at least 40% of $C_{max}$ is reached within 30 min after administration in order to obtain a fast onset of action. In specific preferred embodimentd, at least 75% of $C_{max}$ is reached within 45 min after administration and/or $T_{max}$ is reached within 60 min after administration of the composition via a mucosa of the subject.

Details concerning other aspects of the invention are described hereinbefore and apply also to the method aspect of the invention.

The method according to the invention can be carried out by the patient itself or by non-medically trained persons due to the fact that the one or more glucocorticoids are not presented in the form of a composition for injection or infusion. Normally, medically trained personnel can only administer such compositions. Accordingly, the present invention provides a method that compared to the known treatment methods requiring acute glucocorticoids is much more simple to handle without the necessity of specialized equipment. It is therefore contemplated that the present invention provides a method that enables a treatment when the condition of the patient requires it, i.e. there is no need for bringing the patient to a hospital or a medical clinic in order to be able to give the necessary treatment.

Moreover, due to the development of compositions that enable a fast onset of action after administration and that can be administered without the need of the patient to swallow the composition (e.g. compositions of the invention in the form of films, bio/mucoadhesive compositions, patches, gingival patches, sprays etc.), the patient may be unconscious or otherwise unable to swallow normal tablets and still be correctly treated with glucocorticoids in acute situations.

*Use of a composition or a kit according to the invention*

In another separate aspect, the invention relates to the use one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined hereinbefore for the treatment of a disorder requiring acute glucocorticoid therapy and to provide a serum level as defined herein.

In the above is given a detailed description of the invention relating one or more aspects of the invention, in particular relating to pharmaceutical compositions. However, all details and particulars disclosed under this aspect of the invention apply *mutatis mutandis* to the other aspects of the invention.

**Legends to figures**

Figure 1 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject.

Figure 2 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition B to a human subject.

Figure 3 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition C to a human subject.

Figure 4 shows results from Example 12. The plasma concentration-time profile of cortisol following a single dose administration of film A to a human subject. Non-mucoadhesive thin-layer film, 6 $cm^2$, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids.

Figure 5 shows results from Example 12. The plasma concentration-time profile of cortisol following a single dose administration of film B to a human subject. Non-mucoadhesive thin-layer film, 6 $cm^2$, 11.2 mg hydrocortisone acetate, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids.

Figure 6 shows results from Example 13. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject. In vivo plasma profile. Muocadhesive thin-layer film, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 7 shows results from Example 13. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject. Mucoadhesive thin-layer film, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 8 shows results from Example 14. The plasma concentration-time profile of cortisol following a single dose administration of composition C. In vivo plasma profile. Mucoadhesive rapid-release tablet, 10 mg hydrocortisone, buccal administration.

Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 9 shows results from Example 15 (Composition C from Example 14).

Figure 10 shows results from Example 15 (Composition A from Example 13).

Figures 11 and 12 illustrates different administration sites within the oral cavity

The invention is further illustrated in the following non-limiting examples.

**Materials**

The materials used in the following examples were

| *Trade name* | *Chemical substance* | *Manufacturer* |
|---|---|---|
| Betamethasone | USP/NF | |
| Carboxymetylcellulose | USP/NF | |
| Chitosan glutamate | USP/NF | |
| Crospovidone | USP/NF | |
| Hydrocortisone | Ph. Eur., Qual. D | Aventis, Switzerland (by Apoteksbolaget) |
| Hydrocortisone acetate | USP/NF | |
| Hydrocortisone 21-hemisuccinate sodium | Ph. Eur | Aventis, Switzerland (by Apoteksbolaget) |
| 2-OH-propyl-β-cyclodextrin | | |
| Hydroxypropylmethylcellulose | USP/NF | |
| Levomenthol | USP/NF | |
| Menthol | USP/NF | |
| Methocel E5 | Hydroxypropyl-methyl cellulose | Dow Chemicals, USA (by Colorcon) |
| Methocel® KV 100 LV | USP/NF | Dow Chemicals, USA (by Colorcon) |
| Metolose® | | |
| Microcrystalline cellulose, Avicel® PH-102 | USP/NF | FMC Corporation |

| | | |
|---|---|---|
| Paraffin powder | USP/NF | |
| PEG 300 | USP/NF | |
| PEG 6000 | Polyethylene glycol | Svenska Hoechst AB |
| PEG 400 | Polyethylene glycol | Fluka, Switzerland |
| Prednisolone | USP/NF | |
| Polyox WSR 301 | Polyethylene oxide | Dow Chemicals, USA |
| Na-alginate PH157 | | |
| Sodium dihydrogen phosphate | $NaH_2PO_4 \cdot 2\ H_2O$ | |
| Sodium stearyl fumarate | USP/NF | |
| Sorbitol | USP/NF | |
| Sugar | USP/NF | |
| Sugar/starch seeds | USP/NF | |
| Talc | USP/NF | |
| Triethyl citrate | USP/NF | |
| Xylitab 300<br>Xylisorb 300 | | Xyrofin Kotka, Finland<br>(Danisco Sweeteners Ltd, UK |
| Xylitol | USP/NF | Roquette, France |

**Methods**

The in vivo experiments reported herein were carried out on healthy volunteers. At 6 pm and 11 pm the day before administration of the test composition, the endogenous cortisol secretion was suppressed by oral administration of 2 mg of betamethasone. The test composition was administered to healthy volunteers. The volunteers were in fasted state and were not allowed to take any food until noon. In the case a tablet is administered, it is ingested together with 200 ml of water. The test composition is administered between 8 am and 10 am on the day following the suppression of endogenous glucocorticoid secretion.

**Examples**

**Example 1**

**Capsules containing an immediate release pellets (IR pellets)**

*IR pellets*

| | |
|---|---|
| Sugar/starch seeds, diameter 0.25-0.35 mm | 1 kg |

are coated in a fluidised bed equipped with a Wurster column with a water suspension containing

| | |
|---|---|
| Hydrocortisone 21-hemisuccinate sodium | 10 % |
| Hydroxypropyl methylcellulose, 6 cps | 3 % |
| Talc | 10 % |

to a weight gain of approximately 75 %.

An amount of IR pellets containing 13.4 mg of hydrocortisone 21-hemisuccinate sodium (approximately 70 mg) are filled into hard gelatine capsules size No 3 in a capsule-filling machine.

70 mg pellets will easily fit into a capsule size No. 3 (or even size No. 4) and can be filled in a normal capsule filling machine.

**Example 2**

**Immediate release (IR) tablet**

IR tablets for oral or sublingual use:

| | Mg per tablet |
|---|---|
| Betamethasone | 0.4 |
| Xylitab®300[a] | 40 |
| Lactose anhydrous USP/NF | 5 |
| Microcrystalline cellulose USP/NF | 10 |
| Crospovidone USP/NF | 4 |
| Sodium stearyl fumarate | 1 |
| Water | qs |

[a] Direct compression xylitol from Danisco Sweeteners Ltd UK

Dry mix lactose and microcrystalline cellulose. Dissolve betamethasone in a small amount of water and disperse the solution over the powder blend. Mix and dry. Add Xylitab and crospovidone and dry mix until the blend is homogeneous.

Add sodium stearyl fumarate and continue blending for another 2 minutes.
Compress the blend to tablets in a tablet press using 6 mm round concave punches.

**Example 3**

**Immediate release (IR) film**

Thin films for administration to the oral cavity:

| | % by weight |
|---|---|
| Prednisolone | 0.75 |
| PEG 400 USP/NF | 2 |
| Methocel E5, Dow Chemical | 4 |
| Xylitol, Roquette France | 1 |
| Water | up to 100 |

Methocel was added to approximately 90% of the total amount of distilled water and stirred with a magnetic stirrer until Methocel was completely dissolved. PEG 400 was added under continued stirring, followed by xylitol and prednisolone. Water was added to final weight and stirring was continued during four hours.

330 µl of the solution was pipetted into 16 mm diameter flat-bottomed PVC blisters. The solutions were allowed to dry at room temperature over night and the blister packs were sealed with heat-seal lacquered aluminium foil.

**Example 4**

**Immediate release (IR) oral solution**

Oral solution:

| | |
|---|---|
| Prednisolone acetate | 0.9 mg |
| Sorbitol | 60 mg |
| Menthol | 1.2 mg |
| Sterile water | 5 ml |

Make a solution and fill into a moisture tight aluminium foliated sachet.

**Example 5**

**Immediate release (IR) sublingual spray**

Sublingual spray of hydrocortisone:

| | mg/ml |
|---|---|
| Hydrocortisone acetate | 10 |
| Carboxymetylcellulose | 0.8 (0.08%) |
| 2-OH-propyl-β-cyclodextrin | 40 |
| PEG 300 | 5 |
| Menthol | 0.3 |
| Sorbitol | 12 |
| Levomenthol | 2.0 |
| $NaH_2PO_4 \cdot 2\ H_2O$ | 2 |
| Water | qs |

Dissolve hydrocortisone acetate in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and $NaH_2PO_4 \cdot 2\ H_2O$. Add water up to final volume. Dispense into a spray package that delivers 0.58 ml per dose (5 mg of hydrocortisone).

**Example 6**

**Betamethasone IR tablet for peroral or buccal administration**

| | Mg per tablet |
|---|---|
| Betamethasone | 0.4 |
| Xylitab®300[a)] | 45 |
| Microcrystalline cellulose NF | 10 |
| Crospovidone NF | 4 |
| Water | qs |
| Sodium stearyl fumarate NF | 1 |

[a)] Direct compression xylitol from Danisco Sweeteners Ltd, UK

Dissolve betamethasone in a small amount of water.

Disperse the solution over the microcrystalline cellulose. Mix and dry.

Add Xylitab and crospovidone and dry mix in a suitable mixer until a homogeneous blend is achieved.

Then add sodium stearyl fumarate and continue mixing another two minutes.

Compress the powder blend in a suitable tablet press using 6 mm round concave punches.

**Example 7**

**Sublingual spray of betamethasone**

| | mg/ml |
|---|---|
| Betamethasone | 0.4 |
| Carboxymetylcellulose | 0.8 (0.08%) |
| PEG 300 | 5 |
| Menthol | 0.3 |
| Sorbitol | 12 |
| Levomenthol | 2.0 |
| $NaH_2PO_4$*2 $H_2O$ | 2 |
| Water | qs |

Dissolve betamethasone in a small amount of water. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and $NaH_2PO_4$*2 $H_2O$. Add water up to final volume.

**Example 8**

**Sublingual spray of betamethasone**

| | mg/ml |
|---|---|
| Betamethasone | 0.4 |
| Chitosan glutamate | 10 |
| Menthol | 0.1 |
| Levomenthol | 1.5 |
| $NaH_2PO_4$*2 $H_2O$ | 2 |
| Water | qs |

Dissolve betamethasone in a small amount of water. Add chitosan glutamate and mix. Filter through 0.2µm membrane filter. Add menthol, levomenthol and $NaH_2PO_4$*2 $H_2O$. Add water up to final volume.

**Example 9**

**Sublingual spray of hydrocortisone**

| | mg/ml |
|---|---|
| Hydrocortisone acetate | 10 |
| Carboxymetylcellulose | 0.8 (0,08%) |
| 2-OH-propyl-β- cyclodextrin | 40 |
| PEG 300 | 5 |
| Menthol | 0.3 |
| Sorbitol | 12 |
| Levomenthol | 2.0 |
| $NaH_2PO_4$*2 $H_2O$ | 2 |
| Water | qs |

Dissolve hydrocortisone in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and $NaH_2PO_4$*2 $H_2O$. Add water up to final volume.

**Example 10**

**Sublingual spray of hydrocortisone**

| | mg/ml |
|---|---|
| Hydrocortisone acetate | 10 |
| Chitosan glutamate | 10 |
| 2-OH-propyl-β- cyclodextrin | 40 |
| Menthol | 0.1 |
| Levomenthol | 1.5 |
| $NaH_2PO_4$*2 $H_2O$ | 2 |
| Water | qs |

Dissolve hydrocortisone in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add chitosan glutamate and mix. Filter through 0.2

µm membrane filter. Add menthol, levomenthol and $NaH_2PO_4$*2 $H_2O$. Add water up to final volume.

**Example 11**

**Thin-layer film of hydrocortisone**

Composition A:

| | % w/w |
|---|---|
| Hydrocortisone | 3% |
| Na-alginate PH157 | 2% |
| Water | 95% |

Composition B:

| | |
|---|---|
| Hydrocortisone acetate | 3.4% |
| Na-alginate PH157 | 2% |
| Water | 94.6% |

Composition C:

| | |
|---|---|
| Hydrocortisone | 3% |
| Metolose 60SH-50 | 2% |
| Water | 95% |

The films were made as described in the following:

1. Amount polymer, glucocorticoid and $H_2O$ were weighed.
2. The glucocorticoid was added to the water during stirring.
3. The formulation was kept on stirring until a suspension was obtained.
4. The polymer was added to the suspension.
5. The formulation was kept on stirring until a uniform gel was obtained (minimum 2h).
6. 0.5g gel was weighed in empty blisters and placed in a heating cupboard (Drying: 25°C for 22h).

Table. In vitro dissolution (rotating basket 100 rpm, phosphate buffer pH=7.0, one unit per 500 ml medium) after 1, 3 ,5, 10 and 15 min as a percentage of 10 mg

hydrocortisone. Units with 10 mg hydrocortisone in polymers of sodium alginate (Na-alg), hypromellose (HPMC) and approx. 7 mg/unit. Two units were tested with Na-alg and HPMC. The mean value is tabulated. The results in the following table reflect the rank order regarding viscosity, i.e. HPMC has the lowest viscosity and Na-alg the highest.

| Composition | Polymer | 1 min,% | 3 min,% | 5 min,% | 10 min,% | 15 min,% |
|---|---|---|---|---|---|---|
| A | Na-alg | 15 | 25 | 38 | 65 | 84 |
| B | Na-alg | 15 | 25 | 38 | 65 | 84 |
| C | HPMC | 18 | 48 | 67 | 88 | 92 |

In vivo plasma profiles in humans, N=1 per composition
Dexamethasone suppression test, fasting state, otherwise as described in the paragraph denoted "Method".

The results show that the use of hydrocortisone acetate does not seem to be suitable for an immediate release composition. This was further investigated in the following example.

**Example 12**
**Non-mucoadhesive immediate release films**

Two films were prepared essentially similar to Example 13 – composition A. Film A contains 10 mg of hydrocortisone and film B contains 11.2 mg of hydrocortisone acetate. The results from in vivo testing after buccal administration are shown in Figures 4 and 5. The results show that even if the films are not bioadhesive, a fast onset of the absorption into the systemic circulation after single dose administration of Film A is obtained. In contrast, the results obtained with the film containing hydrocortisone acetate indicate that this compound does not seem to be suitable when a fast onset of the absorption into the systemic circulation of the glucocorticoid is required.

**Example 13**
**Thin-layer films for immediate release**

Batches of glucocorticoid films were prepared from the following compositions A and B:

Rapid-release composition A:

| *Component* | *% w/w* |
|---|---|
| PEG 400 | 2.0 |
| Hydrocortisone | 3.0 |
| Methocel E5 | 4.0 |
| Xylitol | 1.0 |
| Water | 90 |

Slower release composition B:

| *Component* | *w/w %* |
|---|---|
| PEG 400 | 1.3 |
| Hydrocortisone | 3.0 |
| Methocel E5 | 5.7 |
| Water | 90 |

To distilled water (18 ml) in 50 ml round-bottomed glass flask provided with a magnetic stirred was added Methocel E5. After the Methocel had dissolved completely PEG 400 was added under continued stirring, followed by xylitol (Composition A only) and hydrocortisone. Stirring was continued for 4 h.

Into flat-bottomed PVC-blisters (Inpack AB, Lund, Sweden) 16 mm in diameter was pipetted (Finnpipette; automatic) 330 µl of solution A or B into each blister trough. The solutions were allowed to dry at room temperature over night. The next day 10 films were removed for dose analysis. Each film was dissolved in 100 ml of water/ethanol (95%) 9:1 (w/w). The solutions were analysed by UV spectroscopy at 242 nm. Mean contents of 10.19 mg and 9.83 mg hydrocortisone per blister (SD 0.29 and 0.14, respectively) were found for Compositions A and B, respectively.

The hydrocortisone compositions were tested in two human subjects after labial administration. The subjects had their endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids. The plasma concentration of cortisol was monitored during 360 min after the labial administration, and the serum concentration time profiles from these two subjects are shown in Figures 6 and 7.

It is clearly seen that the rate and extent of mucosal uptake of hydrocortisone is high and the appearance of cortisol in serum is rapid, as the first measured plasma concentration was attained already at 10-15 min.

These serum pharmacokinetic data illustrate that a formulation of the invention for oral mucosa administration results in a high rate and extent of mucosal absorption of the active drug, even though a small volume of fluid is available for dissolution at the site of administration and absorption in this route drug delivery.

**Example 14**

**Glucocorticoid tablets for immediate release**

Glucocorticoid tablets were manufactured by direct compression of the dry-mixed powderous components to the following composition C:

Rapid-release composition C:

| *Component* | *Per Batch* |
|---|---|
| PEG 6000 | 8.7 g |
| Hydrocortisone | 2.5 g |
| Xylitab 300 | 8.7 g |
| Mg stearate | 0.16 g |

Batch size 100 tablets

The powderous components were sieved (mesh size 0.7 mm) and dry-mixed by shaking by hand in a small tin can for five min. The homogeneity of the mixture was analyzed by the same method as used for analysis of the tablets. Tabletting was carried out with a DIAF tabletting machine using a flat circular punch 7 mm in diameter (with a dividing score). The hydrocortisone dose in 10 tablets was assessed by the same method as used for the films. Mean contents of 9.53 mg hydrocortisone per tablet (SD 0.15) were found for composition C.

Tablet thickness (10 tablets): 1.72-1.76 mm (C);
Friability (20 tablets): 0.6% (C);
Tablet hardness (10 tablets): 23.7 N (C).

The compositions were tested after oral administration to two human subjects (see Figure 8).

The rate of absorption of the glucocorticoid into the systemic circulation from the solid dosage forms of Example 14 was somewhat slower than that of compositions from Example 13, which means that it is possible to adjust the absorption rate of hydrocortisone into the systemic circulation by introducing changes in the composition and function of the labial pharmaceutical formulation.

**Example 15**

**In vitro dissolution profile**

The *in vitro* dissolution profiles of hydrocortisone from drug formulations according to Example 20 and 21 were followed over time in a standardized controlled *in vitro* environment. A United States Pharmacopoeia dissolution apparatus II (paddle) coupled to automatic sampling devices and software was used for acquiring release profiles of the drug formulations in a neutral pH environment. The dissolution profile was acquired at 37 °C, 50 rpm of the paddles, in a total of 300 ml of water. Sampling was performed at 0, 1, 3, 5, 7, 10 and 15 minutes following the insertion of the pharmaceutical composition in the example in the dissolution medium.

The dissolution profile from each formulation was monitored in two experiments up to 360 min after administration, and the corresponding dissolution time profiles are shown in Figs. 9 and 10, respectively. The release rate is given as the per cent of dose over time.

The release rate from the solid dosage forms of Example 21 was somewhat slower (Fig. 10). This means that it is possible to adjust the release rate of hydrocortisone by introducing changes in the composition and function of the oronasopharyngeal pharmaceutical preparation.

## Claims

1. A pharmaceutical composition comprising one or more glucocorticoids for substantially immediate release, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 30 min after start of an in vitro dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and a suitable dissolution medium, and wherein a glucocorticoid serum level of a subject of at least 20% of $C_{max}$ is reached within 20 min after administration of the composition via a mucosa of the subject.

2. A pharmaceutical composition according to claim 1, wherein at least 40% of $C_{max}$ is reached within 30 min after administration of the composition via a mucosa of the subject.

3. A pharmaceutical composition according to claim 1 or 2, wherein at least 75% of $C_{max}$ is reached within 45 min after administration of the composition via a mucosa of the subject.

4. A pharmaceutical composition according to any of the preceding claims, wherein $T_{max}$ is reached within 60 min after administration of the composition via a mucosa of the subject.

5. A pharmaceutical composition according to any of the preceding claims, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 20 min or 15 min of the dissolution test defined in claim 1.

6. A pharmaceutical composition according to any of the preceding claims, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 10 min or 5 min of the dissolution test defined in claim 1.

7. A pharmaceutical composition according to any of the preceding claims, wherein at least about 70% of the one or more glucocorticoids are released from the composition within the first 15 min such as, e.g., within the first 10 min or 5 min of the dissolution test defined in claim 1.

8. A pharmaceutical composition according to any of the preceding claims, wherein at least about 80% of the one or more glucocorticoids are released from the composition within the first 15 min of the dissolution test defined in claim 1.

9. A pharmaceutical composition according to any of the preceding claims, wherein at least about 80% of the one or more glucocorticoids are released from the composition within the first 10 min of the dissolution test defined in claim 1.

10. A pharmaceutical composition according to any of the preceding claims, wherein at least about 90% of the one or more glucocorticoids are released from the composition within the first 15 min or within the first 10 min of the dissolution test defined in claim 1.

11. A pharmaceutical composition according to any of the preceding claims for administration to the systemic circulation via a mucosa.

12. A pharmaceutical composition according to claim 11, wherein the mucosa is selected from the mucosa in the oral cavity, the nasal cavity, the lung, the bronchia, the rectum, and the vagina.

13. A pharmaceutical composition according to claim 12, wherein the mucosa is the mucosa in the oral cavity.

14. A pharmaceutical composition according to any of the preceding claims designed for administration to the oral cavity.

15. A pharmaceutical composition according to any of the preceding claims in liquid, semi-solid or solid form.

16. A pharmaceutical composition according to any of the preceding claims in the form of a solid dosage form.

17. A pharmaceutical composition according to claim 35, wherein the solid dosage form is selected from the group consisting of granules, beads, pellets and powders.

18. A pharmaceutical composition according to any of the preceding claims in unit dosage form.

19. A pharmaceutical composition according to claim 18, wherein the unit dosage form is in the form of a tablet including a chewable tablet, a suckable tablet, an effervescent tablet, a sublingual tablet, a rapid-burst tablet, an immediate release tablet, a rapidly dissolvable tablet or the like.

20. A pharmaceutical composition according to any of claims 142-15 in the form of a spray, a wafer, a film, a gel, a hydrogel, a patch, a gingival patch, a bioadhesive patch, a sachet, a pulmonary, bronchial or respiratory inhaler including a powder inhaler, a suppository, a vagitory, a clysma, a solution or the like.

21. A pharmaceutical composition according to any of the preceding claims, wherein the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 200 mg.

22. A pharmaceutical composition according to claim 21, wherein the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 100, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1 to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

23. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids is selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone or mixtures thereof, including pharmaceutically acceptable esters, salts and complexes thereof.

24. A pharmaceutical composition according to claim 23, wherein the pharmaceutically acceptable salt is a phosphate, a succinate, a lysinate, an acetate, a cypionate, a valerate, a hemisuccinate, a butyrate or a trometamole salt.

25. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are cortisone or hydrocortisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1-200.

26. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are betamethasone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1 to about 20 mg.

27. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are prednisolone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1 to about 10 mg.

28. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are dexamethsone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 0.1 to about 2 mg.

29. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are fludrocortisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 0.05 to about 5 mg.

30. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are prednisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 10 to about 50 mg.

31. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are methylprednisolone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 2 to about 20 mg.

32. A pharmaceutical composition according to any of the preceding claims in the form of a film, patch, wafer, gel, sachet, gingival patch, lozenge or the like.

33. A pharmaceutical composition according to claim 32, wherein the composition comprises a pharmaceutically acceptable excipient selected from the group consisting

of an acrylic polymer including a derivative thereof, a cellulose derivative, modified starch, polyethylene oxide, chitosan, gelatin, sodium alginate, pectin, scleroglucan, xanthan gum, guar gum, or poly-co-(methyl vinyl ether-maleic anhydride), alone or in combinations thereof.

34. A pharmaceutical composition according to claim 33, wherein the cellulose derivative is selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, modified cellulose gum, or crosscaramellose.

35. A pharmaceutical composition according to any of the preceding claims further comprising one or more bio/mucoadhesion promoting agents.

36. A pharmaceutical composition according to claim 35, wherein the one or more bio/mucoadhesion promoting agents are present in concentration of from about 0.1 to about 25% w/w.

37. A pharmaceutical composition according to claim 35 or 36, wherein the one or more bio/mucoadhesion promoting agents are a polymer including a synthetic polymer, a natural polymer and a derivative thereof, and mixtures thereof.

38. A pharmaceutical composition according to claim 37, wherein the polymer is selected from a carbomer, a polyethylene oxide, a poly co-(methylvinyl ether/maleic anhydride, and mixtures thereof.

39. A pharmaceutical composition according to claim 37, wherein the polymer is a polysaccharide.

40. A pharmaceutical composition according to claim 40, wherein the polysaccharide is selected from the group consisting of gelatin, sodium alginate, pectin, scleroglucan, xanthan gum; guar gum, microcrystalline cellulose, crosscaramellose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, moderately cross-linked starch, and chitosan.

41. A pharmaceutical composition according to any of the preceding claims further comprising a dissolution promoting agent.

42. A pharmaceutical composition according to claim 41, wherein the dissolution promoting agent is present in a concentration of from about 0.05 to about 5% w/w.

43. A pharmaceutical composition according to claim 41 or 42, wherein the dissolution promoting agent is selected from the group consisting of sodium lauryl sulphate, a polysorbate, a bile acid, a bile salt, a salt of cholic acid or cholanic acid, isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and a sorbitan ester.

44. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids are present as microparticles or nanoparticles.

45. A pharmaceutical composition according to claim 44, wherein the mean particle size is 10 μm or less.

46. A pharmaceutical composition according to claim 44 or 45, wherein the micro- or nanoparticles are encapsulated.

47. A pharmaceutical composition according to claim 46, wherein the micro- or nanoparticles are encapsulated with a coating comprising a lechitin or a lechitin based compound.

48. A pharmaceutical composition according to any of the preceding claims further comprising a disintegrating agent.

49. A pharmaceutical composition according to claim 48, wherein the disintegrating agent is selected from the group consisting of cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, and cellulose gum.

50. A pharmaceutical composition according to claim 48 or 49, wherein the disintegrating agent is present in a concentration of from about 0.5 to about 10% w/w.

51. A pharmaceutical composition according to any of the preceding claims further comprising a taste-masking agent.

52. A pharmaceutical composition according to claim 51, wherein the taste-masking agent is selected from the group consisting of menthol, peppermint, vanillin, a terpene based compound, or an artificial sweetener.

53. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids are taste masked by incorporation into an inclusion complex by means of alpha-, beta-, or gamma-cyclodextrins, preferably by beta-cyclodextrins.

54. A pharmaceutical composition according to any of the preceding claims for buccal administration.

55. A pharmaceutical composition according to claim 54 in the form of a gel, a gum, a wafer, a thin-layer film, a patch, a gingival patch, a tablet, a sachet, a lozenge, a fast-dissolving tablet, a cream or an ointment.

56. A kit for treating a subject suffering from a disorder requiring acute glucocorticoid therapy comprising one or more containers for housing a pharmaceutical composition according to any of claims 1-55, and instructions for use thereof.

57. A kit according to claim 56, wherein the one or more containers are in the form of blisters or blister packs.

58. A method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of $C_{max}$ within 20 min after administration.

59. A method according to claim 58, wherein at least 40% of $C_{max}$ is reached within 30 min after administration.

60. A method according to claim 58 or 59, wherein at least 75% of $C_{max}$ is reached within 45 min after administration.

61. A method according to any of claims 58-60, wherein $T_{max}$ is reached within 60 min after administration of the composition via a mucosa of the subject.

62. A method according to any of claims 58-61, wherein the disorder requiring acute glucocorticoid therapy is an acute adrenal crisis.

63. A method according to claim 62, wherein the acute adrenal crisis relates to a primary, secondary or tertiary adrenal insufficiency, an anaphylactic reaction, an Addison crisis, a status asthmaticus, a blood transfusion reaction, a brain edema, a severe allergic reaction, acute asthma, acute anaphylaxia, septic shock, acute bacterial meningitis, acute RSV (respiratory syncytial virus) infection with bronchiolitis in children, acute croup-children, mononucleosis with complications (airway obstruction, thrombocytopenia or haemolytical anaemia), or tonsillitis/peritonsillitis e.g. in children with airway obstruction.

64. A method according to any of claims 58-62, wherein the disorder requiring acute glucocorticoid therapy relates to an inflammatory disorder, an autoimmune disorder, or a medical disorder in which a glucocorticoid forms a part of the first line emergency medical treatment or intense short-time medical treatment.

65. A method according to any of claims 58-64, wherein the mucosa is selected from the mucosa in the oral cavity, the nasal cavity, the lung, the bronchia, the rectum and the vagina.

66. A method according to any of claims 58-65, wherein the mucosa is the mucosa in the oral cavity.

67. A method according to any of claims 58-66, wherein the effective amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 200 mg.

68. A method according to claim 67, wherein the effective amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 125 mg, from about 1 to about 100 mg, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1

to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

69. A method according to any of claims 58-68, wherein the one or more glucocorticoids is selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone or mixtures thereof, including pharmaceutically acceptable esters, salts and complexes thereof.

70. A method according to claim 69, wherein the pharmaceutically acceptable salt is a phosphate, a succinate, a lysinate, an acetate, a cypionate, a valerate, a hemisuccinate, a butyrate or a trometamole salt.

71. A method according to any of claims 58-70, wherein the effective amount of the one or more glucocorticoid is contained in a pharmaceutical composition suitable for administration by the subject itself or by non-medically trained persons.

72. A method according to claim 71, wherein the composition is in a form that can be administered to the subject even if he is unconscious.

73. A method according to claim 71 or 72, wherein the composition is in a form that can be administered to the subject and have effect even if he is unable to swallow the composition.

74. A method according to any of claims 58-73, wherein the one or more glucocorticoids are cortisone or hydrocortisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 1 to about 100 mg.

75. A method according to any of claims 58-73 wherein the one or more glucocorticoids are betamethasone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 1 to about 20 mg.

76. A method according to any of claims 58-73, wherein the one or more glucocorticoids are prednisolone including pharmaceutically acceptable esters, salts

and complexes thereof and wherein the effective amount is in a range of from about 1 to about 10 mg.

77. A method according to any of claims 58-73, wherein the one or more glucocorticoids are dexamethsone including pharmaceutically acceptable esters, salts and complexes and wherein the effective amount is in a range of from about 0.1 to about 2 mg.

78. A method according to any of claims 58-73, wherein the one or more glucocorticoids are fludrocortisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 0.05 to about 5 mg.

79. A method according to any of claims 58-73, wherein the one or more glucocorticoids are prednisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 10 to about 50 mg.

80. A method according to any of claims 58-73, wherein the one or more glucocorticoids are methylprednisolone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 2 to about 20 mg.

81. A method according to any of claims 58-80, wherein the effective amount is administered in the form of a pharmaceutical composition as defined in any of claims 1-55.

82. A method according to any of claims 58-80, wherein the effective amount is administered in the form of a pharmaceutical kit as defined in claims 56 or 57.

83. Use of an amount of one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined in any of claims 1-58 for the treatment of a disorder requiring acute glucocorticoid therapy by providing a fast rise in the glucocorticoid serum level to at least 20% of $C_{max}$ within 20 min after administration via a mucosa.

84. Use according to claim 83, wherein at least 40% of $C_{max}$ is reached within 30 min after administration.

85. Use according to claim 83 or 84, wherein at least 75% of $C_{max}$ is reached within 45 min after administration.

86. Use according to any of claims 83-85, wherein $T_{max}$ is reached within 60 min after administration of the composition via a mucosa of the subject.

87. Use according to any of claims 83-86, wherein an effective amount of the one or more glucocorticoid is contained in a pharmaceutical composition suitable for administration by the subject itself or by non-medically trained persons.

88. Use according to any of claims 83-87, wherein the composition is in a form that can be administered to the subject even if he is unconscious.

89. Use according to claim 87 or 88, wherein the composition is in a form that can be administered to the subject and have effect even if he is unable to swallow the composition.

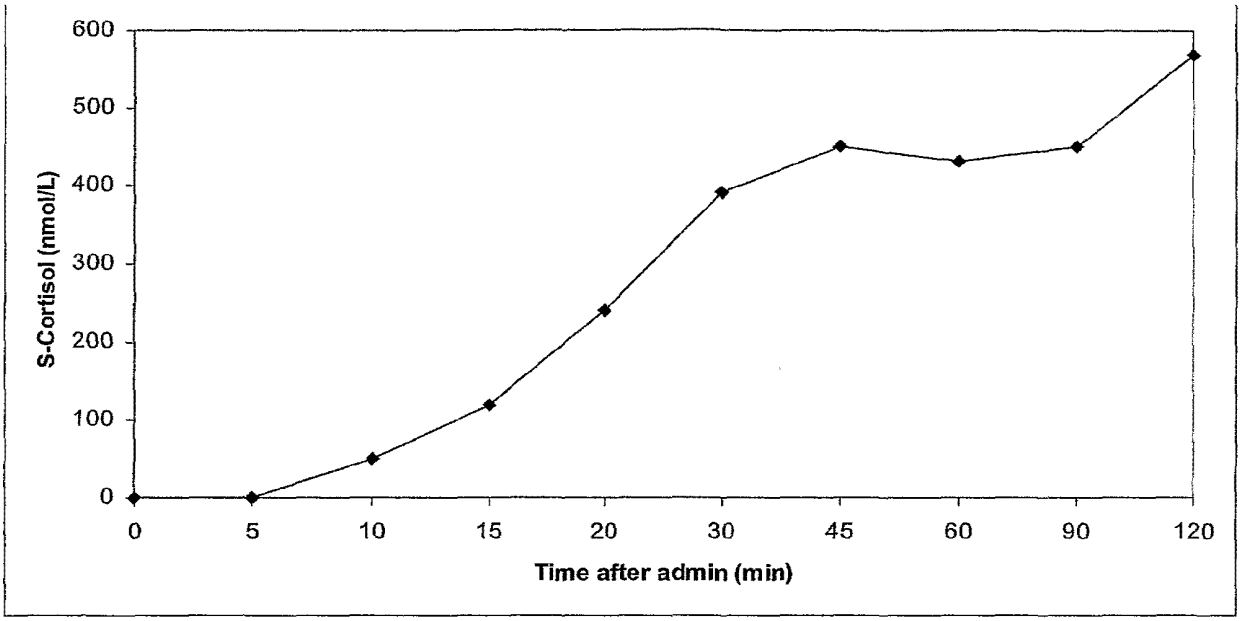


Fig. 1

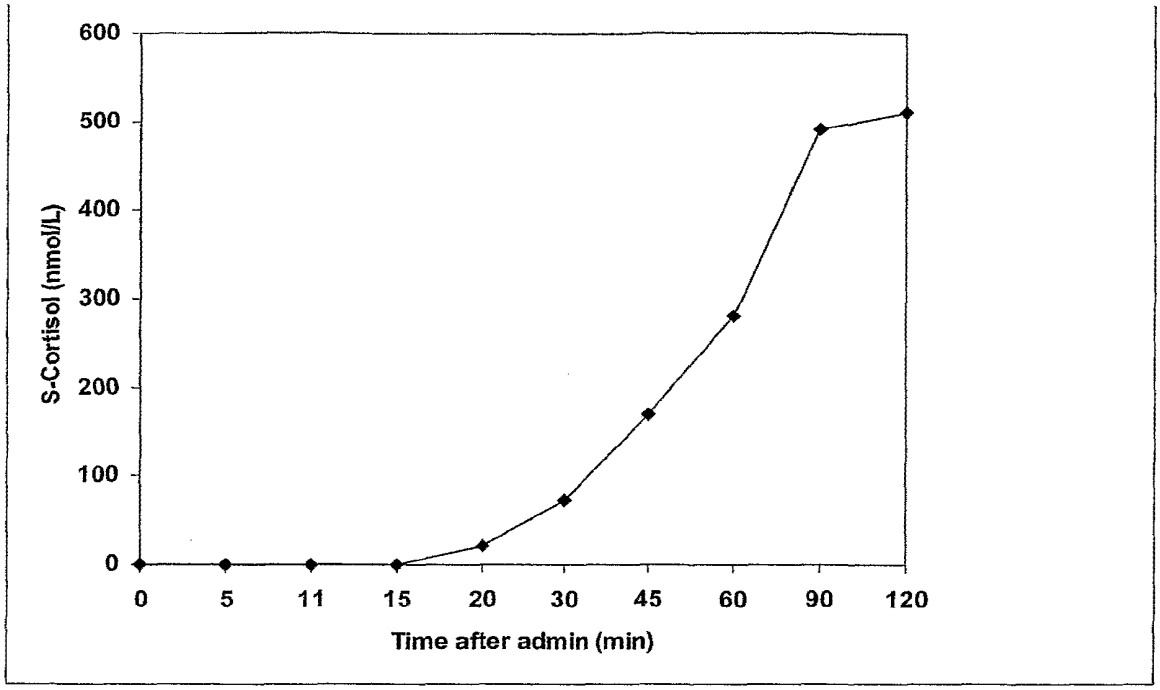


Fig. 2

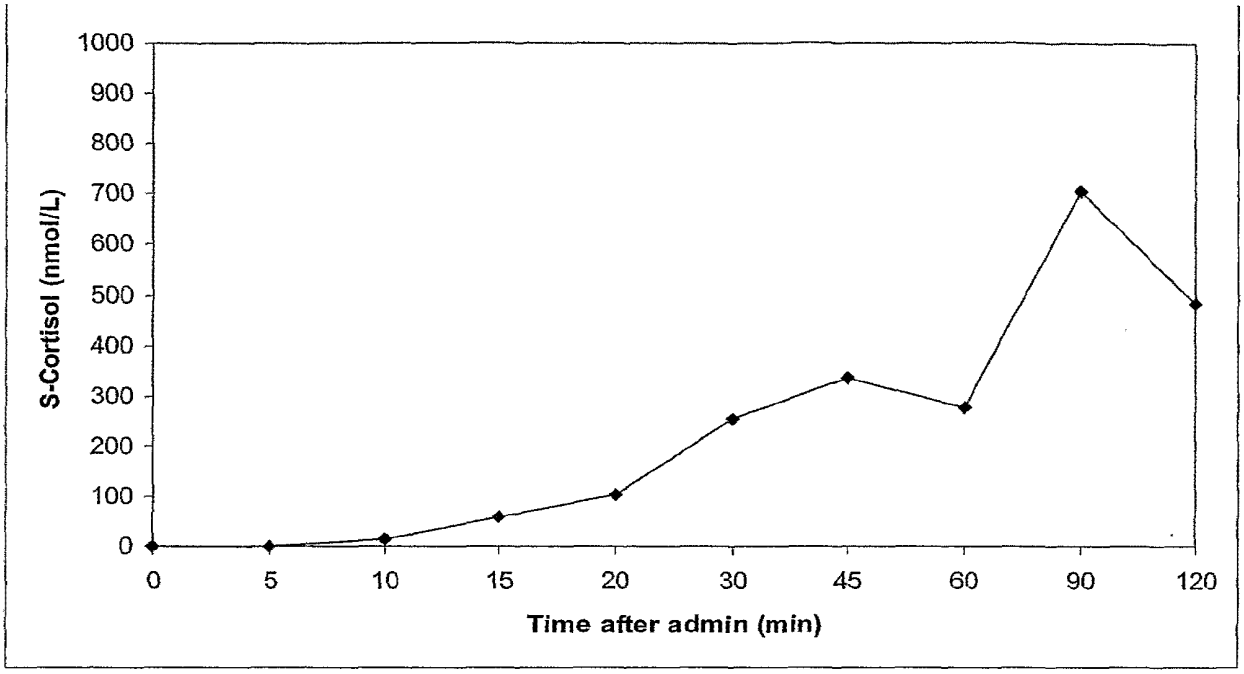


Fig. 3

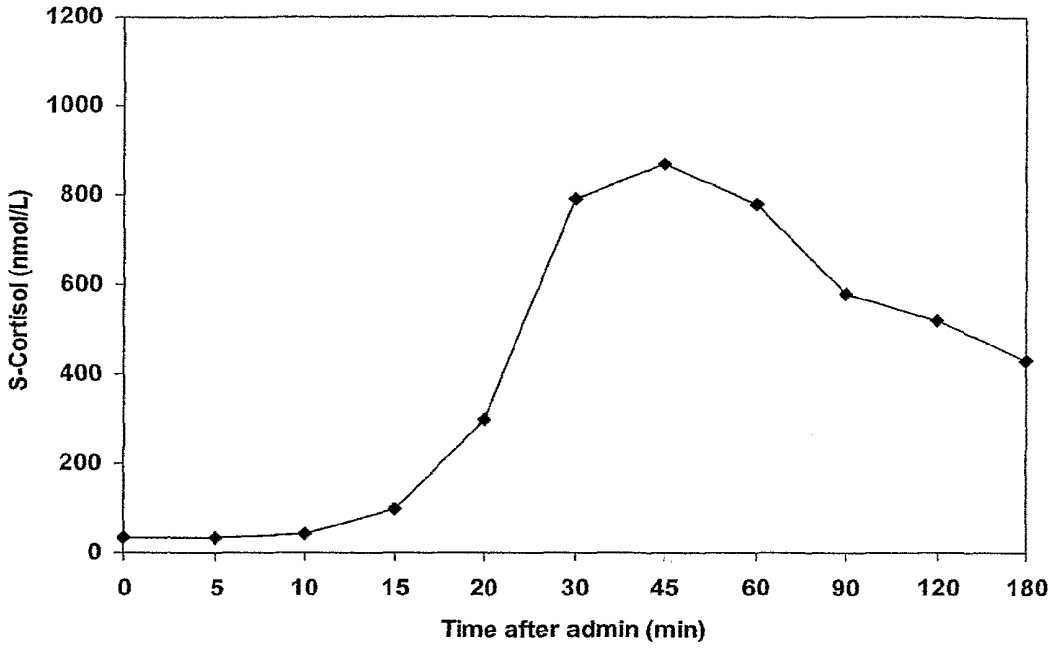


Fig. 4

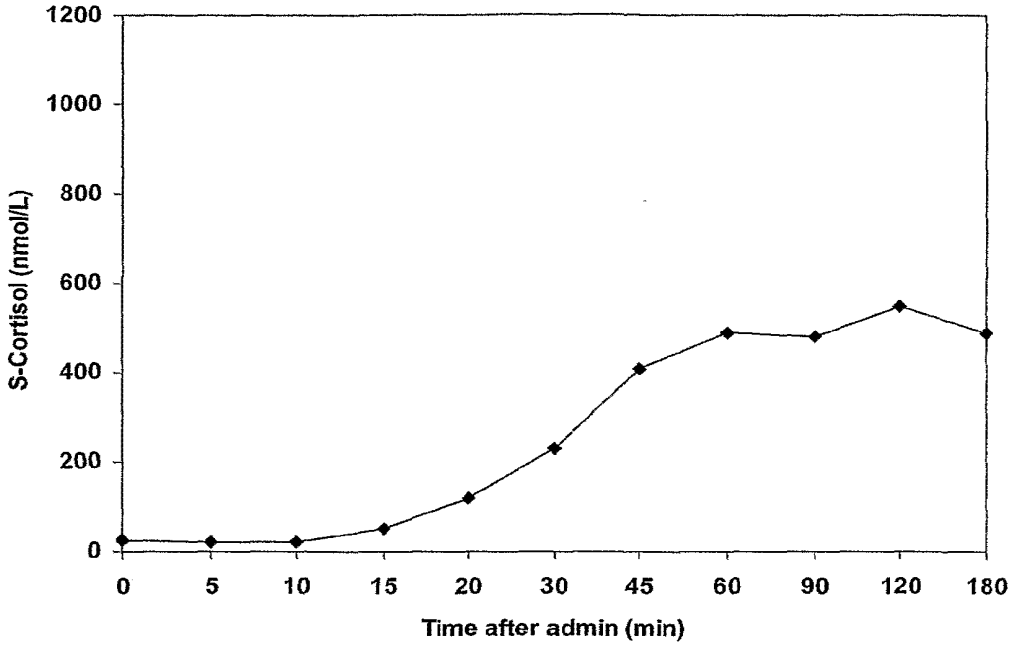


Fig. 5

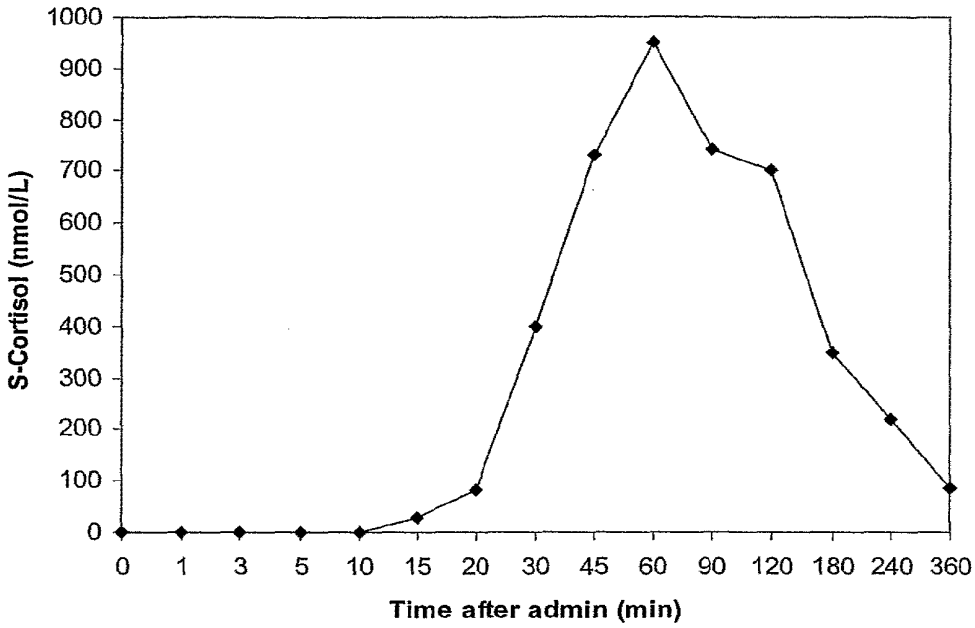


Fig. 6

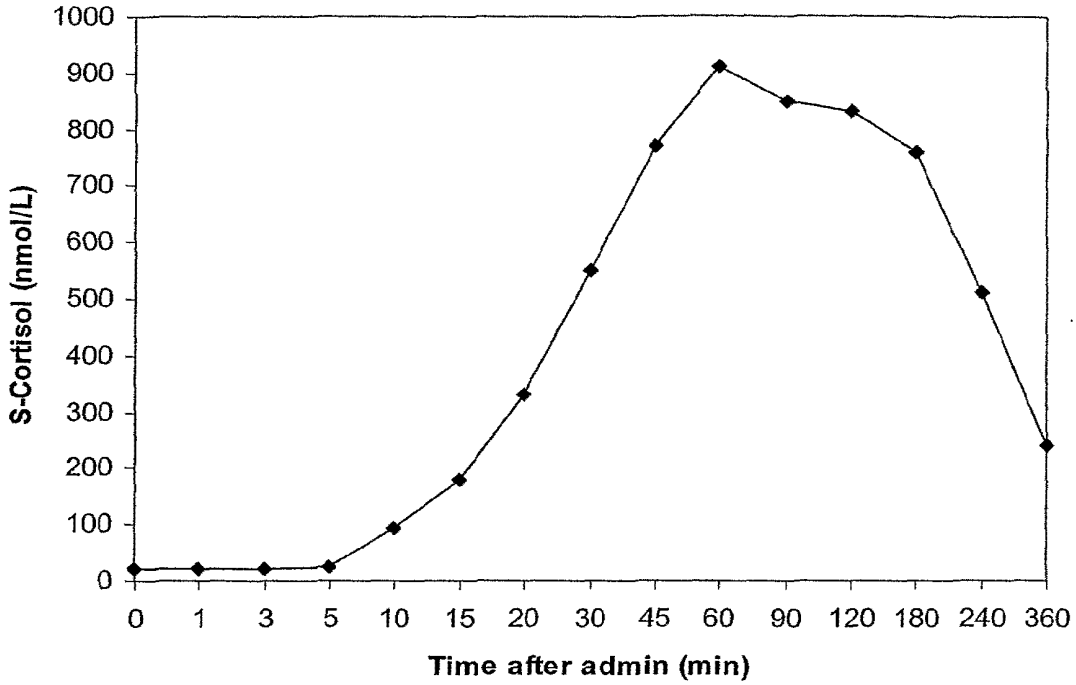


Fig. 7

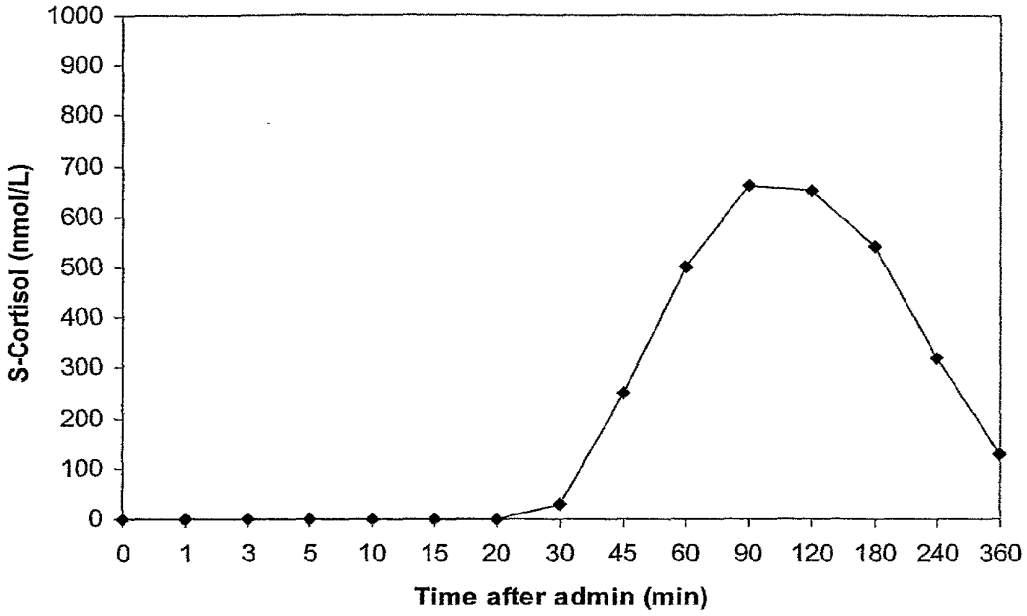


Fig. 8

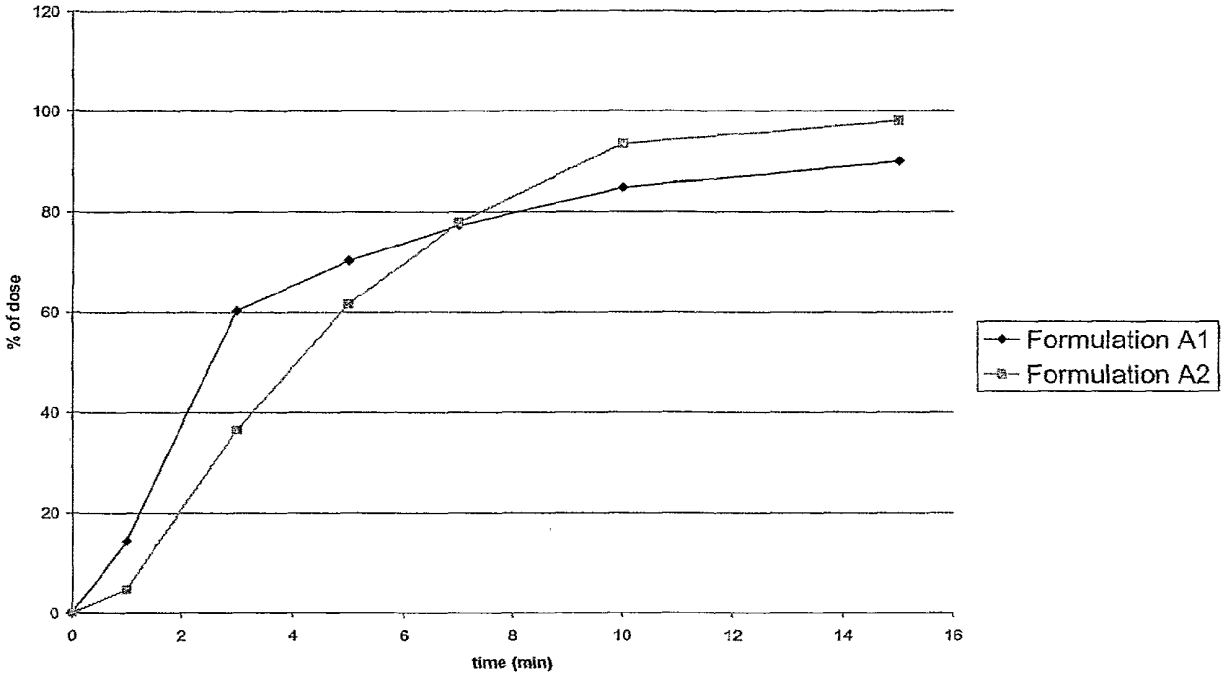


Fig. 9

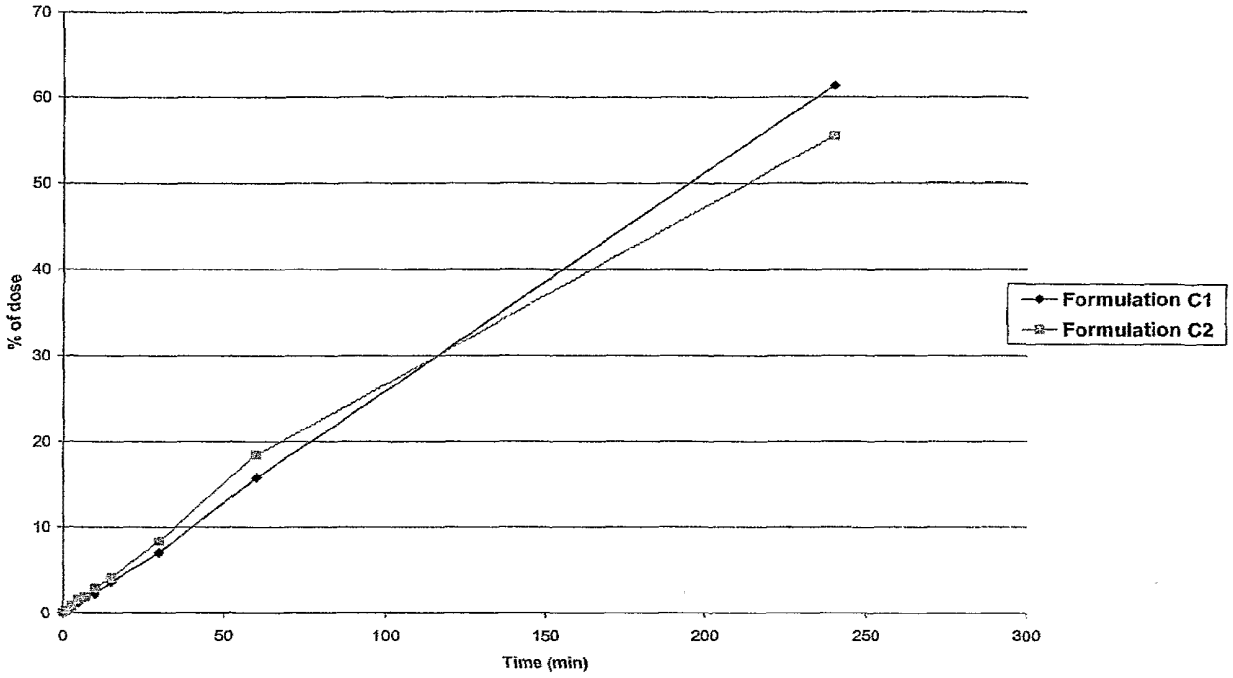


Fig. 10

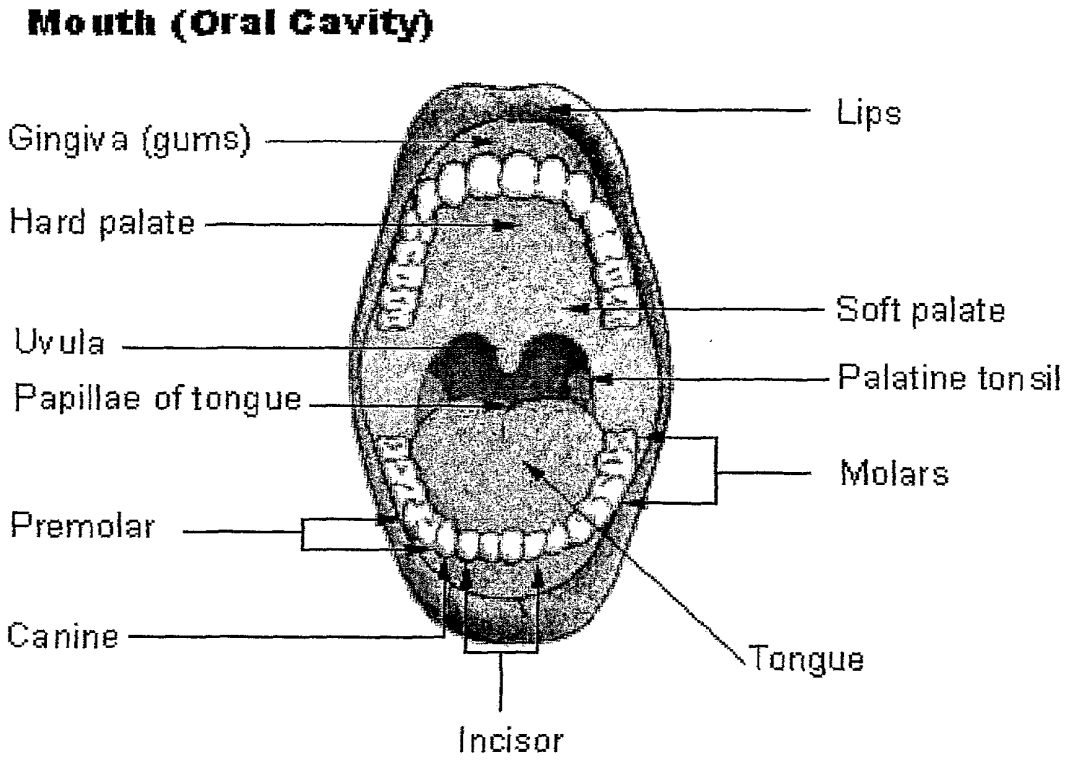
Mouth (Oral Cavity)
Gingiva (gums)
Hard palate
Uvula
Papillae of tongue
Premolar
Canine
Incisor
Lips
Soft palate
Palatine tonsil
Molars
Tongue

Fig. 11

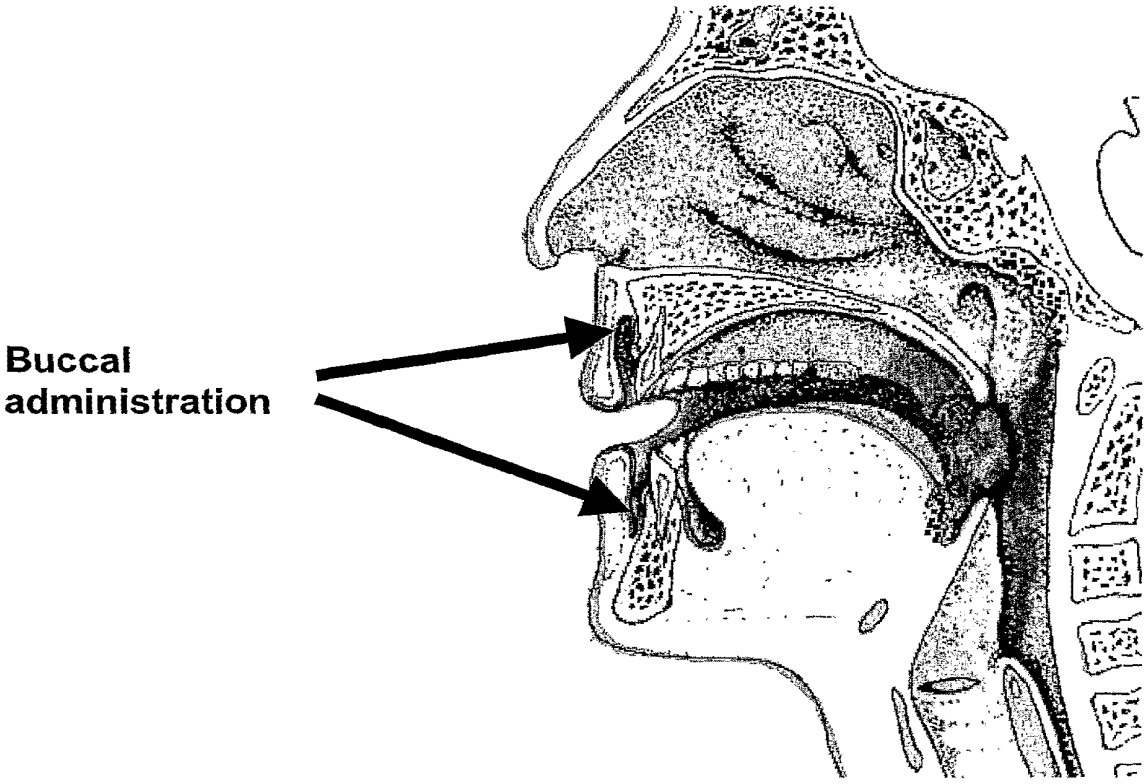


Fig. 12

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(54) **Extrudable compositions for topical or transdermal drug delivery.**

(57) An effective and convenient medicament delivery system comprising novel extrudable compositions. The preferred compositions of the invention contain a thermoplastic water-soluble polymer selected from the group consisting of hydroxypropyl cellulose and polyethylene oxide ; a water-soluble polymer derived from acrylic acid ; medicament ; and plasticizer. The compositions provide an effective medicament delivery system and are especially suitable for use with adhesive bandages.

EP 0 598 606 A1

## BACKGROUND OF THE INVENTION

This invention relates to novel extrudable compositions for the topical application of medicaments to human or animal skin and, more particularly, to bandages containing such compositions. Adhesive bandages, wound dressings, and the like containing the novel compositions of the invention provide a superior wound care system.

Creams, ointments, solutions and powders are known to be useful for the topical application of various drugs to skin. However, the application of these materials typically is non-quantitative and it is difficult for the user to control the amount of drug delivered to the area to be treated. When such materials are used in conjunction with adhesive bandages or wound dressings, they frequently detackify (that is, result in a loss of adhesion) the adhesive portion of the bandage, thereby increasing the risk of contamination. In addition, such materials are messy and inconvenient to use, frequently soiling clothing and the like.

Various wound dressings and bandages for the topical application of medicaments are also known. For example, U.S Patent No. 4,616,644, issued October 14, 1986 in the name of Saferstein et al., describes an adhesive bandage wherein a thin coating of a high molecular weight polyethylene oxide is applied to the surface of the wound release cover of the bandage to stop bleeding faster.

U.S. Patent No. 4,880,416, issued November 14, 1989 in the name of Horiuchi et al. describes a dermal bandage comprised of a film-like adhesive material that comprises vinyl acetate polymer and a polycarboxylic acid or anhydride.

In EPO Application 0297828, Charkoudian et al. describes a bandage which is coated or impregnated with a soft, waxy, low melting composition containing a medicament. In example 1 a solution of polyethylene glycol and benzocaine is coated onto a nonwoven fabric of the type used in bandages. In example 2 Charkoudian et al. further describes impregnating a non-woven fabric with a methanol solution of polyvinyl pyrrolidone (PVP), polyethylene glycol and benzocaine, and letting the methanol evaporate. The resulting composition is extremely tacky and dissolves very slowly upon contact with wound exudate. Moreover, since the compositions have melting points below 40 °C, they cannot be subject to conventional ethylene oxide sterilization techniques.

In U.S. Patent No. 4,713,243, issued December 15, 1987, Schiraldi et al. describes a bioadhesive extruded film that is useful in intra-oral drug delivery. The thin film is comprised of a bioadhesive layer consisting essentially of 40-95 % by weight hydroxypropyl cellulose, 5-60 % of a homopolymer of ethylene oxide, 0-10 % of a water insoluble polymer, and 2-10 % of a plasticizer.

From the foregoing discussion, it will be seen that various compositions and devices useful for topically applying medicaments to the skin are known. However, such compositions have not been found to be entirely suitable when used by themselves or in connection with conventional adhesive bandages. For example, many compositions interfere with a bandage's functions to absorb wound exudate and adhere to the skin. Another problem is that upon dissolution many of these materials form a thin, free-flowing fluid having little structural integrity. As a result, the medicament is dispersed too quickly and readily spreads away from the area to be treated. Yet another problem is that many compositions of the prior art are not stable at higher temperatures and humidities. This property is crucial because the compositions may be stored for lengthy periods under less than ideal warehouse conditions. In addition, they must be able to withstand rigorous sterilization procedures.

Accordingly, it is an object of the present invention to provide a method for topically or transdermally delivering a medicament which comprises applying to the skin a novel, extrudable composition which, upon contact with body fluid, releases a controlled amount of medicament to the area to be treated.

It is another object of the invention to provide an extrudable composition for delivering a medicament to the skin which can be used alone or in conjunction with sterilized and/or adhesive bandages.

It is yet another object of the invention to provide a composition which does not readily dissolve to a free-flowing fluid upon contact with body fluids.

It is a further object of the invention to provide an extruded film that is an effective and convenient medicament delivery system.

## SUMMARY OF THE INVENTION

The inventors have found that various extrudable compositions comprising:

(a) at least one thermoplastic water-soluble polymer;

(b) at least one water-soluble polymer derived from carboxylic acid;

(c) plasticizer; and

(d) at least one medicament,

can achieve the above objects and advantages.

The inventors have further found that extrudable compositions comprising, about 5-70 % by weight of (a); about 1-10 % of (b); about 10-80 % of (c); and about 0.01-10 % of (d), are particularly advantageous. In one preferred group of compositions, (a) comprises at least one polymer selected from the group consisting of hydroxypropyl cellulose and polyethylene oxide, (b) comprises at least one polymer derived from acrylic acid and (c) comprises at least one plasticizer selected from the group consisting of glycerine, propylene glycol and polyethylene glycol. The medicament comprises at least one, and preferably more, pharmaceutically acceptable therapeutic agents.

The compositions of this invention have the consistency of a non-flowing "ointment", as defined in The United States Pharmacopeia, The National Formulary (USP XXII, NF XVII), U. S. Pharmacopeial Convention, Inc., Rockville, MD, p. 1692 (1990), which is hereby incorporated by reference. After contact with body fluids, the composition dissolves into a matrix and releases the medicament, but it still possess good structural integrity.

The compositions of the invention can be placed directly on the skin as a free, extruded, single or multi-layered thin film. Alternatively, the films may be used in conjunction with a substrate like a bandage, wound dressing or blemish patch. For example, the absorbent pad material of a conventional bandage can be coated or at least partially impregnated with the composition, thereby providing a superior wound care product that rapidly delivers moisture-sensitive active ingredients to the area to be treated. Since the composition is extrudable, it can be formed into free films or coated on a substrate without the use of organic solvents.

In another preferred embodiment of the invention the novel extrudable compositions of the invention comprise:

(a) about 20-30% (by weight) of hydroxypropyl cellulose and about 0-10% of polyethylene oxide;

(b) about 1-10% by weight of a copolymer of acrylic acid and allyl sucrose;

(c) about 60-70% by weight of at least one plasticizer selected from the group consisting of glycerin and polyethylene glycol; and

(d) about 0.01-10% by weight of medicament.

The novel extrudable compositions of the present invention alleviate many of the above problems. For example, when used in connection with an adhesive bandage, they do not interfere with the bandage's absorption and adhesion functions. In addition, they may be stored for at least one week at 40 °C and 80% relative humidity without experiencing a significant weight loss (i.e., more than 10% by weight). Moreover, the compositions and their properties are not impaired by ethylene oxide sterilization at 170 °F, or E-beam or cobalt sterilization techniques. In addition, they are also sufficiently flexible so that they are comfortable to wear.

In another preferred embodiment of the invention, the extrudable compositions are used in conjunction with blemish patches to provide anti-acne medicament thereto.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing the relationship between viscosity and temperature for a typical composition of the present invention and a comparative composition.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed toward water-soluble films which rapidly dissolve in body fluids such as blood, perspiration, or wound exudate, and deliver active ingredients to a treatment site in a controlled manner.

In accordance with one embodiment of the present invention, the absorbent component of a bandage or wound dressing of known construction is coated or at least partially impregnated with the extrudable composition of the invention. Upon application to the injured area, the exudate from the wound or moisture from the skin dissolves the film, thereby converting it to a matrix having an ointment-like consistency and making the active ingredient available to treat the injury. Because of these ointment-like properties, the film is tacky and adheres to the skin.

As previously mentioned, the bandages or wound dressings which can be used in conjunction with the present invention comprise conventional adhesive or non-adhesive bandages or wound dressings of the medical or surgical type. Generally such bandages include a plastic film backing having attached thereto an absorbent pad portion. The absorbent pad material may be any of the woven or non-woven fabrics of natural or synthetic fibers heretofore employed as dressings, including for example, cotton, nylon or polyester. Suitable substrates further include woven or standard papers, and plastics. Preferred substrates include absorbent pad materials comprised of a rayon and polypropylene (10:90 weight ratio) spun bonded web, a knitted polyester fabric such as that used for DERMICEL taffeta tape manufactured by Johnson &Johnson Consumer Products,

Inc., Skillman, N.J., and a composite nonwoven fabric made of thin, breathable polyester/polyurethane laminate known as FABRELLE which is manufactured by Fabrite Industries, Woodbridge, N.J..

Suitable plastic film backings include highly plasticized polyvinyl chloride, polyurethane, polyolefins, ethylene vinyl acetate and block copolymers films such as HYTREL® copolyester ether elastomers available from E. I. DuPont, Wilmington, Delaware. These plastic films may or may not contain an adhesive, which may or may not be pressure sensitive.

Adhesive bandages further include one or more release tabs. Release tabs (such as silicone-coated release paper or other alternate materials which can be readily removed at the time of use), are applied so as to cover, in an overlaying manner, the entire adhesive side of an adhesive bandage.

In addition, each bandage can be packaged and sealed in an individual wrapper (which typically is made of glassine-paper or a similar bacterial barrier material). Each bandage is packaged before it undergoes ethylene oxide or irradiation sterilization so as to maintain sterility until the bandage is ready for use.

In another preferred embodiment of the invention, the extrudable compositions may be used in conjunction with blemish patches to treat acne. Generally such blemish patches resemble the conventional adhesive bandages described above, i.e., they comprise a plastic film or fabric backing, an absorbent pad, an adhesive, and one or more release tabs, with the extrudable composition laminated to the absorbent pad.

As an alternate configuration, the blemish patch may simply contain a layer of the extrudable composition laminated to the aforementioned absorbent pad material. The extrudable composition serves as the media for holding the anti-acne medicament as well as an adhesive for adhering the patch to the skin site. Preferably, the pad stock will have some flexibility so that it conforms to facial contours. The patch may also contain a plastic film on the side of the pad opposite to the layer of extrudable composition to control moisture vapor transmission through the patch. A thin polyurethane film will allow for high moisture vapor transmission, whereas a thin polyolefin film will result in low moisture vapor transmission through the patch. This configuration may also be used with other medicaments.

The thermoplastic, water-soluble 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 and copolymers. The term "thermoplastic" as used herein indicates that the polymers are adequately rigid at normal temperatures and under normal conditions of stress, but are capable of deformation under heat and pressure. The term "water-soluble" as used herein indicates that the thermoplastic polymers are soluble or swellable in aqueous or aqueous-based solutions. Hydroxypropyl cellulose has an added advantage; namely, it is also soluble in non-aqueous solvents like methanol.

The compositions of the invention comprise about 5-70% of thermoplastic, water-soluble polymer, preferably about 10-40%, more preferably about 10-30%, even more preferably about 20-30% and most preferably about 23-30%.

Preferably, the thermoplastic, water-soluble polymers of the invention consist essentially of hydroxypropyl cellulose and/or polyethylene oxide. Thus, the hydroxypropyl cellulose and polyethylene oxide polymers useful for this invention can be used singly or a mixture. If a mixture of hydroxypropyl cellulose and polyethylene oxide is used, preferably they are used in a ratio of between about 1:9 to about 9:1, by weight, more preferably between about 4:6 to about 4:0, even more preferably at ratio of about 4:1.

The hydroxypropyl cellulose ("HPC") useful for purposes of the present invention is commercially available from Aqualon, Inc. (Wilmington, DE) under the trade name KLUCEL®. Preferred grades include KLUCEL EF, with an average molecular weight of about 60,000 and having a viscosity of about 300-700 cps (Brookfield) in a 10 percent water solution, or KLUCEL LF, with a molecular weight of about 100,000 and having a viscosity of about 75-150 cps in a 5 percent water solution. In general, any HPC having a number average molecular weight above about 60,000 is useful for purposes of this invention.

The homopolymer of ethylene oxide useful for purposes of this invention has a number average molecular weight of between about 100,000 to 3,000,0000 or even higher. Although polyethylene oxide ("PEO") polymers having an average molecular weight of above 600,000 are useful for several embodiments of the invention, PEO having a number average molecular weight of less than about 600,000 is preferred, less than about 400,000 is more preferred, and between about 100,000 and 400,000 is even more preferred. Such polymers are commercially available from the Union Carbide Corporation under the trade name POLYOX. Preferred grades include POLYOX WSR-N-10, which has an average molecular weight of about 100,000 and POLYOX WSR-N8, which has an average molecular weight of about 200,000.

Small amounts of other (non-thermoplastic or thermoplastic) water-soluble polymers may be used as well, replacing a small portion of the water-soluble, thermoplastic polymers. Other polymers which are useful for the present invention include, for example, homopolymers and copolymers of carboxymethyl cellulose, hydroxyethyl cellulose, polyacrylamide, polyacrylic acid and its homologs, polyvinyl alcohol, polyvinyl pyrrolidone,

polyethylene amines, polymethacrylic acid, polyvinylamine, polymethacrylamide, polyvinylmethylether, and the like. Natural gums such as polysaccharides, alginates, carrageenan, guar gum, gum agar, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust bean gum, pectins, starch and its derivatives, tamarind gum, and xanthan are also useful. The gums are used to adjust the hydrophilic/hydrophobic balance of the composition, which in turn affects the solubility of the medicament in the composition.

Small amounts of polymers derived from carboxylic acids (or from pharmaceutically acceptable salts thereof) provide increased flexibility and stability to the extrudable compositions of the invention. The carboxylic acid polymers useful for the invention include any such polymer having a number average molecular weight of above about 450,000. Preferably, the compositions of the invention comprise at least one such polymer in amounts of between about 1-10% (by weight), preferably between about 3-8%, and most preferably between about 5-7%.

Homopolymers and copolymers derived from acrylic acid are preferred. Copolymers comprised mainly of acrylic acid and allylsucrose, such as those commercially available from B.F. Goodrich under the trade name CARBOPOL, are even more preferred. For example, CARBOPOL 934P, having a molecular weight of about 3,000,000 is especially preferred. Other polymers that are useful for the invention include homopolymers and copolymers derived from methyl acrylate, methacrylic acid, methyl methacrylate or hydroxyethyl methacrylate, or their amide derivatives.

Suitable pharmaceutically acceptable salts of the carboxylic acid polymers include alkali metal salts such as sodium or potassium salts and ammonium salts. The degree of neutralization of salts is not limited. The pharmaceutically acceptable salts may have any molecular weight.

Any pharmaceutically acceptable medicament or pharmaceutical agent may be delivered by the drug delivery system of the present invention. Usable medicaments include those which are capable of withstanding the heats and pressures generated in the extrusion process involved in making the films of the present invention.

Preferred medicaments include:

anesthetics and/or analgesics such as benzocaine, lidocaine, dyclonine HCl, phenol, menthol, aspirin, phenacetin, acetaminophen, ibuprofen, potassium nitrate, and the like;

anti-inflammatories such as hydrocortisone acetate, triamcinolone acetonide, glycyrrhizinate, and the like;

antihistamines such as chlorpheniramine maleate, ephedrine HCl, diphenhydramine HCl, and the like;

antibiotics such as tetracycline, doxycycline hyclate, meclocyline, minocycline, bacitracin zinc, polymyxin B sulfate, neomycin sulfate, and the like;

fungistats such as nystatin, miconazole, ketoconazole, and the like;

anti-acne agents like salicylic acid; and

antiseptics such as benzylalkonium chloride; iodine, silver solfidiazine, chlorohexidine and salts thereof, cetylpyridinium chloride, and the like.

Medicaments that are not capable of withstanding the heats and pressure generated in the extrusion process are also of use in the present invention. Such medicaments can be applied to the extruded compositions using techniques that are well-known to those skilled in the art. For example, such medicaments may be dissolved in a solvent and coated onto the extruded compositions or films. As the solvent evaporates, it leaves behind the medicament. Anti-acne medicaments like retinoic acid and benzoyl peroxide can be utilized in the present invention in this manner.

The medicament should be added in a pharmaceutically effective amount, i.e., an amount sufficient to prevent, cure or treat a disease to which the pharmaceutical preparation of this invention is to be applied. The compositions of the invention typically comprise at least one medicament, and preferably more than one, in amounts ranging from between about 0.01 to 10%, by weight.

Plasticizers useful for purposes of the present invention include block copolymers of polyethyleneoxide and polypropyleneoxide such as PLURONIC® F 127 and TETRONIC® 1302; 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 MYVEROL®; mineral oils; vegetable oils such as castor oil, and the like. These plasticizers may be used singly or in any combination.

The purpose of the plasticizer is several fold; namely, to improve polymer melt processing by reducing polymer viscosity, to increase adhesion to the skin, to increase the dissolution rate in body fluids, and/or to impart flexibility to the final product. In addition, the plasticizer can impart "ointment-like" characteristics to the final product as defined by U.S.P. "Hydrophilic Ointments or Gels."

Compositions of the invention comprise between about 10-80% (by weight) of plasticizer, preferably between about 30-80%, more preferably between about 30-70%, and most preferably between about 60-70%.

Preferred plasticizers include propylene glycol or polyethylene glycol (PEG) polymers having a number

average molecular weight of from about 200 to 20,000. Although PEG polymers having higher average molecular weights are useful in the present invention, such polymers having an average molecular weight between 200 to 3500 are preferred. More preferred are PEG polymers having an average molecular weight of between 200 and 1500, such as CARBOWAX 600 (available from Union Carbide Corporation), which has an average molecular weight of about 600. Glycerin (especially Grade 916 USP, available from Emory), is also preferred plasticizer.

In one preferred embodiment of the invention, the extrudable compositions comprise, and preferably consist essentially of:

a. thermoplastic water-soluble polymer;

b. a water-soluble polymer derived from a carboxylic acid or a pharmaceutically acceptable salt thereof;

c. plasticizer; and

d. medicament.

The inventors have found that the advantages attained by the novel compositions are due to the unique formulations described herein.

Preferably the compositions of this embodiment comprise about 5-70% of (a), about 1-10% of (b), about 10-80% of (c), and about 0.01-10% of (d), by weight. More preferably, they comprise about 10-40% of (a), about 1-10 % of (b), about 30-80% of (c), and about 0.01-10% of (d). Even more preferably, they comprise about 20-30% of (a), about 3-8% of (b), about 30-70% of (c), and about 0.01-10% of (d). Most preferably, the compositions comprise about 23-30% of (a), about 5-7% of (b), about 60-70% of (c), and about 0.01-10% of (d).

In accordance with the teachings above and in another preferred embodiment, the extrudable compositions of the invention comprise about 10-30% of (a), about 1-10% (b), about 60-70% of (c), and about 0.01-10% of (d), by weight.

In yet another embodiment, the compositions of the invention comprise about 20-30% hydroxypropyl cellulose and about 0-10% polyethylene oxide, about 1-10% of a copolymer derived from acrylic acid and allyl sucrose, about 0.01-10% of said medicament, and about 60-70% of glycerin; by weight. Even more preferably, they comprise about 22-29% hydroxypropyl cellulose and about 4-7% polyethylene oxide, about 5-7% of said copolymer, about 0.01-10% of said medicament, and about 60-70% glycerin; by weight.

In yet another embodiment which has been found to be particularly suitable for blemish patches, the extrudable compositions of the invention comprise about 22-27% hydroxypropyl cellulose, about 5-7% of said acrylic acidallyl sucrose copolymer, about 0.01-10% medicament, and about 60-70% glycerin; by weight. Alternatively, such a composition may comprise about 10-15% hydroxypropyl cellulose and 15-20% polyethylene oxide, about 5-7% of said acrylic acid-allyl sucrose copolymer, about 0.01-10% medicament, and about 30-40% of glycerin and 30-40% polyethylene glycol; by weight.

The inventors have further found that for certain applications that are especially suitable for use with adhesive bandages, the carboxylic acid polymer may be left out of the extrudable composition altogether. In practicing this embodiment of the invention the extrudable composition comprises polyethylene oxide, plasticizer and medicament.

Preferably, the extrudable compositions of this embodiment comprise about 15-80% of polyethylene oxide and about 20-85% of plasticizer, by weight. More preferably they comprise about 25-70% of polyethylene oxide and about 30-75% of plasticizer, by weight. Even more preferably they comprise about 35-60% of polyethylene oxide and about 40-65% of plasticizer, by weight. Of course, about 0-10% (preferably 0.01-10%), by weight, of a medicament can replace the equivalent amount of any of the above ingredients. The preferred plasticizer for use in this composition is polyethylene glycol.

The extrudable compositions of the invention may be prepared by mixing the above ingredients in a variety of ways well-known to those skilled in the art. For example, the preweighed ingredients can be added to an intensive mixer such as a Brabender Prep Center or a Baker Perkins Blender and mixed at 80-95 °C, with or without solvent. Thus, the compositions can be prepared as hot melts. Alternatively, aqueous solvents or alcohols (like methanol) can be used.

The resultant blend can be cast at elevated temperatures, at say, about 50 to 140°C. Alternatively, the blend can be extruded using a single or twin extruder, or pelletized. If extruded, film thicknesses may vary from "thin" films of about 1.0 mil to "thick" films of about 20 mils or greater, the thickness depending on the intended use of the product. The film can also be extrusion coated onto a variety of substrates as discussed above and then subjected to heat and pressure to form a laminate. Temperatures on the order of 21°-130°C and contact pressures of up to 40 pounds per linear inch are suitable for forming the laminate. Additional films or insoluble ingredients, such as a water-insoluble medicaments, may be coated or laminated onto the resultant product.

When used in connection with an absorbent pad, the compositions of the invention may be at least partially impregnated into the absorbent pad using any technique well-known to those skilled in the art. Alternatively,

the film or composition can be applied adjacent to the body facing surface of the absorbent pad by the use of elevated temperatures and pressures. In the latter embodiment, the film or composition is distinct or discernable from the underlying absorbent pad.

Moisture sensitive or water-insoluble active ingredients also can be blended into the compositions of the invention without degradation or separation from the solid components, since the remaining components of the extrudable composition are frequently soluble in aqueous and non-aqueous solvents and are also useable as hot melts.

In addition to the polymers and plasticizers, minor amounts of other non-essential but customary ingredients will often be used if desired, e.g., antioxidants, foamers, neutralizing agents, stabilizing agents, fillers, preservatives, flavors, and colorants. For example, the extrudable composition can be modified to impart more or less tack contain a color, or to produce a scent to heighten the sensory cue to the user that the product is working. Another modification includes adding fumed silica to improve absorption and stability of the compositions. The fumed silica is generally added in an amount ranging from about 0.01 to about 5% by weight of the total composition. As another example, sodium bicarbonate and/or citric acid can be added to the compositions to enable them to foam upon contact with moisture. The pH of the extrudable composition is also generally controlled within the range of about 3 to 8.

This invention will now be illustrated in greater detail by reference to the following examples, but it should be understood that they are not intended to limit the present invention. In these examples, all the parts, percents and ratios are by weight unless otherwise indicated.

**EXAMPLE 1**

An ointment film was formed by adding 100 gms of polyethylene oxide (POLYOX N-10) to 200 gms of polyethylene glycol (CARBOWAX 600) in a Brabender heated at 80 °C. The components were blended for five minutes to fully plasticize the polyethylene oxide. Then, 26 gms of copolymer of acrylic acid and allyl sucrose (CARBOPOL 934P), was slowly added to the blend and mixed for an additional 30 minutes. The resultant ointment was extrusion coated onto unitized pad stock to form a flexible, aesthetically pleasing film.

**EXAMPLE 2**

Various antibiotics and antiseptics were added to the composition of Example 1 at the concentrations shown below. The resulting compositions were then coated onto pad stock to form a film layer.

| Sample | Antibiotic/Antiseptic | Concentration |
|---|---|---|
| A | Bacitracin Zinc[1] | 500 units/gm |
| | Neomycin Sulfate[2] | 3.5 mg/mg |
| | Polymyxin B Sulfate[3] | 10,000 units/gm |
| B | Neomycin Sulfate[2] | 3.5 mg/mg |
| | Polymyxin B Sulfate[3] | 10,000 units/gm |
| C | Benzalkonium Chloride | 0.13 (% w/w) |

[1]Activity = 71000 U/gm
[2]Activity = 0.7 gm/gm
[3]Activity = 7700 U/gm

Samples A, B and C were not sterilized.
Additional samples were prepared as follows:
Sample D = Sample A ethylene oxide sterilized at 165°F (with moisture).

Sample E = The film sample of Example 1 without antibiotics/antiseptics or sterilization.

Sample F = NEOSPORIN Maximum Strength Ointment (Burroughs-Welcome Co.) coated onto filter paper.

Sample G = Untreated filter paper.

Sample A-G were then tested to determine their antimicrobial activity using the zone of inhibition method. Agar base layers were poured into petri dishes and allowed to solidify. The base layers were then covered with a seeded (inoculated) agar layer. The seeded agar layer contained three test microorganisms Staphylococcus epidermidis, Micrococcus luteus and Bordetella bronchiseptica (evaluated separately) as recommended in the USP Pharmacopeia XXII for testing neomycin, bacitracin and polymyxin, respectively.

Pieces of each of the Samples (8 sq. mm) were placed active side down on each seeded agar plate (6 squares were evaluated per test organism). The samples were incubated at 35°C for 18 hours. The clear zones of inhibition were measured and are reported below as the average of the six zones:

| Clear Zone in Millimeters | | | |
|---|---|---|---|
| Sample | M. luteus | S. epidermidis | B. bronchiseptica |
| A | 11.7 | 11.0 | 11.7 |
| B | 0.0 | 11.2 | 11.7 |
| C | 17.2 | 16.0 | 4.0 |
| D | 5.8 | 10.5 | 10.7 |
| E | 0.0 | 0.0 | 0.0 |
| F | 10.5 | 14.2 | 7.5 |
| G | 0.0 | 0.0 | 0.0 |

The above results demonstrate that the compositions of the present invention (Samples A-D) exhibit good antimicrobial activity.

**EXAMPLE 3**

Approximately 0.5% (by weight) of fumed silica (CABOSIL M-5) was added to the composition of Example 1. The fumed silica is added to moisture-sensitive active-containing films to absorb moisture and improve the stability of the films.

**EXAMPLE 4**

Approximately 100 gms of sodium bicarbonate and 50 gms of citric acid were added to the ointment blend of Example 1 (after the addition of the copolymer of acrylic acid and ally sucrose) and the blend was mixed for an additional 10 minutes. The resulting film foamed effervescently upon contact with water.

**EXAMPLE 5**

**Blemish Patch**

Two extrudable compositions were prepared. Both vehicles were anhydrous, hydrophilic blends made from the following raw materials:

| | Low Tack Vehicle | High Tack Vehicle |
|---|---|---|
| Acrylic Acid - Ally Sucrose Copolymer (CARBOPOL 934P) | 5.6% | 6.2% |
| Polyethylene Glycol (CARBOWAX 600) | 32.3% | 0 |
| GLYCERIN (USP 99.5%) | 32.3% | 67.0% |
| Hydroxypropyl Cellulose (KLUCEL EF) | 11.1% | 24.8% |
| Polyethylene Oxide (POLYOX N-10) | 16.7% | 0 |
| Salicyclic Acid | 2.0% | 2.0% |

Mixing was performed in a Baker-Perkins Blender at a screw speed of 30 RPM, blade speed of 36 RPM, at 80 °C for about 30 minutes. The polyethylene glycol and/or glycerin were premixed and then added to the mixing bowl of the blender. The hydroxypropyl cellulose, acrylic acid-allyl sucrose, copolymer and polyethylene oxide (low tack only) were also premixed in a "V" blender for about three and a half minutes. After approximately two-three minutes, the premixed powders were added at once to the mixing bowl. The viscosity of the blend quickly increased and began generating sheer force. The blend was masticated for about twenty-five minutes and then salicylic acid was added.

**Pelletizing the Ointment**

After mixing for about thirty minutes (total mixing time), the blend was extruded as a rod directly into the pelletizer. (Prior to reaching the pelletizer, a cooling stage may be added to ensure a solidified ointment.) The pellets had a diameter of approximately 1/4" or less.

**Extruding the Ointment**

A Killian extruder was used for extrusion. Initial settings were as follows:

| ZONE 1 | ZONE 2 | ZONE 3 | ZONE 4 | DIE |
|---|---|---|---|---|
| 150 °F | 160 °F | 175 °F | 180 °F | 200 °F |

| SCREW SPEED | LINE SPEED |
|---|---|
| 50 RPM | 21 FT/MIN |

The extruded film was laminated to two substrates; clear unitized pad stock used in BAND-AID® brand adhesive bandages and flexible fabric. (The roll may require a silicone release sheet as a carrier paper.) No finishing was required.

**EXAMPLE 6**

**Rheological Data**

Figure 1 is a graph showing the relationship between viscosity and temperature of a composition of the present invention (Composition A) and a composition from EP Application No. 0297828 to Charkondian et al. (Composition B). The viscosity is reported in poises.

Composition A was prepared and then extruded into a film. Composition B was prepared in accordance with Example 2 of EP Application No. 0297828, except that benzocaine was omitted, and the viscosity was measured after the methanol solvent was removed.

**Composition A (weight %)**

Acrylic Acid-Allyl Sucrose Copolymer - 6.42%
(CARBOPOL 934P)
Hydroxypropyl Cellulose - 25.7%
(KLUCEL EF NF)
Glycerine - 65.78%
Potassium Hydroxide (dry) - 2.0%
Fumed Silica (CABOSIL M-5) - 0.1%
Dye - trace amount

**Composition B**

Polyvinylpyrrolidone - 40 gms.
Polyethylene Glycol 400 - 60 gms.
Methanol - 125 ml.

The viscosity of Compositions A and B was measured on a Rheometrics RDS-7700 parallel plate rheometer at 10 rad./sec. The resulting data is shown on Figure 1. Since the composition of the present invention is more viscous, it will be more resistant to flow than the composition of EP Appln. No. 0297828. This is an important property of the composition of the present invention, since it is not desirable to have the film and resulting medicament flow from the bandage or the traumatized area of the skin to which it is applied.

**EXAMPLE 7**

An additional extrudable composition suitable for use in a blemish pad was prepared using procedures similar to those described in Example 5. The composition contained (weight%) :

Glycerine - 53%
Acrylic Acid - Ally Sucrose Copolymer
(CARBOPOL 934P) - 6%
Hydroxypropyl Cellulose
(KLUCEL EF NF) - 26%
Fumed Silica (CARBOSIL M-5) - 1%
Salicylic Acid - 2%
Na-Ca Salt of Polyvinyl Menthyl Ether
Maleic Anhydride (GANTREZ MS-955) - 12%

**EXAMPLE 8**

A composition was prepared by blending 28% polyethylene oxide (POLYOX N-80) (having an average molecular weight of about 200,000) with 72% polyethylene glycol (CARBOWAX 600), in a Brabender mixer for one hour at 80 °C. The blend was coated onto release paper and laminated at 60 °C onto unitized pad stock. The resultant films had thicknesses of between 1 to 3 ounces/yd$^2$. The films did not interfere with the conventional absorption of the pad stock, and did not flake or peel.

**EXAMPLE 9**

Blends of polyethylene glycol (PEG) (number average molecular weight of between 200-1450) and polyethylene oxide (PEO) (number average molecular weight of approximately 100,000) having the proportions shown below were prepared and laminated onto unitized pad stock using procedures similar to those described in Example 8.

| Sample | PEG | PEO (% w/w) |
|---|---|---|
| A | 51 | 49 |
| B | 62.5 | 37.5 |
| C | 25 | 75 |
| D | 83.3 | 16.7 |
| E | 5 | 95 |
| F | 86 | 14 |

The films were evaluated for their flexibility, dissolution rate and stability at elevated temperatures and humidity. Samples A and B were preferred because they exhibited good flexibility and dissolution rates. Samples C and D had acceptable properties, and Samples E and F were found to have unacceptable properties.

**EXAMPLE 10**

When the medicament is heat or pressure sensitive, composition of the invention can be blended without medicament, and extrusion coated onto a substrate. Then, the medicament can be deposited onto the film using any technique well-known to those skilled in the art. The following is an example of this technique.

Layer 1 have the composition shown below was blended and extrusion coated onto flexible fabric using procedures similar to those described in Example 5.

| **Layer 1** | **wt %** |
|---|---|
| Acrylic Acid - Allyl Sucrose Copolymer (CARBOPOL 934P) | 6.5 |
| Glycerin (Emory 916 USP) | 54.5 |
| Hydroxypropyl Cellulose (KLUCEL JF EF) | 26.0 |
| Fumed Silica (Cabosil M-5) | 1.0 |
| Na-Ca Salt of a Copolymer of Polyvinyl Menthyl Ether and Maleic Anhydride (GANTREZ MS-955) | 12.0 |

A solution of benzoyl peroxide was prepared by mixing the composition shown below with an equal amount (by weight) of acetone. This solution was then coated onto Layer 1. Layer 2 was dried and the acetone was allowed to evaporate, which resulted in a tacky benzoyl peroxide-containing layer laminated to Layer 1. The resulting structure is suitable for use as a blemish patch.

| Layer 2 | wt % |
|---|---|
| Benzoyl Peroxide | 10.0 |
| Dimethylaminoethyl Methacrylate | 65.0 |
| Triacetine | 25.0 |

Additional solvents may be added to enhance solubility. However, any solvent used must have a low boiling point and high vapor pressure to ensure that critically high temperatures are not reached during the drying step.

**EXAMPLE 11**

Examples of Multilayered Films

A single-layered film containing the medicament "A" is made in accordance with the present invention, and is extruded onto a substrate. A second extruded film containing medicament "B" is then extruded onto the first layer. Thus, the "B-containing" film is in contact with the skin and "B" is the first medicament that comes in contact with the inflamed skin or wound. For example, the B-containing film may contain lidocaine for pain relief and the A-containing film may contain hydrocortisone for reducing inflammation. Additional film laminates containing many separate drug layers and different medication strategies can be constructed.

Diffusion of the "bioactive-type" drugs typically occurs at skin temperature, e.g., 33 to 35 °C. In order to minimize transfer or co-mingling of drugs between separate film layers, the compositions can be stored under cold conditions (say, for example, at approximately 4 °C) and brought to room temperature when needed.

Various modifications can be made to the above-described embodiment without departing from the spirit and scope of the present invention.

## Claims

1. A composition comprising:
   a. thermoplastic water-soluble polymer;
   b. a water-soluble polymer derived from a carboxylic acid or a pharmaceutically acceptable salt thereof; and
   c. plasticizer.

2. The composition of claim 1 further comprising:
   d. medicament.

3. The composition of claim 2 comprising about 5-70% of (a), about 1-10% of (b), about 10-80% of (c), and about 0.01-10% of (d), by weight.

4. The composition of claim 2 comprising about 10-40% of (a), about 1-10% of (b), about 30-80% of (c), and about 0.01-10% of (d), by weight.

5. The composition of claim 2 comprising about 23-30% of (a), about 5-7% of (b), about 60-70% of (c), and about 0.01-10% of (d), by weight.

6. The composition of claim 2 wherein (a) comprises at least one polymer selected from the group consisting of hydroxypropyl cellulose and polyethylene oxide.

7. The composition of claim 6 wherein said polyethylene oxide has a number average molecular weight of greater than about 600,000.

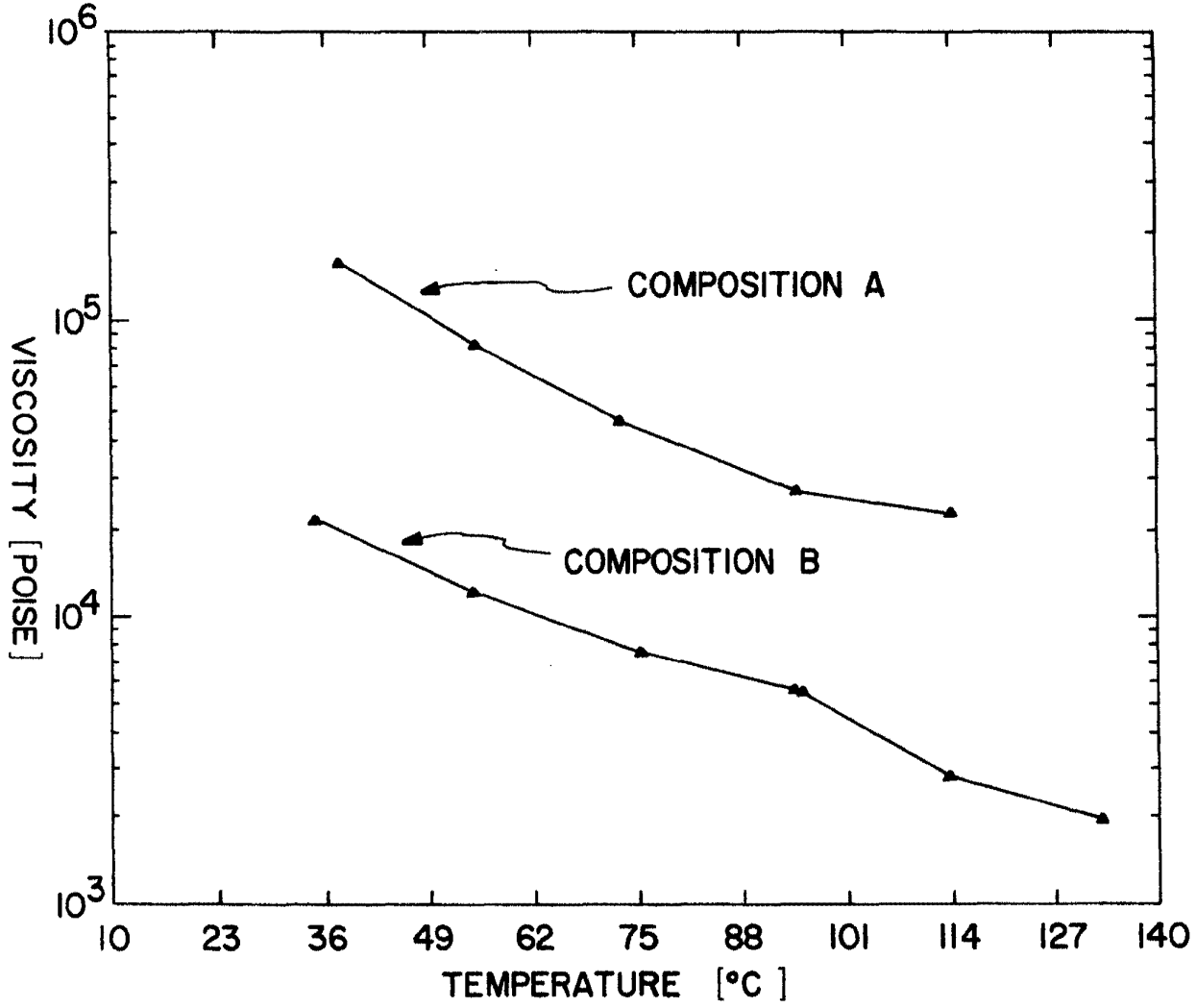
8. The composition of claim 6 wherein said polyethylene oxide has a number average molecular weight of less than about 600,000.

9. The composition of claim 6 wherein said polyethylene oxide has a number average molecular weight of

between about 100,000 and 400,000.

**10.** The composition of claim 6 wherein said hydroxypropyl cellulose has a number average molecular weight greater than about 60,000.

FIG.1



European Patent Office

# EUROPEAN SEARCH REPORT

Application Number
EP 93 30 9172

## 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.5) |
|---|---|---|---|
| X | WO-A-91 05574 (MEDIPRO SCIENCES LIMITED)<br>* examples * | 1 | A61L25/00 |
| D,Y | US-E-RE33093 (MICHAEL T. SCHIRALDEI ET AL.)<br>& US-A-4 713 243 (MICHAEL T. SCHIRALDI ET AL.) | 1-10 | |
| P,Y | EP-A-0 551 626 (LEK)<br>* claims * | 1-10 | |
| A | EP-A-0 386 960 (AMERICAN CYANAMID COMPANY)<br>* claims * | 1 | |
| A | US-A-4 303 066 (MARK J. D'ANDREA)<br>* abstract * | 1 | |

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

A61L

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 10 February 1994 | ESPINOSA, M |

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

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## (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.

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## 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) |
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| 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
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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## ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 31 1610

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(54) **Title:** THIN FILM WITH NON-SELF-AGGREGATING UNIFORM HETEROGENEITY, PROCESS FOR THEIR PRODUCTION AND DRUG DELIVERY SYSTEMS MADE THEREFORM

(57) **Abstract:** The invention relates to the film products and methods of their preparation that demonstrate a non-self-aggregating uniform heterogeneity. Desirably, the films disintegrate in water and may be formed by controlled drying process, or other process that maintains the required uniformity of the film. Desirably, the films contain a pharmaceutical and/or cosmetic active agent with no more than a 10% variance of the active agent pharmaceutical and/or cosmetic active agent per unit area of the film.

WO 03/030882 A1

# THIN FILM WITH NON-SELF-AGGREGATING UNIFORM HETEROGENEITY, PROCESS FOR THEIR PRODUCTION AND DRUG DELIVERY SYSTEMS MADE THEREFROM

## FIELD OF THE INVENTION

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

## BACKGROUND OF THE RELATED TECHNOLOGY

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

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

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. 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.

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

The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present.

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

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.

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

Conventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like. The difficulty in achieving a uniform film is directly

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

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

Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films. Desirably, such films are produced through a selection of a polymer or combination of polymers that will provide a desired viscosity, a film-forming process such as reverse roll coating, and a controlled, and desirably rapid, drying process which serves to maintain the uniform distribution of non-self-

aggregated components without the necessary addition of gel formers or polyhydric alcohols and the like which appear to be required in the products and for the processes of prior patents, such as the aforementioned Horstmann and Zerbe patents. Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product.

## SUMMARY OF THE INVENTION

In one aspect of the present invention, there is provided a film and a method of forming same which 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. 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 amount of drug. Pharmaceutical film dosage forms to date have not been marketed largely due to the inability to achieve this result.

In a further aspect of the present invention, there is provided a film product that is formed by combining a polymer and a polar solvent, forming the combination into a film, and drying the film in a controlled manner, desirably by 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 tops of the films. Once the visco-elastic properties of the film are such that the film components are "locked" in place and cannot move to cause non-uniformity, other methods of heating may then be employed. The polar solvent 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 is one particularly useful coating technique may also be used to form the film.

In another aspect of the invention, there is a process for preparing a film with a substantially uniform distribution of components. The process includes the steps of combining a polymer component and water to form a uniformly distributed matrix. This matrix is then formed into a film and fed onto the top side of a substrate surface having top and bottom sides. Heat is applied to the bottom side of the substrate surface in order to dry the film. The matrix from which the film is formed may also include an active ingredient. Also, either alternatively, or in addition to the particular method used to dry the film, the polymer may be selected in order to provide a viscosity that maintains the non-self-aggregating uniform heterogeneity. Reverse roll coating technique may also be used to form the film.

A further aspect of the present invention is a method of orally administering an active including the steps of:

(a) preparing a film by the steps of:
  (i) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
  (ii) forming the material into a film; and
  (iii) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity; and
(b) introducing the film to the oral cavity of a mammal.

An even further aspect of the present invention is method of introducing an active component to liquid including the steps of:

(a) preparing a film by the steps of:
  (i) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
  (ii) forming the material into a film; and
  (iii) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity; and
(b) placing the film into a liquid; and
(c) allowing the film to dissolve.

A still further aspect of the present invention provides a dosage form for the administration of an active including:

(a) a first layer including a film formed by the steps of:
  (i) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
  (ii) forming said material into a film; and
  (iii) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity; and
(b) a substantially non-water soluble second layer.

Another aspect of the present invention provides a method of preparing a dosage form for the administration of an active including the steps of:

(a) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
(b) forming the material into a film;
(c) applying the film to a substantially non-water soluble support; and
(d) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity.

In still another aspect of the present invention there is provided another method of administering an active including the steps of:

(a) preparing dosage form by the steps of:
  (i) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
  (ii) forming the material into a film;
  (iii) applying the film to a substantially non-water soluble support; and
  (iv) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity;
(b) removing the film from said support; and
(c) applying the film to the oral cavity of a mammal.

Another aspect of the invention provides a film product formed by the steps of:

(a) combining a polymer and a liquid carrier to form a material with a non-self-aggregating uniform heterogeneity;

(b) forming said material into a film; and

(c) removing said liquid carrier, for example, by evaporative methods or by permitting volatilization to occur at selected temperatures, from said film in a manner to maintain said non-self-aggregating uniform heterogeneity.

Also provided is a process for making a film having a substantially uniform distribution of components including:

(a) combining a polymer component and liquid carrier to form a matrix with a uniform distribution of said components;

(b) forming a film from said matrix; and

(c) removing said liquid carrier, for example, by evaporative methods or by permitting volatilization to occur at selected temperatures, from said film in a manner to maintain said uniform distribution.

A still further aspect of the present invention provides process for making a film having a substantially uniform distribution of components including:

(a) combining a polymer component and a polar solvent to form a matrix with a uniform distribution of said components, said polymer selected to provide a viscosity sufficient to maintain said uniform distribution; and

(b) forming a film from said matrix.

The invention also includes films and a process for preparing films having a substantially uniform distribution of components. The process includes the steps of combining a polymer component and water to form a uniformly distributed matrix. This matrix is then formed into a film and fed onto a substrate surface having top and bottom sides where the bottom side is in substantially uniform contact with a bottom drying medium, such as a water bath or heated air space controlled at a temperature sufficient to dry the film. Desirably, no external air currents or heat is applied directly to the exposed top surface of the film during the drying process until the film structure has solidified sufficiently to prevent flow, migration and intermolecular attractive forces from creating aggregates or conglomerates. Desirably the heat is controllably conducted by the substrate surface to the

film to effectuate drying. The matrix from which the film is formed may also include an active ingredient. Also, either alternatively, or in addition to rapidly drying the film, the polymer may be selected in order to provide a viscosity that maintains the non-self-aggregating uniform heterogeneity.

A pharmaceutical and/or cosmetic dosage form is also provided that includes a film having a uniformly dispersed composition including a polymer, a pharmaceutical and/or cosmetic active and a solvent, said film being formed by depositing a wet film of said composition onto a substrate surface and controllably drying the wet film from the side contacting the substrate to prevent self-aggregation and achieve compositional uniformity.

A still further aspect of the present invention includes a pharmaceutical and/or cosmetic dosage form including a polymeric film having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area.

The present invention also provides a pharmaceutical composition in the form of a film for external or topical administration, including a composition having a uniformly distributed combination of a polymer, a polar solvent, and a pharmaceutical active, said composition in its dried film form maintaining the uniform distribution of components through the application of controlled bottom drying of the film.

A pharmaceutical dispenser is also provided that includes individual unit dosage forms of the pharmaceutical compositions and films of the present invention. The dosage forms may be optionally stacked in a dispenser or in a roll.

Yet another aspect of the present invention provides an ingestible water-soluble delivery system in the form of a film composition that includes a water-soluble polymer and an anti-foaming or defoaming agent, such as simethicone, which includes a combination of a polymethylsiloxane and silicon dioxide. Simethicone can act as either an anti-foaming or defoaming agent, or both, which reduces or eliminates air from the film composition. An anti-foaming agent will aid in preventing the introduction of air into a composition, while a defoaming agent will aid in removing air from the composition. The composition may also include a pharmaceutical and/or cosmetic active ingredient, flavors, sweeteners, plasticizers, surfactants, or other ingredients to alter the film properties to produce the desired product.

## BRIEF DESCRIPTION OF THE DRAWINGS

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

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.

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

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.

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

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.

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

## DETAILED DESCRIPTION OF THE INVENTION

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

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

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

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. 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).

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.

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

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

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

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as

drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate ($\rho_p$) and the liquid phase ($\rho_l$) and increase the viscosity of the liquid phase ($\mu$). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

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

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

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

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

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

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

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

where $\mu_o$ is the viscosity of the continuous phase and $\phi$ 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.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle

sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size, and volume fraction. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., <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.

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

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt%, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate

range. During mixing, pumping, and film casting, shear rates in the range of $10 - 10^5$ sec.$^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

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

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

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

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

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

A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch pre-mix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a 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.

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.

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

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film 48 as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical

aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, 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.

Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film 42 prior to the drying of the film 42. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, 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.

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

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus 50 is depicted in 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.

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

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent

content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most desirably less than about 2%. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

**Film-Forming Polymers**

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

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

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

Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, 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).

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

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

The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

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