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571-272-7822

Paper No. 12
Entered: December 19, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIODELIVERY SCIENCES INTERNATIONAL, INC.,
Petitioner,

v.

RB PHARMACEUTICALS LIMITED,
Patent Owner.

Case IPR2014-00998
Patent 8,475,832 B2

Before TONI R. SCHEINER, JACQUELINE WRIGHT BONILLA, and ZHENYU YANG, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
and Dismissing Motion for Joinder
37 C.F.R. §§ 42.108, 42.122

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INTRODUCTION

BioDelivery Sciences International, Inc. ("Petitioner") petitioned for an *inter partes* review of claims 15–19 of U.S. Patent No. 8,475,832 B2 (Ex. 1001, "the '832 patent"). Paper 2 ("Pet."). Petitioner also sought to join this proceeding with IPR2014-00325, an *inter partes* review of the same challenged claims currently pending before the Board. Paper 6. RB Pharmaceuticals Limited ("Patent Owner") timely filed a Preliminary Response. Paper 9 ("Prelim. Resp."). In addition, Patent Owner filed an Opposition to Petitioner's Motion for Joinder. Paper 10. We have jurisdiction under 35 U.S.C. § 314.

For the reasons provided below, we exercise our discretion and deny the Petition under 35 U.S.C. § 325(d). Because we do not institute an *inter partes* review, we dismiss as moot the Motion for Joinder under 35 U.S.C. § 315(c).

Related Proceedings

Parties state that Patent Owner previously asserted the '832 patent against Petitioner in *Reckitt Benckiser Pharmaceuticals, Inc., v. BioDelivery Sciences International, Inc.*, No. 5:13-cv-760 (E.D.N.C.). *See* Pet. 3; Paper 5, 3. The case was later dismissed without prejudice as premature on procedural grounds. *See* Pet. 3; Paper 5, 3.

According to Patent Owner, Petitioner filed *BioDelivery Sciences International, Inc. v. Reckitt Benckiser Pharmaceuticals, Inc.*, No. 14-cv-529

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(E.D.N.C.), seeking a declaratory judgment of invalidity of the '832 patent claims.[1] Prelim. Resp. 1–2.

Petitioner previously petitioned for review of, and the Board instituted trial on, the same challenged claims of the '832 patent in IPR2014-00325 ("the '325 IPR"), currently pending before the Board.

The '832 Patent

The '832 patent relates to compositions and methods for treating narcotic dependence using an orally dissolvable film comprising buprenorphine and naloxone, where the film provides a bioequivalent effect to Suboxone®. Ex. 1001, 4:55–58.

Suboxone® is an orally dissolvable tablet of buprenorphine and naloxone. *Id.* at 4:51–55. Buprenorphine provides an effect of satisfying the body's urge for narcotics, but not the "high" associated with misuse. *Id.* at 1:36–40. Naloxone reduces the effect and, thus, decreases the likelihood of diversion and abuse of buprenorphine. *Id.* at 1:46–52. The tablet form, however, still has the potential for abuse because it can be removed easily from the mouth for later extraction and injection of buprenorphine. *Id.* at 1:55–62. The film of the '832 patent "provides buccal adhesion while it is in the user's mouth, rendering it difficult to remove after placement." *Id.* at 4:58–60.

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[1] Patent Owner does not specify when Petitioner filed the declaratory judgment action in the district court. We observe that, despite pointing to the district court case, Patent Owner does not challenge Petitioner's standing in this proceeding as barred under 35 U.S.C. § 315(a)(1).

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The '832 patent teaches controlling the local pH to maximize the absorption of the buprenorphine while simultaneously minimizing the absorption of the naloxone. *Id.* at 11:28–30. According to the '832 patent, "it has been surprisingly discovered" that, at a local pH level from about 2 to about 4, and most desirably from 3 to 4, the film composition of the invention achieves bioequivalence to the Suboxone® tablet. *Id.* at 11:50–61.

The '832 patent defines bioequivalent as "obtaining 80% to 125% of the Cmax and AUC values for a given active in a different product." *Id.* at 3:48–50. According to the '832 patent, "Cmax refers to the mean maximum plasma concentration after administration of the composition to a human subject;" and "AUC refers to the mean area under the plasma concentration-time curve value after administration of the compositions ." *Id.* at 3:9–14. The '832 patent discloses:

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

Id. at 17:41–47.

Illustrative Claim

Among the challenged claims, claim 15 is the sole independent claim. It reads:

> 15. An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a Cmax of between about

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> 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds, each of which challenges the patentability of claims 15–19:

Basis	Reference(s)
§ 103	Euro-Celtique[2]
§ 103	Euro-Celtique and EMEA Study Report[3]
§ 103	Euro-Celtique, EMEA Study Report, and the '883 Application[4]
§ 103	Euro-Celtique, EMEA Study Report, and Yang[5]

ANALYSIS

Under 35 U.S.C. § 325(d),

> In determining whether to institute or order a proceeding under . . . chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

Patent Owner asks us to exercise our discretion under 35 U.S.C. § 325(d) and deny this Petition. Prelim. Resp. 20–33. Patent Owner argues

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[2] Oksche et al., Int'l Pub. No. WO 2008/025791 A1, published on March 6, 2008 (Ex. 1018) ("Euro-Celtique").
[3] European Medicines Agency (EMEA) Study Report on Suboxone® Tablets, 2006 (Ex. 1015) ("EMEA Study Report").
[4] Fuisz et. al., Int'l Pub. No. WO 03/030883 A1, published on April 17, 2003 (Ex. 1031) ("the '883 Application").
[5] Yang et al., U.S. Patent No. 7,357,891 B2, issued on April 15, 2008 (Ex. 1016) ("Yang").

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that the Petition is redundant "because it substantially repeats the *same arguments* and relies substantially on the *same prior art* that the *same Petitioner* relied upon in its earlier ['325 IPR] Petition regarding the *same claims* of the *same patent*." *Id.* at 1. We agree.

In the '325 IPR, Petitioner challenged claims 15–19 of the '832 patent on numerous grounds, including, among others, (1) grounds based on Labtec[6] as the primary reference (for example, anticipation by Labtec, and obviousness over the combination of Labtec, Birch,[7] and Yang); and (2) grounds based on Euro-Celtique as the primary reference (including anticipation by Euro-Celtique, and obviousness over Euro-Celtique, either alone or in combination with Birch, or with Birch and Yang). *See* the '325 IPR, Paper 8 ("the '325 IPR Pet."). We instituted a trial to review whether the challenged claims are anticipated by Labtec and/or rendered obvious over the combination of Labtec, Birch, and Yang. *See* the '325 IPR, Paper 17.

In the '325 IPR, Petitioner did not explain any meaningful advantage of the Euro-Celtique-based grounds over the Labtec-based grounds. To the contrary, according to Petitioner, the Labtec-based grounds are not cumulative to the Euro-Celtique-based grounds "at least because [Labtec] explicitly 'identifies and understands the criticality of pH' to modify absorption"—a teaching that, according to Petitioner, Patent Owner "stated

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[6] Leichs et al., Int'l Pub. No. WO 2008/040534 A2, published on April 10, 2008 (Ex. 1017) ("Labtec").
[7] Birch et al., U.S. Patent Pub. No. 2005/0085440 A1, published on April 21, 2005 (Ex. 1019) ("Birch").

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was lacking in Euro-Celtique" during the prosecution of the '832 patent. The '325 IPR Pet., 39. As a result, we exercised our discretion and declined to institute an *inter partes* review on all Euro-Celtique-based grounds. *See* the '325 IPR, Paper 17, 20.

Nearly two months after Patent Owner filed its Preliminary Response in the '325 IPR, Petitioner filed this second Petition, challenging claims 15–19 of the '832 patent based on four grounds: obviousness over (1) Euro-Celtique alone, (2) the combination of Euro-Celtique and the EMEA Study Report, (3) the combination of Euro-Celtique, the EMEA Study Report, and the '883 Application, or (4) the combination of Euro-Celtique, the EMEA Study Report, and Yang. Pet. 34–54. Petitioner acknowledges:

> This petition is directed to the same five claims of the same patent as the IPR2014-00325 proceedings. This petition involves the same parties as the IPR2014-00325 proceedings. The grounds in this petition are substantially based on a subset of the references cited in the IPR2014-00325 proceedings. While grounds in this petition cite two references that were not cited in IPR2014-00325, these two references are related to a reference cited in IPR2014-00325.

Id. at 2–3.

The two references allegedly not cited in the '325 IPR are the EMEA Study Report and the '883 Application. Petitioner, however, did present the EMEA Study Report in the '325 IPR Petition. *See* the '325 IPR Pet., iii (showing the EMEA Study Report as Ex. 1015 in the Exhibit list). In addition, Petitioner specifically cited the EMEA Study Report for disclosing the Cmax and AUC values of naloxone. *Id.* at 28, *see also id.* at 40–41 (citing the EMEA Study Report in claim chart for unpatentability grounds

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based on Labtec), 49 (citing the EMEA Study Report in claim chart for unpatentability grounds based on Euro-Celtique). Noting Petitioner's argument, we cited the EMEA Study Report in our decision to institute the '325 IPR. *See* the '325 IPR, Paper 17, 14 (acknowledging Petitioner's reliance on page 12 of the EMEA Study Report). In the present case, Petitioner cites the same page of the EMEA Study Report (page 12) for the same disclosure, i.e., for disclosing "mean Cmax and AUC values for buprenorphine and naloxone following administration of Suboxone tablets that fall within the ranges recited in claims 15-17." Pet. 45.

Petitioner did not cite the '883 Application in the '325 IPR petition. But, according to Petitioner, Euro-Celtique, "a primary reference in both this petition and the IPR2014-00325 petition . . . repeatedly cites" the '883 Application. *Id.* at 3; *see also id.* at 49 (stating that Euro-Celtique identifies the '883 Application as "describing 'standard technology' for preparing films"). Petitioner explains that the '883 Application is part of a family of patent applications that resulted in Yang, a U.S. patent that Petitioner relied on in the '325 IPR. *Id.* at 49. In its Motion for Joinder, Petitioner further states that the '883 Application "is cited for the same relevant disclosure as a related family member cited in the ['325 IPR] Petition (*i.e.*, *Yang*)." Paper 6, 9.

Having considered the papers filed in this proceeding, as well as the papers filed in the '325 IPR, we agree with Patent Owner that Petitioner has recycled previous art and arguments. *See* Prelim. Resp. 24–32. Petitioner does not provide any persuasive reasoning as to why we should institute

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another *inter partes* review of the same challenged claims over "the same or substantially the same prior art or arguments" that were presented in the '325 IPR.[8] Based on the totality of the facts before us, we exercise our discretion and deny the Petition under 35 U.S.C. § 325(d). We dismiss as moot Petitioner's Motion for Joinder with the '325 IPR.

ORDER

Accordingly, it is

ORDERED that Petitioner's request for an *inter partes* review of claims 15–19 of the '832 patent is *denied*; and

FURTHER ORDERED that the Motion for Joinder with Case IPR2013-00325 is *dismissed*.

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[8] Petitioner contends that "[i]n addition to the recited limitations, Euro-Celtique discloses features that are disclosed in the '832 patent but not required by the claims 15-19," such as a mucoadhesive film and a film that delivers active through the mucosa. Pet. 41. This argument was not presented in the '325 IPR. Petitioner does not, however, explain why these features matter to our patentability analysis, if they are not required by the challenged claims.

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AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

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 Eastern District of North Carolina on the following

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

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
5:14-cv-529-H	9/20/2014	Eastern District of North Carolina

PLAINTIFF	DEFENDANT
BioDelivery Sciences International, Inc.	Reckitt Benckiser Pharmaceuticals, Inc. et al

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,475,832		SEE ATTACHED COPY OF COMPLAINT
2	7,897,080		
3	8,652,378		
4	7,824,588		
5	7,357,891		

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
1	7,425,292		
2			
3			
4			
5			

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
JULIE A. RICHARDS	/s/ Jade Felder	9/22/2014

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

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TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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AO 120 (Rev. 2/99)

TO: Mail Stop 8 Director of the U.S. Patent & Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 § 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 Northern District California on the ☐ Patents or ✔ Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
CV 14-04240 JCS	9/19/14	450 Golden Gate Avenue, 16th Floor, San Francisco CA 94102

PLAINTIFF	DEFENDANT
JACKSON FAMILY WINES, ET AL	CONSTELLATION BRANDS, ET AL

PATENT OR	DATE OF PATENT	HOLDER OF PATENT OR TRADEMARK
1 2,393,573		***see Attach Complaint***
2		
3		
4		
5		

In the above—entitled case, the following patent(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
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Richard W. Wieking	Gina Agustine	September 19, 2014

Copy 1—Upon initiation of action, mail this copy to Commissioner Copy 3—Upon termination of action, mail this copy to Commissioner
Copy 2—Upon filing document adding patent(s), mail this copy to Commissioner Copy 4—Case file copy

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Paper 17
Entered: July 29, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIODELIVERY SCIENCES INTERNATIONAL, INC.,
Petitioner,

v.

RB PHARMACEUTICALS LIMITED,
Patent Owner.

Case IPR2014-00325
Patent 8,475,832 B2

Before TONI R. SCHEINER, JACQUELINE WRIGHT BONILLA, and ZHENYU YANG, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

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INTRODUCTION

BioDelivery Sciences International, Inc. ("Petitioner") petitioned for an *inter partes* review of claims 15-19 of U.S. Patent No. 8,475,832 B2 (Ex. 1001, "the '832 patent"). Paper 8 ("Pet."). RB Pharmaceuticals Limited ("Patent Owner") timely filed a Preliminary Response. Paper 15 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314.

For the reasons provided below, we determine that Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a) and established a reasonable likelihood that it would prevail in showing the unpatentability of the challenged claims. Therefore, we institute an *inter partes* review of claims 15-19 of the '832 patent.

The '832 Patent

The '832 patent relates to compositions and methods for treating narcotic dependence using an orally dissolvable film comprising buprenorphine and naloxone, where the film provides a bioequivalent effect to Suboxone®. Ex. 1001, 4:55-58.

Suboxone® is an orally dissolvable tablet of buprenorphine and naloxone. *Id.* at 4:51-55. Buprenorphine provides an effect of satisfying the body's urge for the narcotics, but not the "high" associated with misuse. *Id.* at 1:36-40. Naloxone reduces the effect and, thus, decreases the likelihood of diversion and abuse of buprenorphine. *Id.* at 1:46-52. The tablet form, however, still has the potential for abuse because it can be removed easily from the mouth for later extraction and injection of buprenorphine. *Id.* at 1:55-62. The film of the '832 patent "provides buccal adhesion while it is in

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the user's mouth, rendering it difficult to remove after placement." *Id.* at 4:58-60.

The '832 patent teaches controlling the local pH to maximize the absorption of the buprenorphine while simultaneously minimizing the absorption of the naloxone. *Id.* at 11:28-30. According to the '832 patent, "it has been surprisingly discovered" that, at a local pH level from about 2 to about 4, and most desirably from 3 to 4, the film composition of the invention achieves bioequivalence to the Suboxone® tablet. *Id.* at 11:50-61.

The '832 patent defines bioequivalent as "obtaining 80% to 125% of the Cmax and AUC values for a given active in a different product." *Id.* at 3:48-50. According to the '832 patent, "Cmax refers to the mean maximum plasma concentration after administration of the composition to a human subject;" and "AUC refers to the mean area under the plasma concentration-time curve value after administration of the compositions . . . ." Ex. 1001, 3:9-14. The '832 patent discloses:

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

Id. at 17:41-47.

Illustrative Claim

Among the challenged claims, claim 15 is the sole independent claim. It reads:

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

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds, each of which challenges the patentability of claims 15-19:

Basis	Reference(s)[1]
§ 102(b)	Suboxone Tablet Label
§ 103	Suboxone Tablet Label
§ 103	Suboxone Tablet Label and Yang
§ 103	Suboxone Tablet Label, Yang, and Birch
§ 102(b)	Labtec
§ 103	Labtec
§ 103	Labtec and Birch
§ 103	Labtec, Birch, and Yang
§ 102(b)	Euro-Celtique
§ 103	Euro-Celtique
§ 103	Euro-Celtique and Birch
§ 103	Euro-Celtique, Birch, and Yang

[1] Suboxone Tablet Label, Revised September 2006 (Ex. 1013); Yang et al., U.S. Patent No. 7,357,891 B2 (Ex. 1016) ("Yang"); Leichs et al., Int'l Pub. No. WO 2008/040534 A2 (Ex. 1017) ("Labtec"); Oksche et al., Int'l Pub. No. WO 2008/025791 A1 (Ex. 1018) ("Euro-Celtique"); Birch et al., U.S. Patent Publication No. 2005/0085440 A1 (Ex. 1019) ("Birch").

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ANALYSIS

Preliminary Matters

Reitman Declaration

In support of the Petition, Petitioner submits a declaration by Dr. Maureen Reitman, who testifies that the pH of Suboxone® tablets "was measured to be 3.5." Ex. 1004 ¶ 5. Patent Owner asks us to disregard the Reitman Declaration because (1) Suboxone® tablets do not constitute prior art for an *inter partes* review; and (2) the Reitman Declaration fails to provide sufficient and reliable evidence. Prelim. Resp. 20-22.

Patent Owner's argument is moot because we do not need to rely on Reitman Declaration at this stage of the proceeding. Petitioner, in discussing several asserted grounds, refers to pH 3-3.5 allegedly emphasized in the '832 patent. *See, e.g.*, Pet. 36 (asserting that "[t]o the extent the pH range of about 3 to about 3.5 is read into the challenged claims, the use of that pH range was already described and obvious in view of *Birch*"). As Patent Owner points out, however, "pH is not recited in the challenged claims." Prelim. Resp. 5. Thus, for purposes of this Decision, we do not address Petitioner's argument or the Reitman Declaration discussing the pH of Suboxone® tablets.

Lack of expert testimony on claim construction

Patent Owner faults Petitioner for presenting no expert testimony on how one of ordinary skill in the art would understand the term "film formulation." Prelim. Resp. 12. As explained below, in this case, disclosures in the Specification provide sufficient guidance for claim

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construction. Thus, given the record before us, the absence of expert testimony on claim construction is inconsequential. Patent Owner also criticizes Petitioner for only relying on attorney argument. Prelim. Resp. 12. We, however, are satisfied that evidence of record, as supplied by both parties, is sufficient to allow us to construe claim terms for purposes of this Decision.

Lack of expert testimony on anticipation and obviousness

To support the Petition, Petitioner submits two expert declarations: Reitman Declaration addressing the pH of Suboxone® tablets (Ex. 1004), and a declaration by Dr. Philip T. Lavin discussing certain data in the '832 patent (Ex. 1005). Patent Owner urges us to deny the Petition for the sole reason that neither declaration presents direct analysis on anticipation or obviousness. Prelim. Resp. 4-5; *see also id.* at 33-37. We decline to do so.

Patent Owner is correct that "[t]he Board expects that most petitions and motions will rely upon affidavits of experts." Prelim. Resp. 4 (quoting Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,763 (Aug. 14, 2012)). Especially in complex cases where obviousness is asserted as a ground of unpatentability, "expert testimony may be critical, for example, to establish the existence of certain features in the prior art or the existence (or lack thereof) of a motivation to combine references." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1240 n.5 (Fed. Cir. 2010) (citations omitted). But expert testimony is not a *per se* requirement—where the technology is simple, where the references are easily understandable without the need for expert explanatory testimony, or where the factual inquiries underlying the

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obviousness determination are not in material dispute, expert testimony, though it might be helpful, may not be indispensable. *Allergan, Inc. v. Barr Labs., Inc.*, 501 F. App'x 965, 972 (Fed. Cir. 2013). In addition, a reason to combine prior art teachings may exist "in the content of the public prior art, in the nature of the problem addressed by the invention, or even in the knowledge of one of ordinary skill in the art." *Princeton Biochemicals Inc. v. Beckman Coulter Inc.*, 411 F.3d 1332, 1338-39 (Fed. Cir. 2005). And in some cases, "the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony." *Wyers*, 616 F.3d at 1239. Therefore, we reject a bright-line rule requiring expert testimony analyzing unpatentability for all petitions for *inter partes* review.

At this stage of the proceedings, Petitioner has provided sufficient evidence and we understand the prior art disclosures and a possible reasoning to modify or combine the references without guidance of an expert.

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b). Under that standard, we assign claim terms their ordinary and customary meaning, as understood by a person of ordinary skill in the art, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

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Petitioner asks us to construe the terms "film formulation" and "provides an in vivo plasma profile" recited in independent claim 15. The parties propose the following constructions:

Term	Patent Owner's Construction	Petitioner's Construction
film formulation	film composition or dosage	combination of components capable of being used to prepare a single film
provides an in vivo plasma profile	No construction needed	results in an in vivo plasma profile after a resulting film is administered to a human subject

Prelim. Resp. 11; *see also* Pet. 22.

We address each term in turn.

"*Film formulation*"

Both parties argue that the Specification and prosecution history of the '832 patent, as well as dictionary definitions support their respective proposed claim constructions. Pet. 15-19; Prelim. Resp. 10-19.

According to Petitioner, during the prosecution of the '832 patent,

> Applicant admitted that "[d]elivery of compounds such as buprenorphine and naloxone was previously known, however, the previously-accepted form of the delivery is in the form of a tablet (*e.g.*, a Suboxone® tablet)." Applicant explained: "The present invention is directed to formulation of a suitable film product that provides a certain release profile."

Pet. 16 (citations omitted, emphasis added by Petitioner). Based on this, Petitioner concludes that "Applicant distinguished a film formulation from a resulting film product that provides a release profile." *Id.* In other words,

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Petitioner contends that "film formulation" does not require a film, but broadly encompasses a combination of components that are capable of forming a single film, even if such components are not in the form of a film. *Id.* at 15, 22.

Patent Owner points out that Petitioner emphasizes and relies on misquoted language from the prosecution history. Prelim. Resp. 12-13. Patent Owner contends that it explained the invention as directed to the "**formation** of a suitable film product." *Id.* at 13 (quoting Ex. 1007, 7 (emphasis added)). Patent Owner persuades us that the quotes from the prosecution history do not support Petitioner's position.

In addition, Petitioner, citing two sentences from two U.S. patents incorporated into the '832 patent by reference, asserts that "the specification [of the '832 patent] distinguishes a film formulation from a resulting film product." Pet. 16-17. The '832 patent incorporates the two U.S. patents by reference, however, to exemplify suitable processes to form the film compositions. Ex. 1001, 15:29-32. An isolated sentence from each of those two patents does not persuade us to read "film" out of the term "film formulation," as Petitioner suggests.

Nor do we find the rest of the Specification to support Petitioner's construction. Petitioner directs our attention to Table 5 of the '832 patent, entitled "Formulations of Test Films . . . ." Pet. 17 (citing Ex. 1001, 18:44-67). According to Petitioner, each of the three formulations listed in Table 5 "consists of a combination of components used in the preparation of a test film." *Id.* Petitioner contends that this table, together with excerpts

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referencing information in this table, provides the context to support its construction. *Id.*

We disagree. First, we construe the term "film formulation," not "formulation." In the context of the Specification, the use of the word "formulation" alone does not inform the meaning of "film formulation." More importantly, the two paragraphs preceding Table 5 support Patent Owner's position that the term "film formulation" is synonymous with "film product, film composition, or film dosage." Prelim. Resp. 10. Indeed, the Specification explains:

> Film dosages were prepared for use in an in vivo study to determine the bioavailability of buprenorphine/naloxone **tablets and film formulations**. Specifically, the **films** were tested to determine whether the film provides a bioequivalent effect to that of a **tablet formulation**.
>
> Three **film formulations** including 8 mg buprenorphine and 2 mg naloxone were prepared, each being buffered to a different pH. The first **film** did not include any buffer, providing a local pH of about 6.5. The second was buffered to a local pH level of about 3-3.5. The third was buffered to a local pH value of about 5-5.5. The formulations are set forth in Table 5 below.

Ex. 1001, 18:30-42 (emphases added). Other passages in the Specification provide additional examples:

> This demonstrates that even less absorption of the naloxone occurs for the **film formulation** at a local pH of 3.5 than the **tablet formulation**. Given the goal of reducing the absorption of naloxone, it appears that the **film product** . . . provides even better results than the Suboxone® **tablet formulation**.

Id. at 23:49-55 (emphases added). The juxtaposition of "tablets" and "film formulations," the comparison of "film," "film formulation," and "film product" with "tablet formulation," as well as the reference to the first of the

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"three film formulations" as "film," all indicate that "film formulation" refers to a film product, not merely components capable of being used to prepare a film.

Petitioner also contends that Patent Owner could have claimed a "film," but "instead chose to claim a 'film formulation' in the challenged claims." Pet. 19. We find this argument unpersuasive because Petitioner does not point adequately to where a distinction appears in the '832 patent between the usage of "film formulation" and "film dosage, film product, film composition, film strip, and film," or otherwise suggests that a "film formulation" is not necessarily in the form of a film.

We conclude that Petitioner's proposed construction of "film formulation" is unreasonably broad in view of the Specification. The broadest-construction rubric does not allow an unfettered license to interpret claims to embrace anything remotely related to the claimed invention. *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010). Accordingly, we conclude that "film formulation" encompasses film dosage, film composition, or film, but not a formulation that is not in the form of a film.

"Provides an in vivo plasma profile"

Petitioner contends the term "provides an in vivo plasma profile" means "results in an in vivo plasma profile after a resulting film is administered to a human subject." Pet. 20-22. Patent Owner argues that the term, having "a plain and unambiguous meaning on its face and in the context of the specification," needs no construction. Prelim. Resp. 11, 19. We agree with Patent Owner.

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The challenged claims require the claimed "film formulation" to provide the recited in vivo plasma profile. Ex. 1001, 24:56-58. Petitioner correctly recognizes that it is the film product that provides the in vivo plasma profile. Pet. 20-21. Because Petitioner insists that "film formulation" means "combination of components capable of" forming a film, and not a film product, however, it adds the "resulting film" language into the construction of "provides an in vivo plasma profile." In other words, Petitioner would have us read "film" out of "film formulation" and into "provides an in vivo plasma profile." We decline to do so. Because a "film formulation" is a film, it is unnecessary to include an additional element of "resulting film" into "provides an in vivo plasma profile." In view of the plain and unambiguous meaning on its face and in the context of the Specification, we see no need to construe the term "provides an in vivo plasma profile" beyond its ordinary meaning.

Patentability Analysis

Anticipation

Anticipation by Suboxone Tablet Label (Ex. 1013)

Petitioner asserts that Suboxone Tablet Label anticipates claims 15-19 of the '832 patent based on Petitioner's proposed claim construction of "film formulation." *See* Pet. 27.

As discussed above, the term "film formulation," as recited in independent claim 15, requires a formulation in the form of a film. As conceded by Petitioner, Suboxone Tablet Label does not disclose a formulation in the form of a film. Pet. 39. Thus, Petitioner has not

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established a reasonable likelihood that it would prevail in showing that Suboxone Tablet Label anticipates the challenged claims. We deny this ground.

Anticipation by Labtec (Ex. 1017)

Petitioner asserts that Labtec anticipates claims 15-19. Pet. 38-41. Labtec describes "non-mucoadhesive orally disintegrating film dosage forms that mimic the pharmacokinetic profile of orally administered drug products such as tablets . . . ." Ex. 1017, 3.[2] One such tablet is Suboxone®. *Id.* at 23.

According to Petitioner, Labtec describes a film formulation comprising buprenorphine and naloxone that mimics the pharmacokinetics (*i.e.*, in vivo plasma profile including Cmax and mean AUC) of Suboxone® in relation to both active ingredients. Pet. 38-40. Petitioner points us to Table A of Labtec, which lists "[e]xamples of doses for specific pharmaceutically active agents that can be delivered per one strip of rapidly dissolving oral film . . . along with preferred dosing schedules and pharmacokinetic parameters." Ex. 1017, 21; Pet. 38-40. Petitioner contends that one example in Table A includes the combination of buprenorphine HCl/naloxone HCl dehydrate, the active ingredients of Suboxone®, as the pharmaceutical active agents for the described film. Pet. 39-40; Ex. 1017, 23. Petitioner points to the example describing a

[2] We cite to exhibit page numbers of Ex. 1017, rather than page numbers of the published PCT application itself.

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Cmax of 1.84 and 3.0 ng/ml for buprenorphine, which Petitioner contends falls within "a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine," as recited in claim 15. Pet. 40 (citing Ex. 1017, 23). Petitioner also points to the example further describing that "[m]ean peak naloxone levels range from 0.11 to 0.28 ng/ml in dose range of 1-4 mg," which Petitioner contends describes "a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone," also recited in claim 15. *Id.*

In addition, Petitioner points to where Labtec describes AUC_{0-48} of 12.52, 20.22, and 34.89 hr.ng/ml, for 4, 8, and 16 mg buprenorphine, respectively, which Petitioner contends falls within the mean AUC range for buprenorphine as recited in claim 16. *Id.* For claim 17, which recites "a mean AUC of between about 102.88 hr.pg/ml to about 812.00 hr.pg/ml for naloxone," Petitioner contends that Labtec describes "film formulations that provide the same or bioequivalent pharmacokinetic profile as Suboxone tablets." *Id.* (citing Ex. 1017, 3:15-23). Petitioner relies on other evidence, including the '832 patent itself (Ex 1001, 16:53-63) and a "Suboxone Tablet Study Report" (Ex. 1015, 12), to establish that Suboxone tablets, and therefore, films exhibiting the same pharmacokinetic profile, necessarily exhibit mean AUC levels for naloxone that falls within the range recited in claim 17. *Id.* at 40-41.

Petitioner further points to where Labtec describes 2.0/0.5 or 8.0/2.0 mg as the preferred dose for buprenorphine/naloxone in a film, and 12-16 mg/day as the preferred dosing schedule, which Petitioner contends meets the elements recited in dependent claims 18 and 19. *Id.* at 41.

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In its Preliminary Response, Patent Owner first argues that "the purpose of the '832 patent is to provide an orally dissolvable, ***mucoadhesive***, film dosage form containing buprenorphine and naloxone," while Labtec, in contrast, concerns "non-mucoadhesive" film dosages. Prelim. Resp. 30-31. The challenged claims, however, only require a film formulation without indicating whether it is mucoadhesive or non-mucoadhesive. Thus, we are not persuaded that Petitioner's challenge based on Labtec fails on this basis.

Patent Owner also asserts that Labtec teaches away because the claimed invention provides a mucoadhesive film whereby buprenorphine is absorbed through the oral mucosa, while Labtec only discloses a non-mucoadhesive film whereby the active ingredients are absorbed predominantly through the gastrointestinal tract. Prelim. Resp. 30-32. Teaching away, however, is legally irrelevant to the question of anticipation. *Celeritas Technologies, Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998). In addition, Patent Owner does not propose that we construe "film formulation" to require muco-adhesiveness or mucosal absorption of buprenorphine, and we decline to read those unrecited features into the challenged claims.

Patent Owner argues that Labtec does not "direct the skilled artisan to that [claimed] composition 'without *any* need for picking, choosing, and combining various disclosures.'" Prelim. Resp. 32. Petitioner points to one row in Table A of Labtec, however, when asserting disclosure of recited elements regarding in vivo plasma profiles of buprenorphine and naloxone. Pet. 39-41 (citing Ex. 1017, 23).

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Patent Owner further contends that "Labtec merely states the desired goal of having films that are bioequivalent [to] Suboxone® tablets" without "***a single, specific embodiment of a film containing*** buprenorphine alone or together with naloxone, let alone one tested to determine a pharmacokinetic profile." Prelim. Resp. 31-32. Specifically, according to Patent Owner, the buprenorphine pharmacokinetic values referenced in Labtec "are simply those provided in the Suboxone® tablet label, and do not reflect the pharmacokinetics of any film disclosed in Labtec." *Id.* at 32 n.13.

"[A]nticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art." *Novo Nordisk Pharm., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005); *see also Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003) ("A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter.").

As discussed above, Petitioner points us to where Labtec discloses a rapidly dissolving oral film with buprenorphine and naloxone as its active agents. Pet. 38-40 (citing Ex. 1017, 21, 23). Petitioner also points us to where Labtec discloses the film can be formulated to include pharmaceutical active agents, a film-forming agent, and other ingredients. Pet. 39 (citing Ex. 1017, 14-15). In addition, Petitioner explains where Labtec describes formulating a film to ensure bioequivalence between the film and an existing product, such as the Suboxone® tablet. Pet. 40 (citing Ex. 1017, 4-5, 13). Specifically, according to Petitioner, Labtec discloses the pharmacokinetic

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values of the Suboxone® tablet as the preferred pharmacokinetic parameters for a film. Pet. 39-40 (citing Ex. 1017, 23). As a result, according to Petitioner, one of ordinary skill in the art reading Labtec would have known how to prepare buprenorphine/naloxone films as described in Table A, *i.e.*, the film formulations recited in challenged claims 15-19. Pet. 38-41 (citing, for example, Ex. 1017, 16:13-15, 16:29-17:5).

Based on the foregoing and the record before us, we are persuaded that Petitioner has shown a reasonable likelihood that it would prevail in demonstrating that Labtec anticipates claims 15-19.

Anticipation by Euro-Celtique (Ex. 1018)

Petitioner contends that Euro-Celtique anticipates claims 15-19. Pet. 46-50. We determine that this ground is redundant in light of our decision to institute review of anticipation of the same claims based on Labtec. Thus, we exercise our discretion not to institute on this ground. 37 C.F.R. § 42.108(a).

Obviousness

Obviousness over Labtec, Birch (Ex. 1019), and Yang (Ex. 1016)

Petitioner argues that the challenged claims would have been obvious over the combination of Labtec, Birch, and Yang. Pet. 44-45. Petitioner relies on Birch "[t]o the extent the pH range of about 3 to about 3.5 is read into the challenged claims." Pet. 43. As noted above, pH levels are not recited in the challenged claims. Thus, we do not rely on Birch in our

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obviousness determination, except to note that Patent Owner has not asserted that Birch teaches away from the claimed film formulations.

According to Petitioner, Labtec discloses components suitable for making films that are bioequivalent to the Suboxone® tablets. *Id.* at 38, 45. Petitioner contends that to the extent Labtec, together with the knowledge of one skilled in the art, insufficiently teaches how to make a film (and thus fails to anticipate the challenged claims), Yang explicitly supplies such teaching. *Id.* at 45. As noted by Petitioner, Yang is one of the two U.S. patents incorporated by reference into the '832 patent for the disclosure of suitable processes to form the claimed film. *Id.* (citing Ex. 1001, 15:30-31).

Patent Owner argues that Petitioner fails to provide sufficient evidence to meet the threshold for instituting a trial on any obviousness ground. Prelim. Resp. 33. First, according to Patent Owner, Petitioner does not provide expert testimony on, or otherwise explain, the level of ordinary skill in the art. Patent Owner contends that we should deny all asserted obviousness grounds "for this reason alone." *Id.* at 36. We disagree.

The skill-level determination is an important guarantee of objectivity in an obviousness analysis. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). But where the prior art itself reflects an appropriate level, and a need for testimony is not shown, a specific finding on the level of skill in the art is not required. *Litton Indus. Products, Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163-64 (Fed. Cir. 1985); *In re Gentile*, 11 F.3d 1069 (Fed. Cir. 1993). Petitioner's failure to explicitly state the level of skill in the art is not fatal for purposes of this Decision because we are persuaded that prior art in

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general, and Labtec and Yang specifically, reasonably reflect an appropriate level of skill.

Second, Patent Owner argues that Petitioner does not provide any objective evidence, such as expert testimony, to support Petitioner's asserted reason to combine teachings in the references. Prelim. Resp. 37. But testimony of an expert, as we explained above, is not the only source for such evidence. Indeed, the reason to combine references sometimes may be explicit or implicit from the prior art. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1290-91 (Fed. Cir. 2006). Here, Petitioner contends that Labtec teaches the buprenorphine and naloxone as active ingredients for an orally dissolving film with a preferred pharmacokinetics profile. Pet. 38-40. If it does not do so adequately by itself, Petitioner contends that Labtec would have motivated one skilled in the art to look to Yang for the method of making a film. *Id.* at 45. We are persuaded that Petitioner reasonably establishes that it would prevail in showing that an ordinary artisan would have had a reason to consider the methods disclosed in Yang when reading Labtec.

Third, Patent Owner alleges that

> Labtec clearly teaches away from the subject matter claimed in the '832 patent (directed to mucoadhesive film that delivers its active through the oral mucosa), since Labtec is focused on a non-mucoadhesive film that delivers its active not through the oral mucosa (indeed, Labtec seeks to block oral absorption) but in the intestinal tract.

Prelim. Resp. 39. Teaching-away is a proper inquiry for determining obviousness. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). We find Patent Owner's argument, however, unpersuasive. As noted above, the

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challenged claims do not recite either the muco-adhesiveness or mucosal absorption that Patent Owner emphasizes. We are persuaded Petitioner reasonably establishes that Labtec's teaching of a non-mucoadhesive film that delivers its active in the gastrointestinal tract would not have discouraged one skilled in the art from developing a film that meets all limitations of the challenged claims.

Based on the record before us, we are persuaded that Petitioner has shown a reasonable likelihood that it would prevail in demonstrating that the combination of Labtec, Yang, and Birch renders claims 15-19 obvious.

Other obviousness grounds

Petitioner also asserts that claims 15-19 would have been obvious over: (1) Suboxone Tablet Label; (2) Suboxone Tablet Label and Yang; (3) Suboxone Tablet Label, Yang, and Birch; (4) Labtec; (5) Labtec and Birch; (6) Euro-Celtique; (7) Euro-Celtique and Birch; (8) Euro-Celtique, Birch, and Yang. We determine that these grounds are redundant in light of our decision to institute review of obviousness of the same claims based on Labtec, Yang, and Birch. Thus, we exercise our discretion not to institute on these grounds. 37 C.F.R. § 42.108(a).

CONCLUSION

For the foregoing reasons, the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 15-19 of the '832 patent.

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The Board has not made a final determination on the patentability of any challenged claim.

ORDER

Accordingly, it is

ORDERED that the Petition is granted as to claims 15-19 of the '832 patent with respect to the following alleged grounds:

1. Claims 15-19 under 35 U.S.C. § 102 as anticipated by Labtec;

2. Claims 15-19 under 35 U.S.C. § 103 as obvious over the combination of Labtec, Yang, and Birch;

FURTHER ORDERED that no ground other than those specifically granted above is authorized for the *inter partes* review as to claims 15-19; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '832 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

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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
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	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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DECISION/JUDGEMENT
See attached Order

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

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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
2	8,017,150	9/13/2011	MonoSol RX LLC
3	8,603,514	12/10/2013	MonoSol RX LLC
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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
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

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AO 120 (Rev. 08/10)

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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
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DATE INCLUDED	INCLUDED BY
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-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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	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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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

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

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

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
1	8,603,514	12/10/2013	MonoSol RX, LLC
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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 Eastern District of North Carolina on the following

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

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
5:13-CV-760-BO	10/29/2013	Eastern District of North Carolina

PLAINTIFF	DEFENDANT
Reckitt Benckiser Pharmaceuticals, Inc., et al	BioDelivery Sciences International, Inc.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,475,832		SEE ATTACHED COPY OF COMPLAINT
2			
3			
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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	
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

CLERK	(BY) DEPUTY CLERK	DATE
JULIE A. RICHARDS	Lauren Moore	10/30/2013

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37. The Onsolis™ film product, like Bunavail™ also, according to BDSI, uses BDSI's BEMA film technology.

38. The '292 and '891 patents were subject to *ex parte* reexamination proceedings before the United States Patent and Trademark Office ("USPTO"), initiated by BDSI in Application Serial No. 90/012,097 and Application Serial No. 90/012,098, respectively. The '588 patent is also subject to an *inter partes* reexamination proceeding before the USPTO, Application Serial No. 95/001,753, requested by BDSI.

39. BDSI moved to stay the proceedings in the New Jersey Action pending resolution by the USPTO of the *inter partes* reexamination of the '588 patent and the *ex parte* reexaminations of the '292 and '891 patents. The motion to stay was granted on March 7, 2012.

40. The *inter partes* reexamination of the '588 patent is still pending before the USPTO, but the *ex parte* reexaminations of the '292 and '891 patents have been resolved. The USPTO issued reexamination certificates for both the '292 and '891 patents on July 3, 2012 and August 21, 2012, respectively. Having failed to invalidate the '292 and '891 patents through the *ex parte* reexaminations, on June 12, 2013, BDSI filed petitions to institute *inter partes* review of the '292 and '891 patents with the USPTO, Case No. IPR2013-00315 and Case No. IPR2013-00316, respectively. The petitions are still pending before the USPTO.

41. Accordingly, there is a real, substantial, and continuing justiciable case or controversy between Plaintiffs and Defendant BDSI regarding whether Defendant's commercial manufacture, use, sale, offer for sale, or importation into the United States of Bunavail™ according to BDSI's 505(b)(2) NDA, will infringe one or more claims of the patent-in-suit. Plaintiffs are entitled to a declaration that the making, using, sale, offer for sale, and importation

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TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

into the United States of Bunavail™ according to BDSI's 505(b)(2) NDA would infringe one or more claims of the patent-in-suit.

COUNT I
(Declaratory Judgment as to U.S. Patent No. 8,475,832)

42. Plaintiffs reallege paragraphs 1-41 above as if fully set forth herein.

43. On information and belief, BDSI's Bunavail™ product is covered by one or more claims of the '832 patent.

44. On information and belief, unless enjoined by this Court, BDSI intends to engage in the commercial manufacture, use, sale, or offer for sale within the United States or importation into the United States of Bunavail™, upon approval of its pending 505(b)(2) application.

45. Pursuant to 35 U.S.C. § 271(a)-(c), Defendant BDSI's commercial manufacture, use, sale, offer for sale, or importation into the United States, of Bunavail™ will infringe, contribute to the infringement of, and/or induce the infringement of one or more claims of the '832 patent.

46. On information and belief, by seeking approval to distribute BDSI's Bunavail™, BDSI intends to cause others -- specifically, for example, medical professionals and patients -- to perform acts that BDSI knows will infringe one or more claims of the '832 patent.

47. On information and belief, BDSI knows (a) that its Bunavail™ product is especially made or adapted for use in infringing one or more claims of the '832 patent and (b) that the Bunavail™ product is not suitable for any substantial noninfringing use.

48. The acts of infringement by BDSI set forth above will cause Plaintiffs irreparable harm for which they have no adequate remedy at law, and those acts will continue unless enjoined by this Court.

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Case 5:13-cv-00760-BO Document 1 Filed 10/29/13 Page 10 of 14 TEVA PHARMACEUTICALS USA, INC. V. BIODELIVERY SCIENCES PHARMACEUTICALS LTD.

49. There is a real, substantial, and continuing justiciable case and controversy between Plaintiffs and Defendant BDSI regarding whether Defendant BDSI's commercial manufacture and/or sale of Bunavail™ will infringe one or more claims of the '832 patent. Plaintiffs are entitled to a declaration that such activities would infringe one or more claims of the '832 patent.

COUNT II
(Infringement of U.S. Patent No. 8,475,832)

50. Plaintiffs reallege paragraphs 1-49 above as if fully set forth herein.

51. The submission of BDSI's 505(b)(2) NDA is an act of infringement by BDSI of one or more claims of the '832 patent under 35 U.S.C. § 271(e)(2)(A), which provides that:

> It shall be an act of infringement to submit—
>
> (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent,
>
> . . .
>
> if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

52. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including, *inter alia*, an Order of this Court that the FDA set the effective date of approval for BDSI's 505(b)(2) NDA to be a date which is not any earlier than the expiration date of the '832 patent, including any extensions of that date.

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PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that this Court enter:

A. A declaratory judgment that the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of BDSI's Bunavail™ would infringe the '832 patent under 35 U.S.C. § 271(a)-(c);

B. A judgment that BDSI has infringed the '832 patent by submitting BDSI's 505(b)(2) NDA under 35 U.S.C. § 271(e)(2);

C. Preliminary and permanent injunctions, restraining and enjoining BDSI, its officers, agents, attorneys, affiliates, divisions, successors and employees, and those acting in privity or concert with them, from engaging in, causing, or inducing the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of drugs and formulations, or from contributing to and/or inducing the use of methods, claimed in the '832 patent;

D. An Order that the effective date of any approval of BDSI's 505(b)(2) NDA be a date that is not earlier than the expiration of the '832 patent, including any extensions thereof and any later expiration of exclusivity associated with the patent;

E. A judgment and order finding that this is an exceptional case within the meaning of 35 U.S.C. § 285 and awarding to Plaintiffs their reasonable attorneys' fees;

F. A judgment granting Plaintiffs compensatory damages in an amount to be determined at trial including both pre-judgment and post-judgment interest, if Defendant BDSI commercially manufactures, uses, offers to sell, or sells in the United States, or imports into the United States BDSI's Bunavail™ before the expiration of the '832 patent, including any extensions; and

G. Any and all other relief as the Court deems just and proper.

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Dated: October 29, 2013

Respectfully submitted,

/s/ Michael E. Ray

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TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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MonoSol Rx, LLC

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IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NORTH CAROLINA
WESTERN DIVISION

RECKITT BENCKISER PHARMACEUTICALS, INC., RB PHARMACEUTICALS LIMITED, and MONOSOL RX, LLC, Plaintiffs, v. BIODELIVERY SCIENCES INTERNATIONAL, INC., Defendant.	)	Civ. No. 5:13-cv-760

COMPLAINT

Plaintiffs Reckitt Benckiser Pharmaceuticals, Inc. ("RBP"), RB Pharmaceuticals Limited ("RBP UK"), and MonoSol Rx, LLC ("MonoSol") ("collectively, "Plaintiffs") hereby file this Complaint against Defendant BioDelivery Sciences International, Inc. ("BDSI"), and allege as follows:

NATURE OF THE ACTION

1. This is an action for infringement of United States Patent No. 8,475,832 ("the '832 patent"), arising under the Food and Drug Laws and Patent Laws of the United States, Titles 21 and 35 of the United States Code, respectively, and for a declaratory judgment of patent infringement under 28 U.S.C. §§ 2201 and 2202.

2. Pursuant to New Drug Application 22-410, the United States Food and Drug Administration ("FDA") authorized Plaintiffs to market a pharmaceutical drug product used to treat opioid dependence that is sold under the name Suboxone®. Suboxone® is a sublingual, transmucosal film that contains the active ingredients buprenorphine hydrochloride and naloxone

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hydrochloride. Plaintiffs have manufactured and continue to manufacture and sell Suboxone® for the U.S. market.

3. BDSI has submitted a New Drug Application under 21 U.S.C. § 355(b)(2) (the "505(b)(2) NDA") to the FDA seeking approval to manufacture and sell a competing pharmaceutical drug product to Suboxone® that contains the same active ingredients and is intended to treat the same medical indications. BDSI intends to market its competing product under the name Bunavail™.

4. BDSI's submission of its application to the FDA constitutes an act of patent infringement under 35 U.S.C. § 271(e). Furthermore, a real and justiciable controversy exists between Plaintiffs and BDSI regarding whether Bunavail™ infringes the '832 patent. Therefore, Plaintiffs also seek a declaration that the sale of BDSI's proposed product will infringe the '832 patent under 35 U.S.C. § 271(a)-(c).

THE PARTIES

5. Plaintiff RBP is a Delaware corporation having a principal place of business at 10710 Midlothian Turnpike, Suite 430, Richmond, Virginia.

6. Plaintiff RBP UK is a United Kingdom corporation having a principal place of business at 103-105 Bath Road, Slough, UK.

7. Plaintiff MonoSol is a Delaware limited liability company having a principal place of business at 30 Technology Drive, Warren, New Jersey.

8. Defendant BDSI is a Delaware corporation having a principal place of business at 801 Corporate Center Drive, Suite 210, Raleigh, North Carolina.

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JURISDICTION AND VENUE

9. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202, and 35 U.S.C. § 271.

10. This Court has personal jurisdiction over BDSI because BDSI resides in this judicial district.

11. Venue is proper in this district under 28 U.S.C. §§ 1391 and 1400.

THE PATENT-IN-SUIT

12. Plaintiff RBP UK is the lawful owner of the '832 patent. The '832 patent, entitled "Sublingual and Buccal Film Compositions," was duly and legally issued on July 2, 2013, to Garry L. Myers, Samuel D. Hilbert, Bill J. Boone, B. Arlie Bogue, Pradeep Sanghvi, and Madhusudan Hariharan as inventors. The named inventors assigned their rights to MonoSol, who subsequently assigned its rights in the '832 patent to Reckitt Benckiser Healthcare (UK) Limited, which then assigned its rights to RBP UK. MonoSol manufactures Suboxone® for the US market. A true copy of the '832 patent is attached hereto as Exhibit A.

PLAINTIFFS' SUBOXONE® PRODUCTS

13. Plaintiff RBP is the owner of New Drug Application ("NDA") No. 22-410 for Suboxone® (buprenorphine hydrochloride and naloxone hydrochloride) sublingual film.

14. On August 30, 2010, the FDA approved NDA No. 22-410 for the manufacture, marketing, and sale of Suboxone® sublingual film for the maintenance treatment of opioid dependence. Plaintiff RBP has sold Suboxone® sublingual film since its approval.

15. RBP also owns NDA No. 20-733 for Suboxone® sublingual tablet. Suboxone® sublingual tablet contains the same active ingredients as Suboxone® sublingual film (buprenorphine hydrochloride and naloxone hydrochloride).

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BDSI's ATTEMPT TO CIRCUMVENT THE HATCH-WAXMAN ACT

16. In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act, commonly known as the "Hatch-Waxman Act" and codified at 21 U.S.C. § 355. The Hatch-Waxman Act was intended to balance two important public policy goals. First, Congress wanted to ensure that drug manufacturers would have meaningful patent protection and a period of marketing exclusivity to enable them to recoup their investments in the development of valuable new drugs. Second, Congress sought to ensure that, once the patent protection and marketing exclusivity for these drugs expire, consumers would benefit from the availability of lower priced generic versions of approved drugs.

17. Under 21 U.S.C. § 355(b)(1), the NDA applicant is required to submit extensive testing and safety information concerning the drug ("505(b)(1) applications"). In addition, the NDA applicant must submit information on "any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted." Once the NDA is approved, the FDA lists this patent information in its Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the "Orange Book."

18. Both the NDA for the Suboxone® sublingual film and the NDA for the Suboxone® sublingual tablet are 505(b)(1) applications. The '832 patent is listed in the FDA's Orange Book as covering Suboxone® sublingual film. There are no unexpired patents listed on the Orange Book for Suboxone® sublingual tablet.

19. The Hatch-Waxman Act amended the FD&C Act to provide for applications filed under 21 U.S.C. § 355(b)(2) ("505(b)(2) applications"), which allow applicants to obtain FDA approval for other versions of previously-approved drugs without having to repeat the extensive

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TEVA PHARMACEUTICALS LTD.

testing required for a new drug application. Section 505(b)(2) applications can rely, in part, on FDA's previous findings of safety and efficacy for an approved drug product.

20. If a 505(b)(2) applicant relies on previous FDA findings of safety and efficacy for a previously-approved drug product, the 505(b)(2) applicant must identify the drug application which formed the basis for FDA approval ("Reference Listed Drug" or "RLD").

21. Under 21 U.S.C. § 355(b)(2)(A), the 505(b)(2) applicant must make one of the following four certifications with respect to each of the patents listed in the Orange Book for the previously-approved drug product: (i) that the patent information has not been filed ("Paragraph I" certifications); (ii) that the patent has expired ("Paragraph II" certifications); (iii) that the patent will expire on a specific date ("Paragraph III" certifications); or (iv) that the "patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted" ("Paragraph IV" certifications).

22. If a 505(b)(2) applicant makes a Paragraph IV certification, the Hatch-Waxman Act, 21 U.S.C. § 355(b)(3), requires the 505(b)(2) applicant to give notice to the patent owner of the factual and legal basis for the applicant's opinion that the patent is invalid or will not be infringed.

23. If the 505(b)(2) application includes a Paragraph IV certification, the patent owner can file an infringement action within 45 days of receiving the notice of Paragraph IV certification. Such a filing by the patent owner triggers a 30-month injunction or stay of FDA approval, beginning on the date of receipt of the notice. *See* 21 U.S.C. § 355(c)(3)(C). This 30-month period is intended to allow time for judicial resolution on the merits of any patent infringement, validity, and/or enforceability claims, before the competitor is allowed entry into the market.

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24. On July 31, 2013, Defendant BDSI submitted a 505(b)(2) NDA to the FDA, seeking approval to engage in the commercial manufacture and/or sale of Bunavail™. See BDSI's August 1, 2013 press release, attached as Exhibit B. BDSI has not made a certification under 21 U.S.C. § 355(b)(2)(A)(iv) as to the '832 patent or any other patent.

25. Although the most similar alternative to Defendant BDSI's Bunavail™ film product is Suboxone® sublingual film (NDA No. 22-410), BDSI's 505(b)(2) application uses Suboxone® sublingual tablet (NDA No. 20-733) as the reference drug.

26. On information and belief, BDSI's Bunavail™ product, like Suboxone® film and unlike Suboxone® tablet, is a mucoadhesive, erodible, high surface area to weight ratio polymeric dosage form, that is orally delivered and applied to a mucosal surface. Additionally, the excipient profile and associated functionality are distinct from those of the Suboxone® tablet. *See* MonoSol's FDA Citizen Petition dated August 12, 2013, attached as Exhibit C. According to BDSI, Bunavail™ uses BDSI's BioErodible MucoAdhesive ("BEMA") drug delivery technology.

27. Further, while BDSI has not yet announced the strength of the Bunavail™ product, BDSI has enrolled patients into a clinical trial with the following strengths: 3.5/0.6 mg and 5.25/0.9 mg (buprenorphine/naloxone). The strengths of BDSI's buprenorphine/naloxone product in the clinical trial are "most similar" to the 4 mg/1 mg (buprenorphine/naloxone) strength of the Suboxone® film product. *See* BDSI, Clinical Trial, An Open Label Study to Assess the Safety and Tolerability of BEMA® Buprenorphine NX In Opioid Dependent Subjects, attached as Exhibit D.

28. BDSI's decision to use Suboxone® tablet as the reference drug instead of Suboxone® film was a blatant attempt to avoid providing RBP with a notice of Paragraph IV

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certification to the '832 patent, thereby preventing RBP from filing an infringement action within 45 days of receiving the notice of Paragraph IV certification and obtaining a 30-month injunction against BDSI, as permitted under 21 U.S.C. § 355(c)(3)(C).

29. In a Citizen's Petition dated December 2, 2011, Docket No. FDA-2011-P-0869, Plaintiffs requested that the FDA "[r]efuse the submission of any 505(b)(2) NDA for a buprenorphine/naloxone drug product consisting of a polymer film for application to the oral mucosal membranes unless such 505(b)(2) NDA references NDA No. # 22-410 (Suboxone®), which is the NDA for the sublingual film formulation of this product, and makes the appropriate certifications with respect to all patents listed for NDA #22-410."

30. After BDSI submitted its 505(b)(2) application, a different FDA regulation applied; and on August 12, 2013, the Plaintiffs re-filed the Citizen's Petition which was assigned docket number FDA-2013-P-0995.

31. On September 18, 2013, the FDA responded to both Citizen's Petitions, granting them in part and denying them in part (attached as Exhibit E). Importantly, the FDA did not reject BDSI's 505(b)(2) application and found that "[i]n the absence of a pharmaceutically equivalent product, a 505(b)(2) applicant is not required to select a listed drug that is the 'most similar' (in [petitioner's] view) to the proposed product as long as reliance on the listed drug is scientifically justified."

32. Bunavail™ will compete directly with Suboxone® sublingual film. In its 2012 annual report, attached as Exhibit F, BDSI stated that:

> Currently, we remain on track to file the NDA for BUNAVAIL™ with the U.S. Food and Drug Administration (FDA) in mid-summer 2013, putting BDSI in the position to introduce the next branded transmucosal buprenorphine/naloxone film into the marketplace for opioid dependence. This filing will include data from our positive pivotal bioequivalence study completed in the second half of 2012, as well as data from the

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> "Suboxone conversion" safety study which completed in early 2013. In the latter, we were able to demonstrate favorable tolerability of BUNAVAIL™ in opioid dependent subjects when switched from Suboxone. We believe that BUNAVAIL™ will offer an alternative treatment option with advantages over Suboxone, a product that generated sales in excess of $1.5 billion in 2012, according to Wolters Kluwer. As we stated earlier this year, we are evaluating strategic options for the commercialization of BUNAVAIL™, including partnerships as well as leading the commercialization on our own. We plan to finalize this strategy and decision in the second half of 2013.

33. In a press release dated August 9, 2013, attached as Exhibit G, BDSI stated that "[i]f approved, BUNAVAIL will be the first buccal film dosage form containing buprenorphine for the treatment of opioid dependence that will compete with the market leader Suboxone . . . ."

34. On October 9, 2013, BDSI issued another press release, attached as Exhibit H, announcing that its NDA for Bunavail™ "has been accepted for filing by the [FDA]" and that "the review of the BUNAVAIL NDA is expected to be completed by early June 2014."

35. Plaintiffs have been deprived of relief available under the Hatch-Waxman Act, including a stay by the FDA of any approval of BDSI's 505(b)(2) NDA until "the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under subsection (b)(3) of this section or such shorter or longer period as the court may order." 21 U.S.C. § 355(c)(3)(C).

BDSI's REPEATED PATTERN OF INFRINGEMENT, FILING ADVERSARY PROCEEDINGS AGAINST MONOSOL'S PATENTS, AND DELAY

36. In an action pending in the United States District Court for the District of New Jersey, Docket No. 3:10-cv-05695-FLW-DEA ("the New Jersey Action"), Plaintiff MonoSol asserted patent infringement claims against BDSI in connection with the Onsolis™ film product. Plaintiff MonoSol asserted infringement of U.S. Patent No. 7,425,292 ("the '292 patent") as well as U.S. Patents Nos. 7,357,891 ("the '891 patent") and 7,824,588 ("the '588 patent").

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TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

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

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	12/6/2013	DELAWARE

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

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

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 of Delaware on the following

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

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	10/8/2013	of Delaware

PLAINTIFF	DEFENDANT
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
1	U.S. 8,475,832	7/2/2013	RB Pharmaceuticals Limited
2	U.S. 8,017,150	9/13/2011	MonoSol Rx, LLC
3			
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	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

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 of Delaware on the following

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

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	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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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
1		
2		
3		
4		
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

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.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/537,571	07/02/2013	8475832	1199-82	5630

23869 7590 06/12/2013

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 231 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):

Garry L. Myers, Kingsport, TN;
Samuel D. Hilbert, Jonesboro, TN;
Bill J. Boone, Johnson City, TN;
B. Arlie Bogue, New Carlisle, IN;
Pradeep Sanghvi, Schererville, IN;
Madhusudan Hariharan, Munster, IN;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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

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)

23869 7590 05/24/2013
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.

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
12/537,571	08/07/2009	Garry L. Myers	1199-82	5630

TITLE OF INVENTION: SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	08/26/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
EPPS -SMITH, JANET L	1633	424-435000

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: RB Pharmaceuticals Limited
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Slough, United Kingdom

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 08-2461 (enclose an extra copy of this form).

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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

☐ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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 /Stephen J. Brown/ Date May 29, 2013

Typed or printed name Stephen J. Brown Registration No. 43,519

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.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Electronic Patent Application Fee Transmittal

Application Number:	12537571
Filing Date:	07-Aug-2009
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Filer:	Daniel A. Scola/Ivory Edwards
Attorney Docket Number:	1199-82

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	1780	1780
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2080**

Electronic Acknowledgement Receipt

EFS ID:	15894088
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Daniel A. Scola/Ivory Edwards
Filer Authorized By:	Daniel A. Scola
Attorney Docket Number:	1199-82
Receipt Date:	29-MAY-2013
Filing Date:	07-AUG-2009
Time Stamp:	13:44:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2080
RAM confirmation Number	15029
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	Issue Fee Payment (PTO-85B)	1199_82_RCE_Issue_Fee.PDF	267985 0a5869ae5831f00006acb30fc504e1b00837751e	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31886 ba7979d41d857fc3f0a0ed1d1e01882004b12279	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	299871		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	12/537,571	MYERS ET AL.	
	Examiner	Art Unit	
	Janet Epps-Smith	1633	

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

(1) *Janet Epps-Smith*. (3)_____.

(2) *Stephen Brown*. (4)_____.

Date of Interview: *20 May 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

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

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1 and 17*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicants explained that the prior art is silent regarding the use of a buffer to provide a local pH which would achieve optimized absorption of burenorphine and naloxone. The examiner agreed that the prior art does not teach the claimed local pH.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

23869 7590 05/24/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER
EPPS -SMITH, JANET L

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 05/24/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/537,571	08/07/2009	Garry L. Myers	1199-82	5630

TITLE OF INVENTION: SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	08/26/2013

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 ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

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.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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

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)

23869 7590 05/24/2013
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.

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/537,571	08/07/2009	Garry L. Myers	1199-82	5630

TITLE OF INVENTION: SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	08/26/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
EPPS -SMITH, JANET L	1633	424-435000

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).

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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.

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.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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.
12/537,571	08/07/2009	Garry L. Myers	1199-82	5630

23869 7590 05/24/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
EPPS -SMITH, JANET L	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 05/24/2013

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 132 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 132 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.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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. 12/537,571	Applicant(s) MYERS ET AL.	
	Examiner Janet Epps-Smith	Art Unit 1633	AIA (First Inventor to File) Status No

-- 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 *Amendment filed 04/30/2013*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1,4-10,17,18,20-23 and 27-31*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   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: _____.

   Interim copies:

   a) ☐ All b) ☐ Some c) ☐ None of the: Interim copies of the priority documents have been 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.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ 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. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *05/20/2013* .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Janet Epps-Smith/
Primary Examiner, Art Unit 1633

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12537571	MYERS ET AL.
	Examiner	**Art Unit**
	JANET EPPS -SMITH	1633

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION						
CLASS	**SUBCLASS**	**CLAIMED**					**NON-CLAIMED**	
424	435	A	6	1	F	13 / 00 (2006.01.01)		
CROSS REFERENCE(S)		A	6	1	K	9 / 14 (2006.01.01)		
		A	6	1	K	31 / 44 (2006.01.01)		
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**							
424	422	434	484					
514	282							

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 19
/JANET EPPS -SMITH/ Primary Examiner.Art Unit 1633 (Primary Examiner) (Date)	O.G. Print Claim(s) 1 O.G. Print Figure NONE

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	JANET EPPS -SMITH	1633

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 19	
/JANET EPPS -SMITH/ Primary Examiner.Art Unit 1633 (Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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	Examiner	**Art Unit**
	JANET EPPS -SMITH	1633

☒ **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	9	17												
	2	10	18												
	3		19												
2	4	11	20												
3	5	12	21												
4	6	13	22												
5	7	14	23												
6	8		24												
7	9		25												
8	10		26												
	11	15	27												
	12	16	28												
	13	17	29												
	14	18	30												
	15	19	31												
	16														

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 19	
/JANET EPPS -SMITH/ Primary Examiner.Art Unit 1633 (Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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UNITED STATES PATENT AND TRADEMARK OFFICE

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

BIB DATA SHEET

CONFIRMATION NO. 5630

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/537,571	08/07/2009	424	1633	1199-82

APPLICANTS

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Pradeep Sanghvi, Schererville, IN;
Madhusudan Hariharan, Munster, IN;

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

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
08/21/2009

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /JANET L EPPS -SMITH/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		TN	0	31	7

ADDRESS

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791
UNITED STATES

TITLE

SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

FILING FEE RECEIVED		
1188	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12537571	MYERS ET AL.
	Examiner	**Art Unit**
	JANET EPPS -SMITH	1633

✓	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	05/20/2013								
1	1	=								
	2	-								
	3	-								
2	4	=								
3	5	=								
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17	29	=								
18	30	=								
19	31	=								

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TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	1332	(matrix or liposome or polymeric or carrier) and (buprenorphine) and naloxone and buffer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/21 18:48
S2	1236	S1 and pH	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/21 18:48
S3	614	S2 and (film or biofilm)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/21 18:49
S4	580148	film forming polymer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2011/08/21 18:49
S5	22690	film forming polymer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	NEAR	ON	2011/08/21 18:49
S6	56	S3 and S5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	NEAR	ON	2011/08/21 18:49
S7	48	(film dosage).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	NEAR	ON	2011/08/21 18:50
S8	2	S6 and S7	US-PGPUB;	NEAR	ON	2011/08/21

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TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

			USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			18:50
S9	1388	(buprenorphine) and naloxone and buffer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/21 18:56
S10	3	S7 and S9	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/21 18:56
S11	70	US-20070148097-$.DID. OR US-6228863-$.DID. OR US-6310072-$.DID. OR US-6375957-$.DID. OR US-6469170-$.DID. OR US-4582835-$.DID. OR US-4464378-$.DID. OR US-4990617-$.DID. OR US-5272149-$.DID. OR US-4154932-$.DID. OR US-5512578-$.DID. OR US-5512593-$.DID. OR US-5552406-$.DID. OR US-5817665-$.DID. OR US-5834480-$.DID. OR US-5856332-$.DID. OR US-6034091-$.DID. OR US-6277384-$.DID. OR US-6291675-$.DID. OR US-6475494-$.DID. OR US-6696066-$.DID. OR US-6995169-$.DID. OR US-7144587-$.DID. OR US-7172767-$.DID. OR US-7384653-$.DID. OR US-7402591-$.DID. OR US-7419686-$.DID. OR US-7749542-$.DID. OR US-20020010127-$.DID. OR US-20020013301-$.DID. OR US-20020058673-$.DID. OR US-20030004178-$.DID. OR US-20030031712-$.DID. OR US-20030044458-$.DID. OR US-20030068392-$.DID. OR US-20030124185-$.DID. OR US-20030191147-$.DID. OR US-20030211157-$.DID. OR US-20040086561-$.DID. OR US-20050048115-$.DID. OR US-20050063909-$.DID. OR US-20050191340-$.DID. OR US-20050192309-$.DID. OR US-20060058332-$.DID. OR US-20060058333-$.DID. OR US-20060069113-$.DID. OR US-20070122348-$.DID.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/08/22 11:04
S12	1566	(myers-g$ or hilbert-s$ or boone-b$ or bogue-b$ or sanghvi-P$ or hariharan-M$).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 11:12

TEVA EXHIBIT 1002
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S13	1332	(matrix or liposome or polymeric or carrier) and (buprenorphine) and naloxone and buffer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 11:13
S14	5	S13 and S12	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 11:13
S17	918	(matrix or liposome or polymeric or carrier) and (buprenorphine) and naloxone and buffer and absorption	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 14:10
S18	17	naloxone adj25 absorption	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 14:11
S19	5	S17 and S18	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 14:11
S20	1332	(matrix or liposome or polymeric or carrier) and (buprenorphine) and naloxone and buffer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 16:34
S21	70	US-20070148097-$.DID. OR US-6228863-$.DID. OR US-6310072-$.DID. OR US-6375957-$.DID. OR US-6469170-$.DID. OR US-4582835-$.DID. OR US-4464378-$.DID. OR US-4990617-$.DID. OR US-5272149-$.DID. OR US-4154932-$.DID. OR US-5512578-$.DID. OR US-5512593-$.DID. OR US-5552406-$.DID. OR US-5817665-$.DID. OR US-5834480-$.DID. OR US-5856332-$.DID. OR US-6034091-$.DID. OR US-6277384-$.DID. OR US-6291675-$.DID. OR US-6475494-$.DID. OR US-6696066-$.DID. OR US-6995169-$.DID. OR US-7144587-$.DID. OR US-7172767-$.DID. OR US-7384653-$.DID. OR US-7402591-$.DID. OR US-7419686-$.DID. OR US-7749542-$.DID. OR US-20020010127-$.DID. OR US-20020013301-$.DID. OR US-20020058673-$.DID. OR US-	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/08/22 16:39

		20030004178-$.DID. OR US-20030031712-$.DID. OR US-20030044458-$.DID. OR US-20030068392-$.DID. OR US-20030124185-$.DID. OR US-20030191147-$.DID. OR US-20030211157-$.DID. OR US-20040086561-$.DID. OR US-20050048115-$.DID. OR US-20050063909-$.DID. OR US-20050191340-$.DID. OR US-20050192309-$.DID. OR US-20060058332-$.DID. OR US-20060058333-$.DID. OR US-20060069113-$.DID. OR US-20070122348-$.DID.				
S22	5	S21 and (film adj50 dosage)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/08/22 16:39
S23	5	S21 and (film adj50 dosage)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/08/22 16:40
S27	4	("1897543").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/08/29 08:15
S28	2	("20100087470").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/08/29 08:19
S29	2	S28 and naloxone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 08:20
S30	1	S28 and naloxone and absorption and citric	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 08:24
S31	1	S28 and naloxone and absorption and citric and pH	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT;	OR	ON	2011/08/29 08:55

			IBM_TDB			
S32	0	S28 and naloxone and absorption and citric and pH and (suppress or block)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 09:03
S33	0	S28 and naloxone and absorption and citric and pH and block	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 09:03
S34	1	S28 and naloxone and absorption and citric and pH and polymer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 09:26
S35	2	("20110033541").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/08/29 10:22
S36	2	S35 and inhibit	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 10:23
S37	1581	(buprenorphine) and naloxone and buffer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2012/05/01 13:42
S38	692	S37 and sublingual	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2012/05/01 13:43
S39	492	S38 and citric	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2012/05/01 13:43
S40	7	S38 and citric.clm.	US-PGPUB; USPAT; USOCR; FPRS;	OR	ON	2012/05/01 13:43

			EPO; JPO; DERWENT; IBM_TDB			
S41	10	((buprenorphine) and naloxone and buffer).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2012/05/01 13:47
S42	3	suboxone near sublingual	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2012/05/01 13:51
S43	2	("20110262522").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/05/02 14:26

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	5	suboxone near sublingual	US-PGPUB; USPAT; UPAD	OR	ON	2013/05/20 14:25
L3	543	BUPRENORPHINE ADJ5 NALOXONE	US-PGPUB; USPAT; UPAD	OR	ON	2013/05/20 14:26
L4	377	3 AND (POLYMERIC OR FILM)	US-PGPUB; USPAT; UPAD	OR	ON	2013/05/20 14:26
L5	306	4 AND FILM	US-PGPUB; USPAT; UPAD	OR	ON	2013/05/20 14:26
L6	48	4 AND FILM.CLM.	US-PGPUB; USPAT; UPAD	OR	ON	2013/05/20 14:26
L7	7	6 AND PH.CLM.	US-PGPUB; USPAT; UPAD	OR	ON	2013/05/20 14:27
S15	2	"11634280"	US-PGPUB; USPAT; UPAD	OR	ON	2011/08/22 11:21
S16	2	S15 and opiate and (agonist or antagonist)	US-PGPUB; USPAT; UPAD	OR	ON	2011/08/22 11:24
S24	2	"11634280"	US-PGPUB; USPAT; UPAD	OR	ON	2011/08/22 17:05
S25	1	S24 and opiate and (agonist or antagonist) and naloxone and buprenorphine	US-PGPUB; USPAT; UPAD	OR	ON	2011/08/22 17:05

S26	2	S24 and opiate and (agonist or antagonist) and naloxone	US-PGPUB; USPAT; UPAD	OR	ON	2011/08/22 17:06
S44	1	"Term Removed"	US-PGPUB; USPAT; UPAD	OR	OFF	2012/05/02 19:28

5/ 20/ 2013 2:29:01 PM
C:\ Users\ jeppssmith\ Documents\ EAST\ Workspaces\ 12537571.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/537,571	MYERS ET AL.	
	Examiner	Art Unit	
	Janet Epps-Smith	1633	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
Text search only no class searched in UPAD, USPAT, PGPUB		5-20-2013	JLE

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Inventor name search	8-22-11	JLE
Plus search	8-22-11	JLE
East-see attached	8-29-11	JLE
searcH notes updated	4-30-2012	JLE
Search notes updated in EAST-text search only in USPAT, UPAD, PGPUB	5-20-2013	JLE

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset NY 11791

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 12/537,571

1. THE REQUEST FILED April 30, 2013 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination
- A. ☐ for an original nonprovisional application (Track I).
- B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

- A. filing a **petition for extension of time** to extend the time period for filing a reply;
- B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
- C. filing a **request for continued examination**;
- D. filing a notice of appeal;
- E. filing a request for suspension of action;
- F. mailing of a notice of allowance;
- G. mailing of a final Office action;
- H. completion of examination as defined in 37 CFR 41.102; or
- I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to JoAnne Burke at 571-272-4584. In his/her absence, calls may be directed to Brian Brown, 571-272-5338.

/JoAnne Burke/
[*Signature*]

Petitions Examiner
(Title)

TEVA EXHIBIT 1002
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Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12537571	Filing Date	2009-08-07	Docket Number (if applicable)	1199-82 RCE	Art Unit	1633
First Named Inventor	Garry L. Myers			Examiner Name	Epps-Smith, Janet L.		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 082461

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

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TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

PTO/SB/30EFS (07-09)
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Signature of Registered U.S. Patent Practitioner			
Signature	/Stephen J. Brown/	Date (YYYY-MM-DD)	2013-04-30
Name	Stephen J. Brown	Registration Number	43519

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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

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

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

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

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

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

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

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

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

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

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 1199-82 RCE

Application Number: 12537571

Filed: August 7, 2009

For: SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

Art Unit: 1633

Examiner: Epps-Smith, Janet L.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☑ One month (37 CFR 1.17(a)(1))	$200	$100	$50	$ 200
☐ Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☐ Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐ Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐ Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

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

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

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

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 082461.

☐ Payment made via EFS-Web.

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

I am the

☐ applicant/inventor.

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

☑ attorney or agent of record. Registration number 43,519.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Stephen J. Brown/ — Signature

April 30, 2013 — Date

Stephen J. Brown — Typed or printed name

973-331-1700 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 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.**

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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.
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.
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Myers et al.	Examiner:	Janet L. Epps-Smith
Serial No.:	12/537,571	Group Art Unit:	1633
Confirmation No.:	5630	Docket:	1199-82 RCE
Filed:	August 7, 2009	Dated:	April 30, 2013
For:	Sublingual and Buccal Film Compositions		

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Alexandria, Virginia 22313-1450

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I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: April 30, 2013

Signature: Stephen J. Brown \Stephen J. Brown\

AMENDMENT AND RESPONSE WITH REQUEST FOR CONTINUED EXAMINATION

Madam:

In response to the Final Office Action dated May 2, 2012, and Advisory Action dated November 2, 2012, Applications make the following amendments and remarks. This communication is filed concurrently with a Request for Continued Examination.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

Amendments to the Claims:

This listing of claims shall replace all previous listings in this application:

1. (Currently Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffer in an amount to provide a local pH for said composition of a value sufficient to optimize absorption of said buprenorphine, wherein said local pH is from about 3 [[2]] to about 3.5 in the presence of saliva.
2. (Canceled).
3. (Cancelled).
4. (Original) The composition of claim 1, wherein said film dosage composition provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
5. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one polymer in an amount of at least 25% by weight of said composition.
6. (Original) The composition of claim 1, wherein said buffer is present in an amount of from about 2:1 to about 1:5 by weight of buffer to buprenorphine.
7. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one self-supporting film forming polymer.
8. (Original) The film dosage composition of claim 1, wherein said buprenorphine is present in an amount of from about 2 mg to about 16 mg per dosage.
9. (Original) The film dosage composition of claim 1, wherein said buffer comprises sodium citrate, citric acid, and combinations thereof.
10. (Original) The film dosage composition of claim 1, wherein said buffer comprises acetic acid, sodium acetate, and combinations thereof.

11. (Cancelled).
12. (Cancelled).
13. (Cancelled).
14. (Cancelled).
15. (Cancelled).
16. (Cancelled).
17. (Currently Amended) A method of treating narcotic dependence of a user, comprising the steps of:
    a. providing a composition comprising:
        i. A polymeric carrier matrix;
        ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
        iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
        iv. A buffer in an amount to provide a local pH of about 3 [[2]] to about 3.5 for said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and
    b. administering said composition to the oral cavity of a user.
18. (Original) The composition of claim 17, wherein said method provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
19. (Cancelled).
20. (Original) The method of claim 17, wherein said film dosage composition is administered to the user through buccal administration, sublingual administration, and combinations thereof.
21. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of at least 1 minute.
22. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of between about 1 and 1.5 minutes.

23. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of up to 3 minutes.
24. (Cancelled).
25. (Cancelled).
26. (Cancelled).
27. (Original) An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.
28. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 5.431 hr.ng/ml to about 56.238 hr.ng/ml for buprenorphine.
29. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 102.88 hr.pg/ml to about 812.00 hr.pg/ml for naloxone.
30. (Original) The formulation of claim 27, wherein said formulation comprises about 2 to about 16 mg of buprenorphine or a salt thereof.
31. (Original) The formulation of claim 27, wherein said formulation comprises about 0.5 to about 4 mg of naloxone or a salt thereof.

REMARKS

Independent claims 1 and 17 have been amended to recite a local pH range of about 3 to about 3.5. This limitation was previously claimed in claims 3 and 19, respectively. Accordingly, no new matter has been added.

Claims 3, 11-16, 19, and 24-26 have been cancelled without prejudice.

Claims 1, 4-10, 17-18, 20-23, and 27-31 are pending.

Rejection under 35 U.S.C. §103

In the Office Action, the Examiner rejected claims 1 and 3-31 under 35 U.S.C. §103(a) as allegedly obvious over Oksche (WO 2008/025791, counterpart U.S. Patent Application Publication No. 2010/0087470). The Examiner stated that, although Oksche fails to disclose pH values, the determination of a suitable pH range would have been obvious and routine experimentation. The Examiner stated that Oksche discloses a Suboxone tablet, and thus it would have been obvious to modify Oksche accordingly. Finally, the Examiner stated that the "open range" of the pH in the claims (i.e., using the term "about") further demonstrates its obviousness. Applicants respectfully traverse this rejection.

Although believed unnecessary, claims 3, 11-17, 19, and 24-26 have been cancelled to further prosecution. The rejection of these claims has been rendered moot and withdrawal is respectfully requested.

Claims 1, 4-10, 17-18, and 20-23:

Independent claims 1 and 17 have been amended to recite a local pH range of about 3 to about 3.5. Claims 4-10 and 18 and 20-23 depend from claims 1 and 17, respectively.

As previously argued, the claimed pH range achieves the goals of optimizing the absorption of one component (buprenorphine) and minimizing the absorption of a second component (naloxone). The Applicants have repeatedly shown that Oksche is completely devoid of any recitation of any pH range. Thus, there is absolutely no direction in Oksche to allow one of ordinary skill in the art to come up with the claimed invention. And, assuming arguendo that Oksche disclosed a pH, there is simply no predictability in modifying that pH to the claimed level and expecting to achieve the significant results claimed.

Moreover, Applicants have repeated demonstrated that experimental results in the specification show that the claimed pH range has unexpected benefits. A detailed discussion of these results is presented below for completeness. To briefly summarize, , the present applicants have discovered that the suitable buffer capacity actually differs from that which would be expected from pH partition theory. For example, the buffer capacity for a product including both the buprenorphine and naloxone would be one that minimizes the absorption of the naloxone but optimizes the absorption of the buprenorphine – a concept not disclosed nor considered by Oksche. For example, the present inventors have discovered that at a pH of about 3-3.5, the relative absorptions can be controlled effectively.

In response, to these experimental results and argument, the Examiner has essentially conceded that they are sufficient to overcome the rejection over Oksche, but that the claims are not commensurate in scope to the data:

> Applicant's argument that the Examples show significant benefits when a pH of about 3.5 is used is used as compared to a pH of 6.5 and 5.5, Example 8 tested products at a pH of ***from 3.0-3.5*** is not sufficient to provide evidence of unexpected or significant benefits associated with the full scope of the claimed invention, which recites a "local pH of ***about 2 to about 3.5 in the presence of saliva***." Applicant showing is not commensurate in scope with the claimed invention.

(Advisory Action at 2-3 (emphasis original).) Applicants note that the Examiner has not alleged that the experimental results are to be expected or otherwise rebutted the demonstration of unexpected results.

Accordingly, although believed unnecessary and only to further prosecution, Applicants have amended independent claims 1 and 17 to recite the local pH range of about 3 to about 3.5 to provide a scope that is fully and expressly supported by the experimental results. In view of the claims amendments, the Examiner's comments, and the experimental results Applicants submit that the alleged *prima facie* obviousness has been rebutted. For this reason alone, reconsideration and withdrawal of the rejection are respectfully solicited for claims 1, 4-10, 17-18, and 20-23.

As discussed above, previously described in the earlier responses, and as supported throughout the specification, the Applicant has surprisingly identified that the optimized

adsorption of buprenorphine and the optimized limited adsorption of naloxone do not follow traditional or expected adsorption profiles. Both compounds are conjugate organic acids with pKa's at approximately 8, and yet as the pH of the film for delivering the agents decreases, one compound undergoes a optimum adsorption, but the other compound surprisingly trends the opposite direction and is inhibited at the same lower pH levels. This divergence allows the Applicant to produce a film which delivers buprenorphine to the bloodstream and passes the naloxone to the gut where it is ineffective, thus providing a treatment regime for buprenorphine. At the same time, the film is protected from abuse, because if a patient diverts the dosage, the naloxone inhibits the opioid effect when injected, snorted or otherwise administered in a drug abuse attempt.

To counter the experimental evidence and surprising results, the Examiner has offered only a single reference, *Oksche,* in an obviousness rejection. *Oksche* is completely silent regarding adjusting pH to optimize the adsorption of buprenorphine and minimize the adsorption of naloxone. The only evidence offered by the Examiner for such a conclusion is that *Oksche* mentions pH modifiers such as "citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid" in the context of "secondary components such as preservatives, anti-oxidants, surfactants, viscosity enhancers, colouring agents, flavouring agents, pH modifiers, sweeteners or taste-masking agents [that] may be incorporated into the composition." *Oksche*, [0072]. Thus, the Examiner concludes that optimizing the pH is obvious in view of *Oksche* because pH modifiers are mentioned in passing. The Examiner relies on MPEP 2144.05 and asserts that "it would have been obvious to the ordinary skilled artisan… to modify their teachings so as to identify the optimal range of pH/dosage in an effort to identify formulations that would provide optimal adsorption of both agonist and antagonist. As per MPEP 2144.05, … identification of the optimal pH/dosage appears to be a matter of routine experimentation." *Advisory Action* dated November 6, 2012, p. 4.

Applicant submits that the Examiner's arguments are misplaced for at least two reasons. First, MPEP 2144.05 applies for "Obviousness of Ranges," yet nothing within the disclosure of *Oksche* describes any range of pH. *Oksche* is completely silent regarding any amounts of acids, bases, buffers or anything substantive beyond the passing mention of "secondary components." Thus, the Examiner's conclusion that it would be obvious to

provide a specific range of pH for controlling adsorption of one active and inhibiting the adsorption of a similar active cannot be supported by that disclosure. Therefore, the Examiner is impermissibly relying on Applicant's own discovery of the significance of pH ranges in optimizing adsorption.

Second, even accepting for the sake of argument that MPEP 2144.05 applied because *Oksche* somehow provides some concept of pH, the instructions within that section of the MPEP again leads to the conclusion that reliance on *Oksche* is not proper. "A particular parameter must first be recognized as a result-effective variable, i.e. a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." MPEP 2144.05(II)(B) (citing *In re Antonie*, 559 F.2d 618 (CCPA 1977)) (emphasis added.) Here, *Oksche* is completely silent regarding the necessity of adding an acid or buffer. *Oksche* treats such components in the same manner as a flavoring agent, coloring agent, taste masking agent, or any number of other secondary components. *Oksche* does not indicate that the pH of 2-3.5 would lead to an optimized buprenorphine adsorption AND a minimized naloxone adsorption. *Oksche* never identifies nor understands the criticality of pH, and therefore cannot be asserted for the conclusion that it's merely a results effective variable that can be modified.

Moreover, based on the disclosure of Oksche one of skill in the art would have had a no rationale to use pH to modify absorption. Significantly, Oksche actually discusses enhancing absorption of buprenorphine over the mucosa. However, this discussion has nothing to do with pH, but rather points to permeation enhancers:

> In order **to allow absorption of buprenorphine over the mucosa of the mouth**, and particularly sublingually, in one embodiment **the dosage forms may additionally use agents that enhance absorption of the active agent, i.e. so-called permeation enhancers**.
>
> Such permeation enhancers may be selected from the group comprising propandiol, dexpanthenol, and oleic acid. The permeation enhancers may also be selected from the group comprising saturated or unsaturated fatty acids, hydrocarbons, linear or branched fatty alcohols, dimethylsulfoxide, propylene glycol, decanol, dodecanol, 2-octyldodecanol, glycerine, ethanol or other alcohols.

(¶ 0085-86 (emphasis added).) None of these would be considered to modify pH or act as buffers.

Furthermore, this is but one of many variables and ingredients that could be considered to effect absorption of the active ingredients. Accordingly, one of skill in the art with knowledge of the absorption of the actives from a tablet at pH 6.5, would have had no rationale to turn to pH out of all parameters to optimize absorption, much less to drastically reduce the pH to 3 to 3.5 and expect optimum results.

In sum, the rejection is completely devoid of any evidence or reasoning sufficient to demonstrate that one of skill in the art would have had any rationale to modify Oksche to arrive at the claimed invention.

For these additional reasons, the rejection falls short of providing a *prima facie* case for the obviousness of the claims. Reconsideration and withdrawal are respectfully solicited.

As noted above, the previous discussion of the experimental results is included here for completeness:

Experimental Results

Even further, as explained in detail in the application as filed and in the previous response, one of ordinary skill in the art would have expected that a product would follow pH partition theory. According to pH partition theory, one would expect that saliva (which has a pH of about 6.5) would maximize the absorption of both actives. However, it has been surprisingly discovered by the Applicant that by buffering the dosage to a particular pH level, the optimum levels of absorption of the buprenorphine and the naloxone may be achieved. It has been discovered that the desirable local pH of a composition including buprenorphine and naloxone is between about 2 to about 3.5. At this local pH level, the desired absorption of the buprenorphine and the naloxone is achieved. As described in the application as filed and in the Examples (discussed below), controlling the local pH of the film compositions of the present invention provides a system in which the desired release and/or absorption of the components is achieved.

As such, if one of ordinary skill in the art was to simply modify the pH, that person would have followed pH partition theory and used a pH of about 6.5.

The present inventors have undertaken significant experimentation to determine the conditions to effectively and efficiently deliver a suitable dosage of buprenorphine and, in appropriate circumstances, to effectively and efficiently inhibit the absorption of naloxone. The inventors have determined that the buffer selected and the buffer capacity used in the film has a significant and dramatic effect on the absorption of actives. However, the arrival at this invention is not simply limited to mere selection of pH ranges, and must take into account the Cmax and AUC values for the product.

The Examples are set forth in the application as filed, and as can be seen, the Applicant discovered that optimized values can be achieved when the pH of the film falls within the claimed range. These results are surprising, particularly in view of pH partition theory, which would be understood that a pH of about 6.5 would be successful in achieving the desired balance between drug solubility and ionization.

The tests conducted by the Applicant demonstrate surprising and very effective results at the claimed pH levels. Again, these levels are certainly not obvious over Oksche's general disclosure (including lack of any pH range) and the present examples demonstrate the surprising effect that is achieved.

In particular, the Examples show the significant benefits when a pH of about 3.5 is used as compared to a pH of 6.5 and 5.5. See, for example, Example 8, which tested products at a pH of from 3.0-3.5.

As has previously been explained, the present applicants have discovered that the suitable buffer capacity actually differs from that which would be expected from pH partition theory. For example, the buffer capacity for a product including both the buprenorphine and naloxone would be one that minimizes the absorption of the naloxone but optimizes the absorption of the buprenorphine – a concept not disclosed nor considered by Oksche. For example, the present inventors have discovered that at a pH of about 2-3.5, the relative absorptions can be controlled effectively.

Claims 27-31:

Independent claim 27 recites that the "formulation provides an in vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone." Claims 28-31 depend from claim 27.

These claims have not been addressed in any of the art rejections, except by number. Thus, the limitations of these claims have never been addressed by the Examiner. Accordingly, these claims have not been rejected on any grounds.

Moreover, while Oksche does discuss the Cmax for buprenorphine, it is completely silent as to the Cmax for naloxone. Thus, even if the Examiner had applied the reference to the claims 27-31, Oksche would fall far short of supporting a rejection of claims 27-31 as obvious.

For these reasons, the rejection does not present a *prima facie* case for the obviousness of claims 27-31. Reconsideration and withdrawal of the rejection as to these claims are respectfully solicited.

Conclusion

In view of the foregoing, it is submitted that rejection has been met and the claims are in condition for allowance. Prompt entry of the amendments and allowance of the application are respectfully solicited.

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

If there are any questions or if additional information is required, the Examiner is respectfully requested to contact Applicant's attorney at the number listed below.

Respectfully submitted,

/Stephen J. Brown/
Stephen J. Brown
Registration No.: 43,519
Attorney for Applicants

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

Electronic Patent Application Fee Transmittal

Application Number:	12537571
Filing Date:	07-Aug-2009
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Filer:	Stephen J. Brown
Attorney Docket Number:	1199-82

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
OTHER PUBLICATION PROCESSING FEE	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	200	200
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**5530**

Electronic Acknowledgement Receipt

EFS ID:	15654992
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	1199-82
Receipt Date:	30-APR-2013
Filing Date:	07-AUG-2009
Time Stamp:	17:04:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$5530
RAM confirmation Number	4860
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	TrackOne Request	1199-82_RCE_Request_for_Prioritized_Examination.pdf	153663 ee4f91c40fd9dddc0ad86f251e4c9881effe822a	no	2
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	1199-82_RCE_RCE.PDF	797915 a7c54b2ac9cf49a55534c6828aa3a5a0c68dce78	no	3
Warnings:					
Information:					
3	Extension of Time	1199-82_REC_EOT.PDF	187110 29906b3a636d6faf05ea3d86ede1f820fb249d04	no	2
Warnings:					
Information:					
4		1199-82_RCE_Amendment.pdf	54837 c67e87326a16acf2539f25971bfc05dae282c839	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment Submitted/Entered with Filing of CPA/RCE	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	12

Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	35221 d04be5f037b18e98ed20801e81be1e650e7ed3ed	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1228746	

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.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-13)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Garry L. Myers	Nonprovisional Application Number (if known):	12537571
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. The executed inventor's oath or declaration is filed with the application. (37 CFR 1.63 and 1.64)

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Stephen J. Brown, Reg. No. 43,519/	Date April 30, 2013
Name (Print/Typed) Stephen J. Brown	Practitioner Registration Number 43519

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *Total of _____ forms are submitted.

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.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/537,571	Filing Date 08/07/2009	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **04/30/2013**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 19	Minus	** 31	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***7	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/MARISSA BLYTHER/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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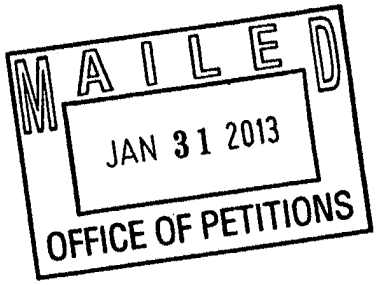

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

In re Application of Myers et al. :
Application No. 12/537,571 : Decision on Petition
Filing Date: August 7, 2009 :
Attorney Docket No. 1199-82 :

This is a decision on the petition under 37 CFR 1.137(a) filed November 15, 2012, to revive the above-identified application.

The petition is **granted.**

On May 2, 2012, the Office mailed a final Office action setting statutory period for reply of three months.

An amendment was filed with payment for a three-month extension of time on October 22, 2012.

The Office issued an Advisory Action on November 6, 2012, which indicates the October 22, 2012 reply is not a proper reply to the final Office action.

Since a proper reply was not timely filed in response to final Office action, the application became abandoned on November 3, 2012.

The instant petition asserts a Notice of Appeal would have been prepared and timely filed on November 2, 2012, absent events involving Hurricane Sandy.

A review of the record indicates the petition satisfies the requirements set forth in 37 CFR 1.137(a). Therefore, the petition is granted, and the application is hereby revived.

The Notice of Appeal filed with the petition has been entered. The two-month period for filing the appeal brief runs from the date of this decision. See MPEP 1205.

The file does not indicate a change of address has been submitted even though the address given on the petition differs from the address of record. If appropriate, a request to change the address of record should be filed. A courtesy copy of this decision is being mailed to the address given

on the petition; however, the Office will mail all future correspondence solely to the address of record.

Technology Center Art Unit 1633 will be informed of the instant decision in order to ensure the art unit is aware the application has been revived.

Telephone inquiries regarding this communication should be directed to Petitions Attorney Steven Brantley at (571) 272-3203.

Charles Steven Brantley
Senior Petitions Attorney
Office of Petitions

cc: Hoffman & Baron LLP
6 Campus Drive
Parsippany, NJ 07054

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
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.

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

Docket Number (Optional): 1199-82

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: Garry Myers

Application Number	Filed
12/537,571	August 7, 2009

For: SUBLINGUAL BUCCAL ADHESION

Art Unit	Examiner
1633	Janet L. Epps-Smith

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)) $ 630.00

☐ 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. 082461 .

☐ 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 43,519.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____

/Stephen J. Brown/
Signature

Stephen J. Brown
Typed or printed name

973-331-1700
Telephone number

November 15, 2012
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.

PTO/SB/61 (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.

PETITION FOR REVIVAL OF AN APPLICATION FOR PATENT ABANDONED UNAVOIDABLY UNDER 37 CFR 1.137(a)	Docket Number (Optional) 1199-82

First Named Inventor: Garry Myers Art Unit: 1633
Application Number: 12/537,571 Examiner: Janet L. Epps-Smith
Filed: August 7, 2009

Title: SUBLINGUAL BUCCAL ADHESION

Attention: Office of Petitions
Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NOTE: If information or assistance is needed in completing this form, please contact Petitions Information at (571) 272-3282.

The above-identified application became abandoned for failure to file a timely and proper reply to a notice or action by the United States Patent and Trademark Office. The date of abandonment is the day after the expiration date of the period set for reply in the Office notice or action plus any extensions of time actually obtained.

APPLICANT HEREBY PETITIONS FOR REVIVAL OF THIS APPLICATION.
NOTE: A grantable petition requires the following items:
(1) Petition fee.
(2) Reply and/or issue fee.
(3) Terminal disclaimer with disclaimer fee – required for all utility and plant applications filed before June 8, 1995, and for all design applications; and
(4) Adequate showing of the cause of unavoidable delay.

1. Petition fee

☐ Small entity – fee $_____ (37 CFR 1.17(l)). Applicant claims small entity status. See 37 CFR 1.27.

☑ Other than small entity – fee $ 630.00 (37 CFR 1.17(l)).

2. Reply and/or fee

A The reply and/or fee to the above-noted Office action in the form of Notice of Appeal (identify the type of reply):

☐ has been filed previously on _____ .

☑ is enclosed herewith.

B The issue fee of $ _____

☐ has been filed previously on _____ .

☐ is enclosed herewith.

This collection of information is required by 37 CFR 1.137(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours 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 Petition, 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.

PETITION FOR REVIVAL OF AN APPLICATION FOR PATENT ABANDONED UNAVOIDABLY UNDER 37 CFR 1.137(a)

3. Terminal disclaimer with disclaimer fee

☑ Since this utility/plant application was filed on or after June 8, 1995, no terminal disclaimer is required.

☐ A terminal disclaimer (and disclaimer fee (37 CFR 1.20(d)) of $ _____ for a small entity or $ _____ for other than a small entity) disclaiming the required period of time is enclosed herewith (see PTO/SB/63).

4. An adequate showing of the cause of the delay, and that the entire delay in filing the required reply from the due date for the reply until the filing of a grantable petition under 37 CFR 1.137(a) was unavoidable, is enclosed.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

/Stephen J. Brown/	November 15, 2012
Signature	Date
Stephen J. Brown	43,519
Typed or printed name	Registration Number, if applicable
Hoffmann & Baron LLP	973-331-1700
Address	Telephone Number
6 Campus Drive, Parsippany, NJ 07054	
Address	

Enclosure ☑ Fee Payment

☐ Reply

☐ Terminal Disclaimer Form

☐ Additional sheets containing statements establishing unavoidable delay

☑ Notice of Appeal and Fee.

CERTIFICATE OF MAILING OR TRANSMISSION (37 CFR 1.8(a))

I hereby certify that this correspondence is being:

☐ deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to **Mail Stop Petition**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

☐ transmitted by facsimile on the date shown below to the United States Patent and Trademark Office at (571) 273-8300.

Date _____ Signature _____

Typed or printed name of person signing certificate _____

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

PTO/SB/61 (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.

PETITION FOR REVIVAL OF AN APPLICATION FOR PATENT ABANDONED UNAVOIDABLY UNDER 37 CFR 1.137(a)

NOTE: The following showing of the cause of unavoidable delay must be signed by all applicants or by any other party who is presenting statements concerning the cause of delay.

/Stephen J. Brown/	November 15, 2012
Signature	Date
Stephen J. Brown	43,519
Typed or printed name	Registration Number, if applicable

(In the space provided below, please explain in detail the reasons for the delay in filing a proper reply.)

On October, 22, 2012, an Amendment and Response After Final Office Action was filed with the United States Patent and Trademark Office in the captioned case in response to the Final Office Action of May 2, 2012. The deadline to file a Notice of Appeal in the captioned case was November 2, 2012, and Applicants had intended to file the Notice of Appeal on November 2, 2012 to provide as much time as possible for the Examiner to consider the Amendment and Response prior to entering the appeals process.

As is common knowledge, Hurricane Sandy struck the Northeast United States on October 29-30, 2012. As a result of the storm, power was knocked out in our Offices in Parsippany, NJ from October 29, 2012 through the evening of November 7, 2012. Moreover, the City of Parsippany issued a notice that no vehicles other than Emergency vehicles were allowed on the streets that lasted to November 4, 2012, and the Governor of New Jersey issued an urgent request to avoid necessary travel through at least November 7, 2012. In sum, we had no access to our Offices until November 8, 2012.

Beginning on November 8, 2012, our attorneys diligently began running and addressing our dockets, which were unavailable without power. On November 12, 2012, the abovesigned was finally able to determine that the deadline to file a Notice of Appeal in the captioned case had passed and immediately contacted the USPTO to determine how this situation should be addressed. Because November 12, 2012, was a Federal Holiday no office personnel were available to answer the abovesigned's questions.

On November 13, 2012, the abovesigned called the Inventor's Assistance Center (Reference No. 1-238269732) and was connected with the Patent Ombudsman Program. The abovesigned left a voicemail message outlining the above facts, inquiring about any provisions for late filing due to the storm, and requesting guidance. No response was received on November 13, 2012.

On November 14, 2012, the above signed again contacted the Patent Ombudsman Program and left a voicemail message outlining the above facts, inquiring about any provisions for late filing due to the storm, and requesting guidance. Later that day, Lola from the Patent Ombudsman Program returned the abovesigned's call. She indicated that they had no guidance as to how to proceed in the face of the above facts. She further indicated that she would contact the Art Unit responsible for the captioned case and inquire as to their guidance. A return email was promised to provide guidance.

On the same day, the abovesigned left a voicemail message for Examiner Janet Epps-Smith requesting guidance.

On November 15, 2012, the undersigned was contacted by Examiner Smith, who indicated that she had no guidance as to how to proceed in the face of the above facts. She further indicated that her only suggestion was to file a Petition for Revival.

On the same day, the abovesigned was called by Ms. Mindy Bickel of the Patent Ombudsman Program, who indicated that the only guidance she had was that deadlines were tolled as long as the U.S. Postal Service was unable to provide service in our area. She further indicated that she had only received that information herself on the previous day. Ms. Bickel then suggested that only way known to her to proceed was to file a petition for revival.

This Petition for Revival and a Notice of Appeal are being filed on November 15, 2012.

In view of the foregoing, the abovesigned submits that the cause of the delay and the entire length of the delay in filing the Notice of Appeal were unavoidable.

(*Please attach additional sheets if additional space is needed.*)

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:	12537571
Filing Date:	07-Aug-2009
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Filer:	Stephen J. Brown/Jane Callahan
Attorney Docket Number:	1199-82

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Petition-revive unavoid. abandoned appl	1452	1	630	630
Patent-Appeals-and-Interference:				
Notice of appeal	1401	1	630	630
Post-Allowance-and-Post-Issuance:				

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1260**

Electronic Acknowledgement Receipt

EFS ID:	14240064
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Stephen J. Brown/Jane Callahan
Filer Authorized By:	Stephen J. Brown
Attorney Docket Number:	1199-82
Receipt Date:	15-NOV-2012
Filing Date:	07-AUG-2009
Time Stamp:	16:10:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1260
RAM confirmation Number	3204
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)

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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	Notice of Appeal Filed	1199-82_Notice_of_Appeal.PDF	244472 8745b025177e840400bc66edb40acb247b55343c	no	2
Warnings:					
Information:					
2	Miscellaneous Incoming Letter	1199-82_-_Petition_for_Revival.PDF	314017 c7e44d3e77bd2704de4af7246ab218345c797d5a	no	4
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32042 e8901a279bf8dc9b9ef6197f98c04eb4889ffc9d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	590531		

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.
12/537,571	08/07/2009	Garry L. Myers	1199-82	5630

23869 7590 11/06/2012

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
EPPS -SMITH, JANET L	
ART UNIT	**PAPER NUMBER**
1633	
MAIL DATE	**DELIVERY MODE**
11/06/2012	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.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

DETAILED ACTION

1. Claims 1 and 3-31 are presently pending for examination.

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

Claim Rejections - 35 USC § 112

3. The rejection of claims 1-10, 13-14, 16-23, 25-26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in response to Applicant's argument.

Response to Amendment/Arguments

Claim Rejections - 35 USC § 103

4. Claims 1, and 3-31 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Oksche et al. (as applied above).

5. Applicant's arguments filed 10/22/2012 have been fully considered but they are not persuasive.

6. Applicants traversed the instant rejection on the grounds that Oksche et al. does not disclose the pH range recited in the instant claims, and does not provide any direction that one of ordinary skill in the art could follow and come up with the claimed invention. Moreover, Applicants traversed that they have discovered that a desirable local pH of a composition including buprenorphine and naloxone is ***between* about 2 to about 3.5** (page 9, 2nd ¶ of the response filed 10/22/2012). Applicants then argued that their Examples show significant benefits when a pH of about 3.5 is used as compared to a pH or 6.5 and 5.5, Example 8 tested products at a pH of ***from 3.0-3.5*** (page 10, 3rd ¶).

Applicants then concluded that: “The present inventors have discovered ***that at a pH of about 2-3.5***, the relative absorptions can be controlled effectively.”

7. Moreover, Applicants argued that their definition of the term “optimize” is expressly an unequivocally defined in the specification. Applicant’s definition appears at ¶ [0013] of the specification as filed. It is noted that Applicant’s definition states that the "optimum" absorption of the instant invention provides “bioequivalent ***absorption as administration of the currently available Suboxone(R) tablet."***

8. Contrary to Applicant’s assertions, Oksche et al. discloses the *Suboxone® tablet* which Applicants assert that the presently claimed invention provides an optimized absorption of buprenorphine, see ¶ [0012] of Oksche et al. which teaches: "[A]nother buprenorphine preparation aimed at preventing this potential possibility of abuse has recently gained administrative approval in the United States (Suboxone®). The Suboxone® preparation comprises buprenorphine hydrochloride and the opioid antagonist naloxone hydrochloride dihydrate. The presence of naloxone is intended to prevent parenteral abuse of buprenorphine as parenteral co-administration of buprenorphine and naloxone in e.g. an opioid-dependent addict will lead to serious withdrawal symptoms.”

9. Applicant’s argument that the Examples show significant benefits when a pH of about 3.5 is used as compared to a pH or 6.5 and 5.5, Example 8 tested products at a pH of ***from 3.0-3.5,*** is not sufficient to provide evidence of unexpected or significant benefits associated with the full scope of the claimed invention, which recites a “local pH

of ***about 2 to about 3.5 in the presence of saliva."*** Applicant's showing is not commensurate in scope with the claimed invention.

10. As stated in the prior Office Action, contrary to Applicant's assertions, and in light of the open range of pH recited in the instant claims (i.e. as it relates to the use of the term "about" to define the claimed pH range), it is clear that the sublingual film formulations of Oksche et al. are designed so as to prevent development of dependency. Thus, it would have been obvious to the ordinary skilled artisan, at the time of the instant invention, to modify their teachings so as to identify the optimal range of pH/dosage in an effort to identify formulations that would provide optimal absorption of both agonist and antagonist. As per MPEP 2144.05 [R-5], since the general conditions of the instantly claimed invention are disclosed in the prior art, identification of the optimal pH/dosage appears to be a matter of routine experimentation.

11. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Epps-Smith whose telephone number is (571)272-0757. The examiner can normally be reached on M-F, 10AM-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571)-272-0739. 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.

/JANET L. EPPS -SMITH/
Primary Examiner, Art Unit 1633

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 12/537,571	**Applicant(s)** MYERS ET AL.
	Examiner Janet Epps-Smith	**Art Unit** 1633

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

THE REPLY FILED 22 October 2012 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. 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 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *6* 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.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.
   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). 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) or (c) 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 amendments 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): See Continuation Sheet.
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.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after 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 the 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 of 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: See attached document.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

STATUS OF CLAIMS

14. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed: .
    Claim(s) objected to: .
    Claim(s) rejected: 1 and 3-31.
    Claim(s) withdrawn from consideration: .

/Janet Epps-Smith/
Primary Examiner, Art Unit 1633

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection of claims 1-10, 13-14, 16-23, 25-26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in response to Applicant's argument..

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Myers et al.	Examiner:	Janet L. Epps-Smith
Serial No.:	12/537,571	Group Art Unit:	1633
Confirmation No.:	5630	Docket:	1199-82
Filed:	August 7, 2009	Dated:	October 22, 2012
For:	Sublingual and Buccal Film Compositions		

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

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: October 22, 2012

Signature: /Jane Callahan/Jane Callahan

AMENDMENT AND RESPONSE AFTER FINAL OFFICE ACTION

Madam:

In response to the Final Office Action dated May 2, 2012, a response to which is due by August 2, 2012, please amend the application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 7 of this paper.

Amendments to the Claims:

This listing of claims shall replace all previous listings in this application:

1. (Previously Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffer in an amount to provide a local pH for said composition of a value sufficient to optimize absorption of said buprenorphine, wherein said local pH is from about 2 to about 3.5 in the presence of saliva.
2. (Canceled).
3. (Previously Amended) The composition of claim 1, wherein the local pH of said composition is from about 3 to about 3.5.
4. (Original) The composition of claim 1, wherein said film dosage composition provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
5. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one polymer in an amount of at least 25% by weight of said composition.
6. (Original) The composition of claim 1, wherein said buffer is present in an amount of from about 2:1 to about 1:5 by weight of buffer to buprenorphine.
7. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one self-supporting film forming polymer.
8. (Original) The film dosage composition of claim 1, wherein said buprenorphine is present in an amount of from about 2 mg to about 16 mg per dosage.

9. (Original) The film dosage composition of claim 1, wherein said buffer comprises sodium citrate, citric acid, and combinations thereof.
10. (Original) The film dosage composition of claim 1, wherein said buffer comprises acetic acid, sodium acetate, and combinations thereof.
11. (Previously Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffer in an amount sufficient to inhibit the absorption of said naloxone, while also optimizing absorption of said buprenorphine when administered orally.
12. (Previously Amended) The composition of claim 11, wherein said composition has a local pH of about 2 to about 3.5.
13. (Previously Amended) The composition of claim 11, wherein said composition has a local pH of about 3 to about 3.5.
14. (Previously Amended) The composition of claim 13, wherein said buffer is present in an amount sufficient to provide-a bioequivalent level of absorption of buprenorphine as a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
15. (Previously Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffering system;

wherein said buffering system comprises a buffer capacity sufficient to maintain the ionization of naloxone during the time which said composition is in the oral cavity of a user, and also sufficient to optimize the absorption of said buprenorphine.

16. (Previously Amended) The composition of claim 15, wherein said composition has a local pH of about 2 to about 3.5.
17. (Previously Amended) A method of treating narcotic dependence of a user, comprising the steps of:
    a. providing a composition comprising:
        i. A polymeric carrier matrix;
        ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
        iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
        iv. A buffer in an amount to provide a local pH of about 2 to about 3.5 for said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and
    b. administering said composition to the oral cavity of a user.
18. (Original) The composition of claim 17, wherein said method provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
19. (Previously Amended) The method of claim 17, wherein said composition has a local pH of about 3 to about 3.5.
20. (Original) The method of claim 17, wherein said film dosage composition is administered to the user through buccal administration, sublingual administration, and combinations thereof.
21. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of at least 1 minute.

22. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of between about 1 and 1.5 minutes.
23. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of up to 3 minutes.
24. (Previously Amended) A process of forming a film dosage composition comprising the steps of:
    a. casting a film-forming composition, said film-forming composition comprising:
        i. A polymeric carrier matrix;
        ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
        iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
        iv. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and
    b. drying said film-forming composition to form a self-supporting film dosage composition.
25. (Previously Amended) The process of claim 24, wherein said composition has a local pH of about 2 to about 3.5.
26. (Previously Amended) A film dosage composition comprising a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, said film dosage composition having a bioequivalent release profile as a tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof, and wherein said composition provides a local pH of from about 2 to about 3.5.
27. (Original) An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a Cmax

of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.

28. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 5.431 hr.ng/ml to about 56.238 hr.ng/ml for buprenorphine.
29. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 102.88 hr.pg/ml to about 812.00 hr.pg/ml for naloxone.
30. (Original) The formulation of claim 27, wherein said formulation comprises about 2 to about 16 mg of buprenorphine or a salt thereof.
31. (Original) The formulation of claim 27, wherein said formulation comprises about 0.5 to about 4 mg of naloxone or a salt thereof.

REMARKS

Claims 1 and 3-31 are pending in this office action.

Rejection Under 35 U.S.C. §112

In the Office Action, the Examiner rejected claims 1-3, 13-14, 16-23, and 25-26 under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. The Examiner stated that the amendments to the pH from about 2 to about 3.5 for buprenorphine was not in the specification. The Examiner pointed to paragraph [0016] which discusses the pH that inhibits naloxone, but alleged that there was no support in the specification for the pH with regard to buprenorphine.

The Applicant respectfully traverses this rejection and directs the Examiner to paragraph [0064], for example. This paragraph states, in relevant part:

> In such combination films [including buprenorphine and naloxone], it has been discovered that the local pH of the film composition should preferably be in the range of about 2 to about 4, and more preferably about 3 to about 4… Most preferably the local pH of the film composition is about 3.5. At this local pH level, absorption of the buprenorphine is optimized while absorption of the naloxone is inhibited.

There is clear and literal support in the application as filed for the local pH of a combination film (e.g., including buprenorphine and naloxone) being from about 2 to about 3.5. Additional support for the pH being about 3.5 may be found in additional paragraphs, including, for example, paragraphs [0067] and [0087], as well as Example 8, which is directly related to an Analysis of *In Vivo* Absorption of a Film Having a Ph of From 3-3.5 (paragraphs [0097]-[0101].

In view of the significant literal support for this pH range in the application as filed, the Applicant respectfully traverses the rejection. There is ample support in the application for the claimed limitations, and thus the rejection should be withdrawn.

Rejection under 35 U.S.C. §103

In the Office Action, the Examiner rejected claims 1 and 3-31 under 35 U.S.C. §103(a) as allegedly obvious over Oksche (WO 2008/025791, counterpart US 2010/0087470). The Examiner stated that, although Oksche fails to disclose pH values, the determination of a suitable pH range would have been obvious and routine experimentation. The Examiner stated that Oksche discloses a Suboxone tablet, and thus it would have been obvious to modify Oksche accordingly. Finally, the Examiner stated that the "open range" of the pH in the claims (i.e., using the term "about") further demonstrates its obviousness.

Applicant's Response

The Applicant respectfully traverses the instant rejection, noting that the reference cited would simply not direct one of ordinary skill in the art to using a pH range that is clearly claimed. In fact, there is no direction in Oksche that one of ordinary skill in the art could follow and come up with the claimed invention. Finally, the Applicant has demonstrated through the examples shown in the application that the presently claimed range demonstrates unexpected and significant improvements, particularly when compared to that of the prior art and when compared to what one of ordinary skill in the art would have been led to believe (i.e., through partition theory, as explained in the application as filed at paragraph [0100]).

In addition, the Applicant traverses the Examiner's opinion that the term "optimize" is not limiting. The Examiner stated that limitations from the specification are not read into the claims, which is correct, however, the term "optimize" is expressly and unequivocally defined in the specification. The Applicant is permitted to be its own lexicographer, and terms that are given definition in the specification are defined as such in the claims. (**CITE**).

The claims specifically identify a particular pH range, which is sufficient to achieve the goals of optimizing the absorption of one component (buprenorphine) and minimizing the absorption of a second component (naloxone). There is absolutely no identified pH range in Oksche, and thus no direction whatsoever to allow one of ordinary skill in the art to come up

with the claimed invention. There is simply no predictability in modifying the pH of Oksche to the claimed level and expecting to achieve the significant results claimed.

Even further, as explained in detail in the application as filed and in the previous response, one of ordinary skill in the art would have expected that a product would follow pH partition theory. According to pH partition theory, one would expect that saliva (which has a pH of about 6.5) would maximize the absorption of both actives. However, it has been surprisingly discovered by the Applicant that by buffering the dosage to a particular pH level, the optimum levels of absorption of the buprenorphine and the naloxone may be achieved. It has been discovered that the desirable local pH of a composition including buprenorphine and naloxone is between about 2 to about 3.5. At this local pH level, the desired absorption of the buprenorphine and the naloxone is achieved. As described in the application as filed and in the Examples (discussed below), controlling the local pH of the film compositions of the present invention provides a system in which the desired release and/or absorption of the components is achieved.

As such, if one of ordinary skill in the art was to simply modify the pH, that person would have followed pH partition theory and used a pH of about 6.5. This is far outside the claimed range.

Experimental Results

The present inventors have undertaken significant experimentation to determine the conditions to effectively and efficiently deliver a suitable dosage of buprenorphine and, in appropriate circumstances, to effectively and efficiently inhibit the absorption of naloxone. The inventors have determined that the buffer selected and the buffer capacity used in the film has a significant and dramatic affect on the absorption of actives. However, the arrival at this invention is not simply limited to mere selection of pH ranges, and must take into account the Cmax and AUC values for the product.

The Examples are set forth in the application as filed, and as can be seen, the Applicant discovered that optimized values can be achieved when the pH of the film falls within the claimed range. These results are surprising, particularly in view of pH partition

theory, which would be understood that a pH of about 6.5 would be successful in achieving the desired balance between drug solubility and ionization.

The tests conducted by the Applicant demonstrate surprising and very effective results at the claimed pH levels. Again, these levels are certainly not obvious over Oksche's general disclosure (including lack of any pH range) and the present examples demonstrate the surprising effect that is achieved.

In particular, the Examples show the significant benefits when a pH of about 3.5 is used as compared to a pH of 6.5 and 5.5. See, for example, Example 8, which tested products at a pH of from 3.0-3.5.

As has previously been explained, the present applicants have discovered that the suitable buffer capacity actually differs from that which would be expected from pH partition theory. For example, the buffer capacity for a product including both the buprenorphine and naloxone would be one that minimizes the absorption of the naloxone but optimizes the absorption of the buprenorphine – a concept not disclosed nor considered by Oksche. For example, the present inventors have discovered that at a pH of about 2-3.5, the relative absorptions can be controlled effectively.

Conclusion

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

If there are any questions or if additional information is required, the Examiner is respectfully requested to contact Applicant's attorney at the number listed below.

Respectfully submitted,

/Stephen J. Brown /
Stephen J. Brown
Registration No.: 43,519
Attorney for Applicant(s)

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

Electronic Patent Application Fee Transmittal

Application Number:	12537571
Filing Date:	07-Aug-2009
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Filer:	Stephen J. Brown/Jane Callahan
Attorney Docket Number:	1199-82

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1290	1290

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1290**

Electronic Acknowledgement Receipt

EFS ID:	14040836
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Stephen J. Brown/Jane Callahan
Filer Authorized By:	Stephen J. Brown
Attorney Docket Number:	1199-82
Receipt Date:	22-OCT-2012
Filing Date:	07-AUG-2009
Time Stamp:	14:06:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1290
RAM confirmation Number	390
Deposit Account	082461
Authorized User	

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

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

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

TEVA EXHIBIT 1002
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Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

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

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	1199-82_Petition_for_Extension_of_Time.PDF	83250 9b443c049d40812e7780a20a68877f3c4a3dc697	no	2
Warnings:					
Information:					
2		1199-82_amendment_and_response_dated_10-22-12.PDF	42569 4ae585c8801148737011b24fae291bc3312bdb95	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	11

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30341 abab3a9e6ad62bd647c7510140fbc592381bd0e4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	156160		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/22 (10-12)
Approved for use through 1/31/2013. OMB 0651-0031
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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.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 1199-82

Application Number: 12/537,571

Filed: August 7, 2009

For: Sublingual and Buccal Film Compositions

Art Unit: 1633

Examiner: Janet L. Epps-Smith

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$150	$75	$
☐ Two months (37 CFR 1.17(a)(2))	$570	$285	$
■ Three months (37 CFR 1.17(a)(3))	$1,290	$645	$ 1,290
☐ Four months (37 CFR 1.17(a)(4))	$2,010	$1,005	$
☐ Five months (37 CFR 1.17(a)(5))	$2,730	$1,365	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

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

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

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

■ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 08-2461.

☐ Payment made via EFS-Web.

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

I am the

☐ applicant/inventor.

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

■ attorney or agent of record. Registration number 43,519.

☐ attorney or agent acting under 37 CFR 1.34. Registration number .

/Stephen J. Brown/ — Signature

October 22, 2012 — Date

Stephen J. Brown — Typed or printed name

973-331-1700 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

■ * Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 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 PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Privacy Act Statement

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

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

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/537,571	08/07/2009	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT	10/22/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 31	= 0	X $ =		OR	X $62=	0
	Independent (37 CFR 1.16(h))	* 7	Minus	***7	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/YOLANDA CHADWICK/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/537,571	08/07/2009	Garry L. Myers	1199-82	5630

23869 7590 05/02/2012
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

EXAMINER	
EPPS -SMITH, JANET L	
ART UNIT	**PAPER NUMBER**
1633	
MAIL DATE	**DELIVERY MODE**
05/02/2012	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.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Office Action Summary	Application No.	Applicant(s)	
	12/537,571	MYERS ET AL.	
	Examiner	Art Unit	
	Janet Epps-Smith	1633	

-- 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 February 2012*.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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

5)☒ Claim(s) *1 and 3-31* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1 and 3-31* is/are rejected.

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

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

Application Papers

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

11)☐ 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).

12)☐ 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

13)☐ 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 *2-29-2012*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

DETAILED ACTION

1. Claims 1 and 3-31 are presently pending for examination.

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

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10, 13-14, 16-23, 25-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

5. Applicants have amended the claims to recite “a local pH....to optimize absorption of buprenorphine, wherein said local pH is from about 2 to about 3.5 in the presence of saliva." According to Applicants, support for this amendment could be found at paragraphs [0013-0017].

6. According to the specification as filed at ¶ [0016] pH 3-3.5 is the Cmax of naloxone. Moreover, the specification defines the Cmax as the mean maximum plasma concentration after administration of the composition to a human subject. The claims are drawn to a composition that produces a local pH of about 3.5, this pH represents the

Cmax of naloxone. However, the claimed compositions are directed to inhibit the absorption of naloxone and optimize absorption of buprenorphine.

7. The specification does disclose a local pH of 2-4 as useful for optimizing the absorption of buprenorphine, paragraph [0013]. However, the disclosure of a local pH of 3.5 is clearly disclosed as related to the absorption of naloxone and is not disclosed as specifically related to the absorption of buprenorphine, paragraph [0016]. After reviewing the specification as filed for support for the limitation "about 3.5" as it relates to the absorption of buprenorphine, it is clear that the specification does not provide support for this limitation.

Response to Amendment/Arguments

Claim Rejections - 35 USC § 102

8. The rejection of claims 1, 4, 5, 7-10, 15, 17, and 20-24 under 35 U.S.C. 102(b) as being anticipated by Oksche et al. WO2008/025791A1 (Citations are taken from US2010/0087470) is withdrawn in response to Applicant's amendment.

Claim Rejections - 35 USC § 103

9. Claims 1, and 3-31 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Oksche et al. (as applied above).

10. Applicant's arguments filed 02/29/2012 have been fully considered but they are not persuasive.

11. Applicants traverse the instant rejection on the grounds that the buffering system used in the instant claims is sufficient to "optimize" the absorption of buprenorphine.

Moreover, Applicants argue that a pH of about 5.5 may be useful for maximizing the absorption of buprenorphine, however not to "optimize" the absorption of buprenorphine (see 1st ¶ on page 9 of reply filed 2/29/2012). The use of the term "optimize" according to Applicants is based upon their definition of the term as set forth in the specification as filed at [0013]. However, contrary to Applicant's assertions, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the definition of the term "optimize") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicant's definition of the term "optimize" provided in the specification is not sufficiently precise and definite such that the ordinary skilled artisan would be able to adequately be apprised of the full scope of the claimed invention.. For example, the specification as filed recites: "***optimizing the absorption***" does not refer to reaching the maximum absorption of the composition, and rather refers to reaching the ***optimum level of absorption*** at a pH of about 2 to about 4. Further, the specification teaches that "***An*** 'optimum' Cmax of buprenorphine is ***about*** 0.67 to about 5.36 mg/ml at dosages of from 2-16 mg buprenorphine at a given pH. The definition here appears to provide an example of optimum buprenorphine (*an optimum).* Moreover, the use of the term "about" provides an open range (i.e. non-precise) regarding the level of buprenorphine concentration.

12. Furthermore, Applicants argued the following (see 1st full ¶ on page 11 of reply filed 2/29/2012): "As can be seen, one must consider a number of variables and consider many different features in order to consider the absorption of the buprenorphine "optimized", as presently claimed, *so as to provide a bioequivalent release level as that of a Suboxone® tablet having similar levels of buprenorphine*. The particular buffering levels and amount play a critical role in determining the effectiveness of the composition. The buffer capacity must be considered so as to provide the desired absorption levels of both actives. The discovery of the desirable buffer capacity was certainly not contemplated in Oksche and would not have been predictable."

13. Contrary to Applicant's assertions, Oksche et al. discloses the *Suboxone® tablet* which Applicants assert that the presently claimed invention provides an optimized absorption of buprenorphine, see ¶ [0012] of Oksche et al. which teaches: "[A]nother buprenorphine preparation aimed at preventing this potential possibility of abuse has recently gained administrative approval in the United States (Suboxone®). The Suboxone® preparation comprises buprenorphine hydrochloride and the opioid antagonist naloxone hydrochloride dihydrate. The presence of naloxone is intended to prevent parenteral abuse of buprenorphine as parenteral co-administration of buprenorphine and naloxone in e.g. an opioid-dependent addict will lead to serious withdrawal symptoms."

14. As stated in the prior Office Action, contrary to Applicant's assertions, and in light of the open range of pH recited in the instant claims (i.e. as it relates to the use of the

term “about” to define the claimed pH range), it is clear that the sublingual film formulations of Oksche et al. are designed so as to prevent development of dependency. Thus, it would have been obvious to the ordinary skilled artisan, at the time of the instant invention, to modify their teachings so as to identify the optimal range of pH/dosage in an effort to identify formulations that would provide optimal absorption of both agonist and antagonist. As per MPEP 2144.05 [R-5], since the general conditions of the instantly claimed invention are disclosed in the prior art, identification of the optimal pH/dosage appears to be a matter of routine experimentation.

15. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Conclusion

16. **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.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Epps-Smith whose telephone number is (571)272-0757. The examiner can normally be reached on M-F, 10AM-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571)-272-0739. 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.

/JANET L. EPPS -SMITH/
Primary Examiner, Art Unit 1633

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12537571
Filing Date	2009-08-07
First Named Inventor	Garry L. Myers
Art Unit	1633
Examiner Name	Epps-Smith, Janet L
Attorney Docket Number	1199-82

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5118508		1992-06-02	Kikuchi et al	
	2	5891461		1999-04-06	Jona et al	
	3	6103266		2000-08-15	Tapolsky et al	
	4	6667060	B1	2003-12-23	Vandecruys et al	

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20030124176	A1	2003-07-03	Hsu et al	
	2	20050118217	A1	2005-06-02	Barnhart et al	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.E./

TEVA EXHIBIT 1008
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12537571
	Filing Date	2009-08-07
	First Named Inventor	Garry L. Myers
	Art Unit	1633
	Examiner Name	Epps-Smith, Janet L
	Attorney Docket Number	1199-82

	3	20100015128	A1	2010-01-21	Finn et al.	
	4	20110189259	A1	2011-08-04	Vasisht et al.	
	5	20110262522	A1	2011-10-27	Finn et al.	

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	1	741362	AU	B2	1998-07-15	Lohmann Therapie-Systeme		☐

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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		☐

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EXAMINER SIGNATURE

Examiner Signature	/Janet Epps Smith/	Date Considered	04/25/2012

*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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.E./

TEVA EXHIBIT 1008
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	Epps-Smith, Janet L
	Attorney Docket Number	1199-82

[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.

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TEVA EXHIBIT 1008
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12537571
	Filing Date	2009-08-07
	First Named Inventor	Garry L. Myers
	Art Unit	1633
	Examiner Name	Epps-Smith, Janet L
	Attorney Docket Number	1199-82

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Jon A. Chiodo Reg. No. 52,739/	Date (YYYY-MM-DD)	2012-02-29
Name/Print	Jon A. Chiodo	Registration Number	52,739

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.E./

TEVA EXHIBIT 1008
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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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:

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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.

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.E./

TEVA EXHIBIT 1008
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/537,571	MYERS ET AL.	
	Examiner	Art Unit	
	Janet Epps-Smith	1633	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Inventor name search	8-22-11	JLE
Plus search	8-22-11	JLE
East-see attached	8-29-11	JLE
searc notes updated	4-30-2012	JLE

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Myers et al.	Examiner:	Janet L. Epps-Smith
Serial No.:	12/537,571	Group Art Unit:	1633
Confirmation No.:	5630	Docket:	1199-82
Filed:	August 7, 2009	Dated:	February 29, 2012
For:	Sublingual and Buccal Film Compositions		

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

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I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: February 29, 2012

Signature: Christine Briscoe/cbriscoe/

AMENDMENT AND RESPONSE

Sir:

In response to the office action dated August 31, 2011, a response to which is due by February 29, 2012 in view of the concurrently filed petition for three month extension of time, please amend the application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 7 of this paper.

Amendments to the Claims:

This listing of claims shall replace all previous listings in this application:

1. (Currently Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffer in an amount to provide a local pH ~~of~~ for said composition of a value sufficient to optimize absorption of said buprenorphine, wherein said local pH is from about 2 to about 3.5 in the presence of saliva.
2. (Canceled).
3. (Currently Amended) The composition of claim 1 ~~2~~, wherein the local pH of said composition is from about 3 to about 3.5 [[4]].
4. (Original) The composition of claim 1, wherein said film dosage composition provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
5. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one polymer in an amount of at least 25% by weight of said composition.
6. (Original) The composition of claim 1, wherein said buffer is present in an amount of from about 2:1 to about 1:5 by weight of buffer to buprenorphine.
7. (Original) The composition of claim 1, wherein said polymeric carrier matrix comprises at least one self-supporting film forming polymer.
8. (Original) The film dosage composition of claim 1, wherein said buprenorphine is present in an amount of from about 2 mg to about 16 mg per dosage.
9. (Original) The film dosage composition of claim 1, wherein said buffer comprises sodium citrate, citric acid, and combinations thereof.

10. (Original) The film dosage composition of claim 1, wherein said buffer comprises acetic acid, sodium acetate, and combinations thereof.
11. (Currently Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffer in an amount sufficient to inhibit the absorption of said naloxone, while also optimizing absorption of said buprenorphine when administered orally.
12. (Currently Amended) The composition of claim 11, wherein said composition has a local pH of about 2 to about 3.5 [[4]].
13. (Currently Amended) The composition of claim 11, wherein said composition has a local pH of about 3 to about 3.5 ~~said buffer is present in an amount sufficient to provide a therapeutically adequate absorption of buprenorphine~~.
14. (Currently Amended) The composition of claim 13, wherein ~~a therapeutically adequate absorption of buprenorphine comprises~~ said buffer is present in an amount sufficient to provide a bioequivalent level of absorption of buprenorphine as a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
15. (Currently Amended) A film dosage composition comprising:
    a. A polymeric carrier matrix;
    b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
    c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
    d. A buffering system;

    wherein said buffering system comprises a buffer capacity sufficient to maintain the ionization of naloxone during the time which said composition is in the oral

cavity of a user, and also sufficient to optimize the absorption of said buprenorphine.

16. (Currently Amended) The composition of claim 15, wherein said composition has a local pH of about 2 to about 3.5 [[4]].
17. (Currently Amended) A method of treating narcotic dependence of a user, comprising the steps of:
    a. providing a composition comprising:
        i. A polymeric carrier matrix;
        ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
        iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
        iv. A buffer in an amount to provide a local pH of about 2 to about 3.5 for said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and
    b. administering said composition to the oral cavity of a user.
18. (Original) The composition of claim 17, wherein said method provides a bioequivalent absorption of buprenorphine to that of a tablet having an equivalent amount of buprenorphine or a pharmaceutically acceptable salt thereof.
19. (Currently Amended) The method of claim 17, wherein said composition has a local pH of about 3 [[2]] to about 3.5 [[4]].
20. (Original) The method of claim 17, wherein said film dosage composition is administered to the user through buccal administration, sublingual administration, and combinations thereof.
21. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of at least 1 minute.
22. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of between about 1 and 1.5 minutes.

23. (Original) The method of claim 17, wherein said film dosage composition remains in the oral cavity of the user for a period of up to 3 minutes.
24. (Currently Amended) A process of forming a film dosage composition comprising the steps of:
    a. casting a film-forming composition, said film-forming composition comprising:
        i. A polymeric carrier matrix;
        ii. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof;
        iii. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and
        iv. A buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine and also sufficient to inhibit absorption of said naloxone; and
    b. drying said film-forming composition to form a self-supporting film dosage composition.
25. (Currently Amended) The process of claim 24, wherein said composition has a local pH of about 2 to about 3.5 [[4]].
26. (Currently Amended) A film dosage composition comprising a therapeutically sufficient amount of buprenorphine or a pharmaceutically acceptable salt thereof and a therapeutically sufficient amount of naloxone or a pharmaceutically acceptable salt thereof, said film dosage composition having a bioequivalent release profile as a tablet containing about 2 times the amount of buprenorphine or a pharmaceutically acceptable salt thereof, and wherein said composition provides a local pH of from about 2 to about 3.5.
27. (Original) An orally dissolving film formulation comprising buprenorphine and naloxone, wherein said formulation provides an in vivo plasma profile having a Cmax of between about 0.624 ng/ml and about 5.638 ng/ml for buprenorphine and an in vivo plasma profile having a Cmax of between about 41.04 pg/ml to about 323.75 pg/ml for naloxone.

28. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 5.431 hr.ng/ml to about 56.238 hr.ng/ml for buprenorphine.
29. (Original) The formulation of claim 27, wherein said formulation provides a mean AUC of between about 102.88 hr.pg/ml to about 812.00 hr.pg/ml for naloxone.
30. (Original) The formulation of claim 27, wherein said formulation comprises about 2 to about 16 mg of buprenorphine or a salt thereof.
31. (Original) The formulation of claim 27, wherein said formulation comprises about 0.5 to about 4 mg of naloxone or a salt thereof.

REMARKS

The present application has been amended. Specifically, the claims have been amended to recite a particular local pH value and/or to recite that the buffer optimizes absorption of buprenorphine while also inhibiting absorption of the naloxone. Support for these amendments may be found, for example, at paragraphs [0013-17] and in the claims of the application as filed. It is noted that terms such as "optimize" and "inhibit" are defined in the application. No new matter is introduced through this Amendment.

Brief Description of the Invention

To aid the Examiner's understanding, the Applicant believes that it is beneficial to provide a concise explanation of the invention. Delivery of compounds such as buprenorphine and naloxone was previously known, however, the previously-accepted form of the delivery is in the form of a tablet (e.g., a Suboxone® tablet). The present invention is directed to the formation of a suitable film product that provides a certain release profile and in some embodiments, is bioequivalent result to, for example, a Suboxone® tablet. The desired result is a product that provides a Cmax that is 80-125% the level provided by, for example, the Suboxone® tablet at the same dosage levels of the buprenorphine and the naloxone.

The desired film product includes the delivery of buprenorphine and naloxone together. The film is either a single-layered film or a multi-layered film. In either case, it is desired to provide a product that is cognizant of both the buprenorphine and naloxone. That is, the absorption of the buprenorphine should be "optimized" (as defined at paragraph [0019] of the application) to provide a desired level of absorption, but at the same time the absorption of the naloxone should be inhibited to provide a minimal, if any, level of absorption. As explained in detail throughout the application, the present applicants have discovered that the film product should include a buffer that provides a specific buffer capacity to the film in order to achieve the desired result.

As set forth in the application as filed, according to pH partition theory, one would expect that saliva (which has a local pH of about 6.5) would maximize the absorption of both actives, given their respective pKa levels. See, for example, the Examples in the application

as filed. As generally understood, absorption of an active depends on the available unionized form of the active. Thus, as the local pH of the surrounding environment is lowered, basic actives will be more ionized, and less will be available for absorption.

Thus, it would be contrary to think of lowering the pH from 6.5 to pH 5.5, and especially to pH 3.5, given the above-mentioned theory. However, as explained in the application as filed, the absorption of the buprenorphine was increased by dropping the pH from 6.5 to 5.5. The absorption at a pH of 5.5 was, however, higher than desired (i.e., it was "maximized", not "optimized"). Extrapolating this further, it was surprising to find that the absorption for the buprenorphine decreased to a desirable level upon further lowering of the pH. As explained in the application as filed and in the Examples, controlling the local pH by providing a buffer having a specific buffer capacity in the film compositions of the present invention provides a system in which the desired release and/or absorption of the components is achieved.

For film products including both buprenorphine and naloxone, it was particularly surprising to find that both may be included in one film by providing a buffer having a pH of from about 2 to about 3.5. At this buffer capacity, it was found that the absorption of the buprenorphine may be optimized to a desirable level, while at the same time the absorption of the naloxone may be inhibited to a desirable level.

The present applicants have discovered that following pH partition theory actually does not result in a suitable product. This discovery was completely surprising and was not known prior to the invention. The claims have been amended where applicable to reflect the essence of the invention.

Response to Rejection

In the Office Action, the Examiner rejected claims 1, 4, 5, 7-10, 15, 17 and 20-24 under 35 U.S.C. §102(b) as allegedly anticipated by Oksche (WO 2008/025791, counterpart US 2010/0087470). The Examiner alleged that Oksche discloses the use of modified cellulose materials to administer buprenorphine and naloxone orally. The Examiner also pointed to the use of citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid.

The applicant respectfully traverses the instant rejection, and notes that the claims recite that the buffering system is sufficient to "optimize" the absorption of buprenorphine. To clarify the claims, the Applicant has amended claim 1 to recite that the pH for the buprenorphine is from 2 to 3.5. This pH allows for absorption of buprenorphine, but, in the case where naloxone is present, its absorption is minimized. The naloxone is included in the formulation, for example, as an antagonistic component if the product is injected or snorted by a product abuser, but its effect is minimized when the product is taken as intended, such as orally. As explained above, a pH of about 5.5 may be useful in maximizing absorption, however, not "optimizing" the absorption as defined in the application as filed. Even further, for the other claims as pending, the claims recite the use of a buffer that is suitable to not only optimize the absorption of buprenorphine, but also at the same time to inhibit the absorption of the naloxone.

The mere disclosure of the use of a pH modifier, for example, citric acid, is not the same as providing a buffer system that is sufficient to provide a buffer capacity suitable to optimize the absorption of the buprenorphine, let alone inhibit the absorption of the naloxone. Oksche completely fails to acknowledge that the pH of the system plays any role in the optimization or inhibition of the actives to be administered. Oksche merely discloses the inclusion of "suitable pH modifiers", without providing any discussion as to their use, their amount, the resulting pH levels, or their relation to the absorption of the buprenorphine. Oksche completely failed to recognize that providing a particular buffer capacity would be beneficial or important in the absorption of the buprenorphine. Oksche does not disclose any particular buffer capacity, either expressly or implicitly. Oksche only generally discloses flavoring agents, pH modifiers, and taste masking agents, each of which may have a pronounced effect on the pH of the material.

The present application is based upon the discovery that the delivery and absorption of buprenorphine can be optimized to a desired level through administration via a film if the pH is balanced appropriately.

Since Oksche fails to disclose the present limitation of a buffer capacity suitable to optimize the absorption of the buprenorphine, it cannot anticipate the claims as pending.

Next, in the Office Action, claims 1-31 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Oksche. The Examiner acknowledged that the reference fails to disclose the specific range of pH in the claims. However, the Examiner alleged that it would have been obvious to identify the optimal pH in an effort to provide optimal absorption of both the buprenorphine and the naloxone. In short, the Examiner alleged that the pH range would be a matter of routine experimentation.

The Applicant respectfully traverses the instant rejection and notes that the general disclosure in Oksche of a buffer is not sufficient to establish a *prima facie* case of obviousness. As an initial matter, it appears that the Examiner has set forth an "obvious to try" rejection. In order to establish that it would have been obvious to try certain variations, there must be a "finite number" of choices to choose from, which provide predictable results. Here, there are a significant number of pH ranges to choose from, ranging from 1-14 and including all fractions thereof. In addition, there are a significantly high number of potential buffers from which to choose, including acids, bases, and combinations thereof. Oksche provides absolutely no teaching as to what a suitable buffer that can provide a suitable buffer capacity is, nor is there simply a finite number of choices available.

Even further, for reasons stated in detail in the application, the proper buffering capacity is not one of routine experimentation nor is it one that can be predictably selected by one of ordinary skill in the art. Those skilled in the art would have simply relied upon pH partition theory and selected a buffering capacity that follows this theory – for example, a pH commensurate with the pKa of the active. However, as explained in the application, following pH partition theory did not result in a suitable product and the proper buffer capacity actually varied from that expected by the theory. Thus, the buffer capacity suitable to optimize the absorption of the buprenorphine and, at the same time, to inhibit the absorption of the naloxone, is not predictable.

The present inventors have undertaken significant experimentation to determine the conditions to effectively and efficiently deliver a suitable dosage of buprenorphine and, at the same time, to effectively and efficiently inhibit the absorption of naloxone. The inventors have determined that the buffer selected and the buffer capacity used in the film has a significant and dramatic affect on the absorption of actives. However, the arrival at this

invention is not simply limited to mere selection of pH ranges, and must take into account the Cmax and AUC values for the product.

As can be seen, one must consider a number of variables and consider many different features in order to consider the absorption of the buprenorphine "optimized", as presently claimed, so as to provide a bioequivalent release level as that of a Suboxone® tablet having similar levels of buprenorphine. The particular buffering levels and amount play a critical role in determining the effectiveness of the composition. The buffer capacity must be considered so as to provide the desired absorption levels of both actives. The discovery of the desirable buffer capacity was certainly not contemplated in Oksche and would not have been predictable.

The claims include both components to be together in a single film, with a buffer capacity that is suitable for both. The inventors have found that the two components may be used together with a single buffer capacity that optimizes the absorption of the buprenorphine but concurrently inhibits the absorption of the naloxone. This discovery was certainly not disclosed or contemplated in Oksche.

Oksche fails to disclose or suggest any buffering capacity and, in fact, fails to even acknowledge that buffering capacity can play a role in the relative absorptions of the components. Oksche merely states that buffers can be used, but includes nothing further. This general disclosure of a buffer is not sufficient to render obvious claims that require a particular buffer capacity to optimize the absorption of buprenorphine and inhibit the absorption of naloxone.

The Examiner alleged that modification of the pH values would be obvious. However, the Applicant respectfully disagrees and notes that there has been undertaken a significant course of experimentation to determine how pH can have an effect on the absorption (which is summarized in the application as filed). Oksche merely discloses that certain additives may be used, including acids as well as bases. One of ordinary skill in the art would therefore be led to believe that any particular pH value, whether neutral, acidic or basic, would be acceptable based upon the disclosure of Oksche. Further, there is no reason to believe, based upon the teachings of Oksche, that pH would even play any role in the effectiveness of the composition.

Some of the claims recite a particular Cmax value for both the buprenorphine and the naloxone – which is not disclosed or even suggested in Oksche. Oksche is completely silent as to the Cmax for the naloxone, and merely discusses values for the buprenorphine. Summarizing the invention, the present invention includes embodiments that provide a bioequivalent release and absorption as that of a Suboxone® tablet, both for the buprenorphine and the naloxone, which is not disclosed in Oksche.

At best, Oksche generally discloses that acids and bases may be used in the system, but does not even consider the pH effect on the absorption, let alone varying pH values in one composition.

As explained above, the present applicants have discovered that the suitable buffer capacity actually differs from that which would be expected from pH partition theory. For example, the buffer capacity for a product including both the buprenorphine and naloxone would be one that minimizes the absorption of the naloxone but optimizes the absorption of the buprenorphine – a concept not disclosed nor considered by Oksche. For example, the present inventors have discovered that at a pH of about 2-3.5, the relative absorptions can be controlled effectively. Alternatively, if the pH of the formulation is 2-3.5, the desired absorption profile may be achieved for buprenorphine while minimizing absorption of the naloxone.

One of ordinary skill in the art reading Oksche would not be led to believe that pH would play any role in the absorption. Even further, with respect to those claims including buprenorphine and naloxone, one of ordinary skill in the art certainly would not believe that varying local pH values would have any determinable or noticeable effect. There is no rational basis to modify Oksche to arrive at the presently claimed invention, and it would not be predictable to one of ordinary skill in the art to arrive at the claimed invention. For these reasons, these claims including the dual-region composition are allowable over Oksche.

There is no rational basis to arrive at the presently claimed invention based upon Oksche. Further, based upon the experimentation undertaken by the Applicants, and summarized in the application, the results obtained were certainly not predictable. Oksche

states nothing about the buffer capacity playing any role whatsoever in the optimum absorption, and one of ordinary skill in the art would not think it plays any role. There would be no reason to modify Oksche to arrive at any of these specific limitations as presently claimed. As such, claims 1-31 are not obvious over Oksche for a multitude of reasons.

Information Disclosure Statement

The Applicant is submitting herewith an Information Disclosure Statement, citing several references. Included in this submission is the citation of U.S. Publication No. 2011/0262522, which specifically claims pH ranges that are outside those presently claimed. In fact, based upon the disclosure of this reference, it would not be obvious to those of ordinary skill in the art to make or use the presently-claimed invention.

Conclusion

The fees for a three month extension of time is also due with this submission, to be charged to Deposit Account No. 08-2461. In addition, the fee for a late filed IDS may also be charged to the same Deposit Account. If any additional fees are due, the Commissioner is hereby authorized to charge payment any fees associated with this communication, or credit any overpayment, to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. § 1.136.

If there are any questions or if additional information is required, the Examiner is respectfully requested to contact Applicant's attorney at the number listed below.

Respectfully submitted,

/Jon A. Chiodo/
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Garry L. Myers	Examiner:	Janet L. Epps-Smith
Application No.:	12/537,571	Group Art Unit:	1633
Confirmation No:	5630	Docket:	1199-82
Filed:	August 7, 2009	Dated:	February 29, 2012
For:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS		

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Dated: February 29, 2012
Signature: Christine Briscoe/cbriscoe/

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Sir:

In fulfillment of the requirements of candor and good faith set forth in 37 C.F.R. §1.56, Applicants submit herewith the following Supplemental Information Disclosure Statement in accordance with the provisions of 37 C.F.R. §1.97 and §1.98. It is understood that the information provided herein is solely for the purpose of fulfilling Applicants' obligations under the law and should not be construed as, nor is it intended to be, an admission of prior art.

Copies of the U.S. patent documents listed on the Form PTO/SB/08a which is being submitted herewith are not provided as the United States Patent and Trademark Office has

waived the requirement for paper submission of U.S. patent documents. A copy of the listed foreign patent document is being submitted herewith.

The fee of $180 pursuant to 37 C.F.R. § 1.17(p) is being submitted herewith. If any additional fees are deemed due, please charge any such fees to Deposit Account No. 08-2461. The Commissioner also is hereby authorized to credit any over payment to Deposit Account No. 08-2461.

Should the Examiner have any questions or comments concerning the above, the Examiner is respectfully invited to contact the undersigned at the telephone number given below.

Respectfully submitted,

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(Not for submission under 37 CFR 1.99)

Application Number	12537571
Filing Date	2009-08-07
First Named Inventor	Garry L. Myers
Art Unit	1633
Examiner Name	Epps-Smith, Janet L
Attorney Docket Number	1199-82

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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	5118508		1992-06-02	Kikuchi et al	
	2	5891461		1999-04-06	Jona et al	
	3	6103266		2000-08-15	Tapolsky et al	
	4	6667060	B1	2003-12-23	Vandecruys et al	

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	1	20030124176	A1	2003-07-03	Hsu et al	
	2	20050118217	A1	2005-06-02	Barnhart et al	

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12537571
	Filing Date	2009-08-07
	First Named Inventor	Garry L. Myers
	Art Unit	1633
	Examiner Name	Epps-Smith, Janet L
	Attorney Docket Number	1199-82

	3	20100015128	A1	2010-01-21	Finn et al.	
	4	20110189259	A1	2011-08-04	Vasisht et al.	
	5	20110262522	A1	2011-10-27	Finn et al.	

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	1	741362	AU	B2	1998-07-15	Lohmann Therapie-Systeme		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12537571
	Filing Date	2009-08-07
	First Named Inventor	Garry L. Myers
	Art Unit	1633
	Examiner Name	Epps-Smith, Janet L
	Attorney Docket Number	1199-82

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	Attorney Docket Number	1199-82

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(12) **PATENT**
(19) **AUSTRALIAN PATENT OFFICE**

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(54) Title

Flat medicament preparation for the application and release of buprenorphine or a pharmacologically comparable substance in the buccal cavity, and method of producing the same

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(54) Title: FLAT MEDICAMENT PREPARATION FOR THE APPLICATION AND RELEASE OF BUPRENORPHINE OR A PHARMACOLOGICALLY COMPARABLE SUBSTANCE IN THE BUCCAL CAVITY, AND METHOD OF PRODUCING THE SAME

(54) Bezeichnung: FLACHE ARZNEIZUBEREITUNG ZUR APPLIKATION UND FREISETZUNG VON BUPRENORPHIN ODER EINER PHARMAKOLOGISCH VERGLEICHBAREN SUBSTANZ IN DER MUNDHÖHLE UND VERFAHREN ZU IHRER HERSTELLUNG

(57) Abstract

The invention concerns a solid medicament preparation which can decompose in aqueous media and has a flat-, foil-, paper- or wafer-type presentation for the application and release of active substances in the buccal cavity. The invention is characterized in that it contains buprenorphine, an active substance which is pharmacologically comparable thereto, or a therapeutically suitable salt of buprenorphine or of the pharmacologically comparable active substance.

(57) Zusammenfassung

Eine feste, in wässrigen Medien zerfallsfähige Arzneizubereitung mit flacher, folien-, papier- oder oblatenförmiger Darreichungsform zur Applikation und Freisetzung von Wirkstoffen in der Mundhöhle ist gekennzeichnet durch einen Gehalt an Buprenorphin, einem dem Buprenorphin pharmakologisch vergleichbaren Wirkstoff, oder einem therapeutisch geeigneten Salz des Buprenorphins oder des pharmakologisch vergleichbaren Wirkstoffes.

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ABSTRACT

A solid pharmaceutical preparation, disintegratable in aqueous media, with a flat, foil-shaped, paper-shaped or wafer-shaped administration form, for application and release of active substances in the oral cavity is characterized by a content of buprenorphine, of an active substance pharmacologically comparable to buprenorphine, or of a therapeutically suitable salt of bruprenorphine or the pharmacologically comparable active substance.

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Flat pharmaceutical preparation for application and release of buprenorphine or of a pharmacologically comparable substance in the oral cavity, and process for the production thereof

The present invention relates to a pharmaceutical preparation for application of buprenorphine or pharmacologically comparable active substances in the region of the oral cavity, respectively the oral mucosa. More particularly, it relates to a preparation that is adapted to be flat and in the form of a foil-, paper- or wafer-shaped administration form.

Flat active substance carriers have already been developed and produced for various purposes. DE-OS 27 46 414 can be regarded as fundamental to this administration form, said document describing a foil-type tape of active substance, binder and further active substances, with a direct relation existing, by reason of the homogeneous thickness, density and width, between a unit of length of the tape and the dose of active substance contained therein. The advantages of the continuous dosage property have been recognized also by other applicants and have been described in specific individual variants. Thus, DE-PS 36 30 603 claims a flat-shaped carrier material, for example in the form of a separating layer, with an active substance-containing coating, the latter being peelable, in doses, off the carrier material after having been previously separated into dosage units.

The practicability of the flat format in general and the advantages afforded in the manufacture of the administration form and in the dosing when employing such administration form have been recognized in the prior art.

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Moreover, further advantages of such administration forms can be derived such as the fact that, relative to the weight of the administration form, a relatively large surface may be printed on the said administration form, thereby making it possible to increase intake safety, as well as affording the possibility of discrete intake without any liquid being available.

Despite these obvious advantages, such flat administration forms have hitherto hardly been successful. Obviously, the advantage as compared to conventional administration forms does not suffice for many manufacturers of pharmaceutics to develop products of this type comprising the usual active ingredients and to pursue the legal drug approval thereof. Moreover, existing production machinery and existing know-how cannot be made use of for these novel products; this means that the necessity of large investments would arise. Despite the above-described advantages of flat, film- or paper-like administration forms, the therapeutic and/or economic advantage in administration of common active substances which are also perorally applicable is apparently not great enough as compared to conventional tablets to justify the costs of switching over to these administration forms.

One of the substances that are little suitable for peroral administration is buprenorphine, an opiate which has been successfully used in the therapy of pain for years. After peroral application it is hardly bioavalable, i.e. it appears in the blood circulation only to the very small extent of a few percent of the dose taken (McQuay & Moore, in: Bupenorphine, ed. Cowan & Lewis, New York 1995). Presumably, the reason for the lack in bioavailability lies in the extensive decomposition of the substance during the first liver passage following gastrointestinal absorption ("first-pass effect"). A possibility of avoiding the first-

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pass effect in oral administration is to bring the active substance to absorption already on the oral mucosa. In order to enter the central systemic circulation, an active substance which enters into the blood via the oral mucosa does not have to first pass the portal system and thus, in concentrated form, the liver, which metabolizes the active substance. A prerequisite for buccal or sublingual application, however, is a sufficient permeability of the oral mucosa to the active substance, taking into consideration the required dose. Permeability in turn depends to a large extent on the physicochemical properties of the active substance. Since buprenorphine is effective in very small doses, and since it has the required physicochemical characteristics, buccal or sublingual application is very attractive.

In fact, apart from injectable administration forms there are - at least in Germany - no commercially available peroral administration forms, but only so-called sublingual tablets, which comprise buprenorphine (Temgesic® sublingual). It is true that such tablets take into account the fact that sublingual application of the active substance is preferable to peroral administration - even though they do so above all by way of their intake directions as only these suggest the sublingual administration, not the tablet itself. However, they offer a vehicle which has considerable drawbacks for this purpose of application. Among these disadvantages is, firstly, the not inconsiderable disintegration time, which in the case of pressed tablets is at least several minutes even under favorable conditions, and in the case of the commercially available tablets is typically about 5 to 10 minutes. For patients suffering from severe, acute pain this disintegration time results in an unwanted delay of the onset of action; in a substitution or withdrawal therapy, however, this puts a strain on the medicinal personnel with

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respect to the time required for administration, since the personnel must supervise that the tablets are used as directed and must prevent improper removal of the non-disintegrated tablet from the mouth. Further disadvantages of the tablet are the foreign body sensation occurring during the disintegration time, but also the great variability in the extent of sublingual absorption, which is caused by the active substance during or after disintegration of the tablet having for the most part no direct contact with the oral mucosa, but being released into the saliva; the saliva, however, can be retained in the oral cavity for a very variable time, which is more or less haphazard, before being swallowed.

The present invention provides, in one aspect thereof, pharmaceutical preparations based on, and having the general advantages of, flat, film-like or paper-like active substance carriers which by reason of the combination with **a special active substance have additional economical and/or therapeutical advantages, apart from those mentioned above, over pharmaceutical preparations of the same active substance based on conventional administration forms such** as tablets. In addition, the present invention preferably provides an administration form for buprenorphine that releases the active substance in the oral cavity while not having the disadvantages described in the prior art.

More specifically, the present invention provides, in one aspect, buccal pharmaceutical preparation for treating acute conditions of pain or for addiction therapy, comprising as active substance buprenorphine or a therapeutically acceptable salt thereof, or an opiate active substance or a therapeutically suitable salt thereof, characterised by a flat, film-like administration form, disintegratable in the aqueous medium of the oral cavity, which has a mucoadhesive, active substance-containing layer based on water-soluble,

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film forming polymers of small thickness, for rapid active substance transfer through short diffusion paths, while having a large surface appropriate to the effective dose.

Additionally, the invention provides method of producing a pharmaceutical preparation as herein before described, characterized in that in a first step the active substance(s), together with a water-soluble polymer capable of film-formation, is (are) dissolved in a suitable, hydrophile solvent, optionally in presence of further dissolved or suspended auxiliary agents, that in a second step the solution or suspension is applied, in a continuous process and with even thickness, to a tape or a process sheet or foil, where, in a third step, it is largely freed from the solvent, thereby forming a sheet-shaped or tape-shaped starting material, wherefrom, in a fourth step, the dosage or multidosage units are separated by cutting or punching.

Further, the invention provides method of producing a pharmaceutical preparation as herein before described, characterized in that in a first step the active substance(s), together with a water-soluble, thermoplastic polymer capable of film-formation, is (are) formed, under action of heat and/or pressure, and optionally in presence of further auxiliary substances, into a sheet-shaped or tape-shaped starting material, from which starting material the dosage or multidosage units are separated by cutting or punching.

The invention may be achieved in accordance with the features of the claims providing an administration form on the basis of flat, foil-, paper- or wafer-like active substance carrier, which administration form contains an active substance buprenorphine, respectively one of its therapeutically acceptable salts, or a therapeutically comparable active substance. As will be explained in the following, an

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administration form according to Claim 1 may be considered by far superior to a conventional administration form for administering buprenorphine – both from the economical as well as the therapeutical point of view – and it is especially suitable, on the one hand, for analgesia in cases of acute conditions of pain, and, on the other hand, for the therapy of opiate or cocaine addiction in the sense of a substitution therapy or a withdrawal program.

The pharmaceutical preparation according to claim 1 can, upon application, be brought into direct contact with the oral mucosa. Due to the flat design, immediately after application about half of the surface of the administration form, which is large anyway, is located directly on the mucosa. The buprenorphine released thus encounters two factors particularly favorable for entry into the body, namely a short diffusion path and a large diffusion area. This reduces the portion of buprenorphine that is swallowed, which in the case of many other active agents would not be a particular problem. However, with buprenorphine, swallowing of the active substance should be avoided if possible, or should be reduced since, for the above mentioned reasons, swallowed buprenorphine is ineffective. Even in the case of the most simple embodiment according to the invention, and given a disintegration time of a few minutes following application or following introduction into aqueous media, the superiority of a buprenorphine-containing film over a buprenorphine-containing tablet will thus become evident.

An improved contact of the pharmaceutical preparation with the oral mucosa can be achieved through selecting auxiliary substances. It is known of certain orally applicable auxiliary agents which are commonly used in pharmaceutics that they have mucoadhesive properties. Examples for such mucoadhesive substances are polyacrylic acid, carboxy-methylcellulose, tragacanth, alginic acid, gelatin,

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hydroxymethylcellulose, methylcellulose and gum arabic. In addition, it is known of various non-mucoadhesive substances that in certain mixing ratios they develop mucoadhesive properties too. An example for such a mixture is glycerol monooleate/water in a ratio of 84:16 (Engström et al., Pharm. Tech. Eur. 7 [1995], No. 2, pages 14-17).

In the case that mucoadhesive auxiliary substances are used, it is preferable for the administration form of the pharmaceutical preparation according to the invention to have a two-layer or multi-layer structure. It can thereby be prevented that the preparation conglutinates various parts of the mucosa with each other, which would lead to sensations of considerable discomfort during application. In addition, it is in such a case preferable for the administration form to have a structure the non-mucoadhesive layer of which has a permeability to the active substance which is relatively smaller than that of the mucoadhesive layer, it thereby being possible to prevent that active substance losses occur due to active substance being released into the saliva instead of to the mucosa.

Pharmaceutical preparations according to the present invention are also those containing, apart from the active substance buprenorphine or an active substance pharmacologically comparable thereto, one or more further active substances. Such a preparation can be advantageous in several respects. On the one hand it is a recognized method for treating several symptoms or conditions occurring simultaneously to administer a fixed active substance combination in a medicament. To this end, it is possible to incorporate any therapeutically appropriate active substances into the preparation according to the present invention. On the other hand, the combination, as according to the invention, of an opiate active substance

with another substance that is capable of reducing the specific risks of opiate administration is especially useful and advantageous.
Thus - possibly partial - opiate antagonists, such as, for example, nalbuphine, naloxone or naltrexone, can be combined with the opiate active substance, which results in the risk of addiction or habituation involved in the repeated administration of the preparation being diminished by reason of the fact that the dose cannot be increased without at the same time accepting an increase of the antagonistic effect. The success of this strategy will depend on the selection of a suitable antagonist as well as the selection of the dose ratio.

Though buprenorphine - optionally in the form of one of its therapeutically acceptable salts - is the most preferred active substance, the invention also relates to such active substances as are pharmacologically similar or comparable to buprenorphine since the advantages of the invention described herein also apply in these cases, though to different extent. Further suitable active substances, which are also described herein as being "pharmacologically similar or comparable", are, in particular, those substances belonging to the opiates or opioids since many of these not only exhibit pharmacodynamic but also pharmacokinetic similarities to buprenorphine, that is a relatively low dose, good capacity for permeating membranes, and a high first-pass effect. Particularly preferred are morphine derivatives or dihydromorphine derivatives as well as substances from the methadone and fentanyl group.

In order not to promote any improper application or one that does not conform to the intended use, pharmaceutical preparations according to the invention will typically be present predivided into doses and separated from each other

in a suitable package, so that when removing a dosage unit it will be possible to remove only one unit at a time, such as in the case of a blister pack, where each dosage unit is sealed individually in a deep-drawn cup. Within programs for treatment of opiate or cocaine addiction it may, however, also be useful to supply physicians who are providing the medical care, for example, with preparations in the form of packaging units wherein said preparations are present as undivided sheet-like or tape-like material, from which the dosage units can be separated for the purpose of application. This facilitates mass application and affords the physicians who are administering the preparations the possibility of separating from one and the same material various dosage units in accordance with the given dosage requirements.

Since the pharmaceutical preparation according to the present invention is expected to exhibit increased bio-availability as compared to known preparations, it will possibly be necessary to adjust the dosage. In the case of buprenorphine the individual analgesic dose will be about 0.1 to 1 mg; in addiction or substitution therapy, however, this value might be considerably higher.
In accordance with the invention the manufacture of the pharmaceutical preparation is performed in several steps. For preparing the web-shaped starting material - from which ultimately either individual doses or entire packaging units will be separated by cutting or punching - two basic process variants are suitable. The first group of processes includes those where a tape, or a process sheet or foil, is evenly coated with aqueous or solvent-containing liquids being in part of higher viscosity, and where this is subsequently subjected to a drying process. To this end, first, a coating mass is prepared, for which purpose at least one water-soluble polymer capable of forming a film, the active substance(s) and a suitable, vaporizable liquid

must be intimately mixed. If required it is possible to incorporate further auxiliary substances such as disintegration-modifying polymers, softeners, fillers, texture-providing substances, pigments, dyes, taste corrigents, solubilizers, substances for adjusting the pH, *smoothing agents, dulling agents, disintegration promoters, etc. As an alternative, the web-like starting material may be made by thermoplastic forming, i.e. without the aid of liquids. Suitable processes are, inter alia, any hot-melt coating methods as well as any extrusion methods. As a prerequisite, the polymer or polymer mixture capable of film-formation must in this case be thermoplastically formable. The required ingredients are mixed and, under action of pressure and/or heat, formed by extruding, blowing or by coating of tapes, sheets or foils, and, after solidification, transferred for further processing. Suitable for the manufacture of preparations according to the present invention that have a multi-layer structure are correspondingly modified methods, it being irrelevant whether several web-shaped materials are simultaneously or subsequently produced and combined.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers or steps but not the exclusion of any other integer or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge in Australia.

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The claims defining the invention are as follows:

1. Buccal pharmaceutical preparation for treating acute conditions of pain or for addiction therapy, comprising as active substance buprenorphine or a therapeutically acceptable salt thereof, or an opiate active substance or a therapeutically suitable salt thereof, characterised by a flat, film-like administration form, disintegratable in the aqueous medium of the oral cavity, which has a mucoadhesive, active substance-containing layer based on water-soluble, film-forming polymers of small thickness, for rapid active substance transfer through short diffusion paths, while having a large surface appropriate to the effective dose.

2. Pharmaceutical preparation according to claim 1, characterized by a mono- or multi-layered structure having a mucoadhesive active substance-containing layer based on water-soluble, film-forming polymers of small thickness for rapid active substance uptake through short diffusion paths.

3. Pharmaceutical preparation according to claim 1 or 2, characterized by a non-mucoadhesive outer layer, opposed to the mucoadhesive surface, which outer layer has a lower permeability to the active substance.

4. Pharmaceutical preparation according to any one of the preceding claims, characterized by a single-dose buprenorphine content of 0.1 - 1 mg.

5. Pharmaceutical preparation according to any one of the preceding claims, characterized in that it is equipped with bioadhesive or mucoadhesive properties by the addition of an adhesion-promoting auxiliary substance or auxiliary substance mixture.

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6. Pharmaceutical preparation according to claim 5, characterized in that further active substance is present which is suitable for treating addiction to opiates.

7. Pharmaceutical preparation according to claim 6, characterized in that further active substance is, at least partially, capable of opiate antagonist action.

8. Pharmaceutical preparation according to claim 7, characterized in that it contains nalbuphine, naloxone or naltrexone.

9. Pharmaceutical preparation according to one or more of the preceding claims, characterized in that it is present as an undivided, sheet-shaped or tape-shaped material, from which it is possible to separate dosage units for the purpose of application.

10. Pharmaceutical preparation according to one or more of the preceding claims, characterized in that it is present predivided into doses.

11. Pharmaceutical preparation according to one or more of the preceding claims, characterized in that, per dosage unit, it has a content of active substance which is suitable for analgesia.

12. Pharmaceutical preparation according to one or more of the preceding claims, characterized in that, per dosage unit, it has a content of active substance which is suitable for opiate or cocaine substitution therapy.

13. Method of producing a pharmaceutical preparation according to one or more of the preceding claims,

characterized in that in a first step the active substance(s), together with a water-soluble polymer capable of film-formation, is (are) dissolved in a suitable, hydrophile solvent, optionally in presence of further dissolved or suspended auxiliary agents, that in a second step the solution or suspension is applied, in a continuous process and with even thickness, to a tape or a process sheet or foil, where, in a third step, it is largely freed from the solvent, thereby forming a sheet-shaped or tape-shaped starting material, wherefrom, in a fourth step, the dosage or multidosage units are separated by cutting or punching.

14. Method of producing a pharmaceutical preparation according to one or more of the preceding claims, characterized in that in a first step the active substance(s), together with a water-soluble, thermoplastic polymer capable of film-formation, is (are) formed, under action of heat and/or pressure, and optionally in presence of further auxiliary substances, into a sheet-shaped or tape-shaped starting material, from which starting material the dosage or multidosage units are separated by cutting or punching.

15. Method of producing a pharmaceutical preparation according to claim 13 or 14, characterized in that a plurality of simultaneously or subsequently prepared, sheet-shaped or tape-shaped starting materials are combined to form a multilayered material, from which the dosage or multidosage units are separated.

16. Buccal pharmaceutical preparations or methods for producing same substantially as herein described with reference to the Examples.

DATED this 20th day of September, 2001

LTS LOHMANN THERAPIE-SYSTEME GMBH
By its Patent Attorneys
DAVIES COLLISON CAVE

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PTO/SB/22 (09-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 1199-82
Application Number 12/537,571	Filed August 7, 2009
For Sublingual and Buccal Film Compositions	
Art Unit 1633	Examiner Janet L. Epps-Smith

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$150	$75	$
☐	Two months (37 CFR 1.17(a)(2))	$560	$280	$
☑	Three months (37 CFR 1.17(a)(3))	$1270	$635	$ 1270
☐	Four months (37 CFR 1.17(a)(4))	$1980	$990	$
☐	Five months (37 CFR 1.17(a)(5))	$2690	$1345	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

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

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

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

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 086421.

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 52,739

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Jon A. Chiodo/ — Signature

February 29, 2012 — Date

Jon A. Chiodo — Typed or printed name

973-331-1700 — Telephone Number

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 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 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:	12537571
Filing Date:	07-Aug-2009
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Filer:	Daniel A. Scola/Christine Briscoe
Attorney Docket Number:	1199-82

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1270	1270

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**1450**

Electronic Acknowledgement Receipt

EFS ID:	12185833
Application Number:	12537571
International Application Number:	
Confirmation Number:	5630
Title of Invention:	SUBLINGUAL AND BUCCAL FILM COMPOSITIONS
First Named Inventor/Applicant Name:	Garry L. Myers
Customer Number:	23869
Filer:	Daniel A. Scola/Christine Briscoe
Filer Authorized By:	Daniel A. Scola
Attorney Docket Number:	1199-82
Receipt Date:	29-FEB-2012
Filing Date:	07-AUG-2009
Time Stamp:	15:42:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1450
RAM confirmation Number	3001
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)

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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		AMENDMENT.pdf	132414 ddb8a730e73096abfabcdfb4b1944f7219c7e2eb	yes	13

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	13

Warnings:

Information:

2	Transmittal Letter	IDS_TRANSMITTAL.pdf	86876 c2ff2a63ab47866d568a400a1f4c8b77b94bfdf6	no	2

Warnings:

Information:

3	Information Disclosure Statement (IDS) Form (SB08)	1199-82_IDS.pdf	5220916 c34ce1b907a4c1aa27be5fc1a3410d9b1ee37c18	no	5

Warnings:

Information:

4	Foreign Reference	AU741362.pdf	428296 d467324c6368164774278765843f1cafa4fde9b8	no	17

Warnings:

Information:

5	Extension of Time	Extension_of_Time.pdf	293176 595cede964fce7f2d662fd64b99a6383c5caf8f0	no	2

Warnings:

Information:

6	Fee Worksheet (SB06)	fee-info.pdf	32101 8a250089baf8ba3bdd30e967aae22fd3965504c1	no	2

Warnings:

Information:	
Total Files Size (in bytes):	6193779

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/537,571	08/07/2009	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT	02/29/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 31	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 7	Minus	***7	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/KAREN VESTAL/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Commissioner for Patents
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HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

MAILED

FEB 09 2012

OFFICE OF PETITIONS

In re Application of Myers et al. :
Application No. 12/537,571 : Letter
Filing Date: August 7, 2009 :
Attorney Docket No. 1199-82 :

This is a notice regarding the request for acceptance of a fee deficiency submission under 37 CFR 1.28(c) filed January 6, 2012.

The deficiency payment of $1,722 is hereby accepted.

The change of status to large entity has been entered and made of record.

Telephone inquiries regarding this communication should be directed to Petitions Attorney Steven Brantley at (571) 272-3203.

Charles Steven Brantley
Senior Petitions Attorney
Office of Petitions

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Myers et al.

Examiner: Epps-Smith, Janet L.

Application No.: 12/537,571

Group Art Unit: 1633

Filed: August 7, 2009

Docket: 1199-82

For: SUBLINGUAL AND BUCCAL FILM COMPOSITIONS

Dated: January 6, 2012

01/09/2012 DALLEN 00000014 082461 12537571
01 FC:1461 1722.00 DA

Confirmation No.: 5630

Mail Stop: Applications Assistance Unit
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	08/07/2009	$82.00	$380.00	$298.00
Utility Search Fee	08/07/2009	$270.00	$620.00	$350.00

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Utility Examination Fee	08/07/2009	$110.00	$250.00	$140.00
Claims				
2 independent claims in excess of three	08/07/2009	$220.00	$500.00	$280.00
11 claims in excess of twenty	08/07/2009	$286.00	$660.00	$374.00
2 independent claims in excess of three	08/20/2009	$220.00	$500.00	$280.00
Total Fees Paid:		**$1188.00**		
Total Fees Due as Large Entity:			**$2910.00**	
Total Fees Due Herewith:				**$1722.00**

A fee of $1,722.00 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,

Jon A. Chiodo, Esq.
Registration No. 52,739
Attorney for Applicant

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

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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Docket No.: 1199-82

DATE: January 6, 2012

2012 JAN -6 PM 4:00
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DIVISION

FACSIMILE TRANSMISSION COVER SHEET

TO: Applications Assistance Unit

FAX NO.: 571-273-8300

FROM: Jon A. Chiodo

SENDER: cbriscoe

HOFFMANN & BARON, LLP
ATTORNEYS AT LAW

NY OFFICE

6900 JERICHO TURNPIKE
SYOSSET, N.Y. 11791

TELEPHONE: 516-822-3550
TELECOPIER: 516-822-3582

• **NJ OFFICE**

6 CAMPUS DRIVE
PARSIPPANY, N.J. 07054

TELEPHONE: 973-331-1700
TELECOPIER: 973-331-1717

NUMBER OF PAGES TO FOLLOW: 2

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TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

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.
12/537,571	08/07/2009	Garry L. Myers	1199-82	5630

23869 7590 08/31/2011

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

EXAMINER	
EPPS -SMITH, JANET L	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
08/31/2011	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.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Office Action Summary	Application No.	Applicant(s)	
	12/537,571	MYERS ET AL.	
	Examiner	Art Unit	
	JANET L. EPPS -SMITH	1633	

-- 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)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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

5)☒ Claim(s) *1-31* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-31* is/are rejected.

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

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

Application Papers

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

11)☐ 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).

12)☐ 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

13)☐ 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 *9-3-09;3-15-11;6-21-11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1, 4, 5, 7-10, 15, 17, and 20-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Oksche et al. WO2008/025791A1 (Citations are taken from US2010/0087470).

3. Instant claim 1 is drawn to the following: A film dosage composition comprising: a. A polymeric carrier matrix; b. A therapeutically effective amount of buprenorphine or a pharmaceutically acceptable salt thereof; c. A therapeutically effective amount of naloxone or a pharmaceutically acceptable salt thereof; and d. A **buffer in an amount to provide a local pH of said composition of a value sufficient to optimize absorption of said buprenorphine.**

4. See the following embodiments of Oksche et al. at the following paragraphs:

5. [0055] In one embodiment one may use non-gelatin film materials, e.g. films of modified cellulose materials as dosage forms. In this case, buprenorphine and optionally opioid antagonists such as naloxone are incorporated into the film matrix and films thus prepared may be administered orally.

6. [0046] The pharmaceutical dosage form in accordance with the invention will be administered such that the maximal dosage per day is 32 mg of buprenorphine. Once a

patient is enrolled in substitution therapy, the initial dosage will be typically between 2 mg to 4 mg of buprenorphine. The formulations may be administered once a day, every two days, preferably every three days or even less frequently.

7. [0072] Suitable pH modifiers include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Suitable sweeteners include aspartame and thaumatin. Suitable taste-masking agents include sodium bicarbonate, ion-exchange resins, cyclodextrin inclusion compounds, adsorbates or microencapsulated actives.

8. [0085] In order to allow absorption of buprenorphine over the mucosa of the mouth, and particularly sublingually, in one embodiment the dosage forms may additionally use agents that enhance absorption of the active agent, i.e. so-called permeation enhancers.

9. [0092] The polymer amount within the matrix may be between approximately 3% by weight and approximately 98% by weight and preferably between 7 and 80% by weight and even more preferably between 20 and 50% by weight, the weight percentages being based on the total weight of the dosage forms.

Claim Rejections - 35 USC § 103

10. 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.

11. Claims 1-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oksche et al. (as applied above).

12. Oksche et al. as describe above is incorporated here. However, the disclosure of this reference does not teach formulations buprenorphine and naloxone, where the buffer is present in an amount sufficient to inhibit the absorption of naloxone. Furthermore, the cited reference does not teach the specific range of pH recited in the instant claims.

13. According to the specification as filed, the buffer is present in such an amount so as to provide optimal release from the film and/or absorption into the body an amount of the agonist and the antagonist, see paragraph [0067]. Additionally, the reference specification as filed teaches that any buffer system may be used, as desired, however they preferably include sodium citrate, and citric acid. These features are already disclosed in Oksche et al., see ¶ [0072], which states that buprenorphine/naloxone formulations may comprise the citric acid as a pH modifier.

The following embodiments of Oksche et al. are also disclosed: [0012] Another buprenorphine preparation aimed at preventing this potential possibility of abuse has recently gained administrative approval in the United States (Suboxone.RTM.). The Suboxone.RTM. preparation comprises buprenorphine hydrochloride and the opioid antagonist naloxone hydrochloride dihydrate. The presence of naloxone is intended to prevent parenteral abuse of buprenorphine as parenteral co-administration of buprenorphine and naloxone in e.g. an opioid-dependent addict will lead to serious withdrawal symptoms.

[0013] However, there remains a need for other diversion and/or abuse-resistant dosage forms of buprenorphine, which can be used in drug substitution therapy as described above. Additionally, it would be desirable to have a buprenorphine preparation available which is diversion and/or abuse-resistant in cases where the preparation is used for drug substitution therapy and which could also provide efficient analgesia in cases where the preparation is administered to alleviate pain in a patient.

It is clear that the sublingual film formulations of Oksche et al. are designed so as to prevent development of dependency. Thus, it would have been obvious to the ordinary skilled artisan, at the time of the instant invention, to modify their teachings so as to identify the optimal range of pH/dosage in an effort to identify formulations that would provide optimal absorption of both agonist and antagonist. As per MPEP 2144.05 [R-5], since the general conditions of the instantly claimed invention are disclosed in the prior art, identification of the optimal pH/dosage appears to be a matter of routine experimentation.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JANET L. EPPS -SMITH whose telephone number is (571)272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. 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.

JANET L. EPPS -SMITH
Primary Examiner
Art Unit 1633

/JANET L. EPPS -SMITH/
Primary Examiner, Art Unit 1633

Notice of References Cited	Application/Control No. 12/537,571	Applicant(s)/Patent Under Reexamination MYERS ET AL.	
	Examiner JANET L. EPPS -SMITH	Art Unit 1633	Page 1 of 1

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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2010/0087470	04-2010	Oksche et al.	514/279
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
X	N	WO 2008025791 A1	03-2008	World Intellect	OKSCHE et al.	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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*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.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12537571
Filing Date	2009-08-07
First Named Inventor	Garry L. Myers
Art Unit	1633
Examiner Name	Joseph T. Woitach
Attorney Docket Number	1199-82

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	3007848		1961-11-07	J.H. Stroop	
	2	5605696		1997-02-25	Eury et al.	
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	4	5806284		1998-09-15	Gifford	
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	7	6800329	B2	2004-10-05	Horstmann et al.	
	8	6824829	B2	2004-11-30	Berry et al.	

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TEVA EXHIBIT 1008
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	Art Unit	1633
	Examiner Name	Joseph T. Woitach
	Attorney Docket Number	1199-82

	9	7005142		2006-02-28	Leon	

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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	20030107149	A1	2003-06-12	Yang et al.	
	2	20040096569	A1	2004-05-20	Barkalow et al.	
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	0598606	EP	B1	1999-06-30	Johnson & Johnson Consumer Products, Inc.		☐

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	Attorney Docket Number	1199-82

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	5	05147140	JP		1993-06-15	Hirofumi et al.	English Abstract	☐
	6	07322812	JP		1995-12-12	Tomoyoshi et al.	English Abstract	☐
	7	2001279100	JP		2001-10-10	Masahiro	English Abstract	☐
	8	03/030882	WO	A1	2003-04-17	Kosmos Pharma		☐

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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	Lazaridou et al., "Thermophysical proprties of chitosan, chitosan-starch and chitosan-pullulan films near the glass transition," Carbohydrate Polymers 48: 179-190 (2002).	☐
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	Attorney Docket Number	1199-82

	3	Repka et al., "Influence of Vitamin E TPGS on the properties of hydrophilic films produced by hot melt extrusion", International Journal of Pharmaceutics 202: 63-70 (2000).	☐

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EXAMINER SIGNATURE

Examiner Signature	/Janet Epps Smith/	Date Considered	08/29/2011

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4	("1897543").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/08/29 08:15
L2	2	("20100087470").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/08/29 08:19
L3	2	2 and naloxone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 08:20
L4	1	2 and naloxone and absorption and citric	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 08:24
L5	1	2 and naloxone and absorption and citric and pH	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 08:55
L6	0	2 and naloxone and absorption and citric and pH and (suppress or block)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 09:03
L7	0	2 and naloxone and absorption and citric and pH and block	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/29 09:03
L8	1	2 and naloxone and absorption and citric	US-PGPUB;	OR	ON	2011/08/29

		and pH and polymer	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			09:26
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S2	1236	S1 and pH	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/21 18:48
S3	614	S2 and (film or biofilm)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/21 18:49
S4	580148	film forming polymer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2011/08/21 18:49
S5	22690	film forming polymer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	NEAR	ON	2011/08/21 18:49
S6	56	S3 and S5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	NEAR	ON	2011/08/21 18:49
S7	48	(film dosage).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	NEAR	ON	2011/08/21 18:50
S8	2	S6 and S7	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT;	NEAR	ON	2011/08/21 18:50

			IBM_TDB			
S9	1388	(buprenorphine) and naloxone and buffer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/21 18:56
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S11	70	US-20070148097-$.DID. OR US-6228863-$.DID. OR US-6310072-$.DID. OR US-6375957-$.DID. OR US-6469170-$.DID. OR US-4582835-$.DID. OR US-4464378-$.DID. OR US-4990617-$.DID. OR US-5272149-$.DID. OR US-4154932-$.DID. OR US-5512578-$.DID. OR US-5512593-$.DID. OR US-5552406-$.DID. OR US-5817665-$.DID. OR US-5834480-$.DID. OR US-5856332-$.DID. OR US-6034091-$.DID. OR US-6277384-$.DID. OR US-6291675-$.DID. OR US-6475494-$.DID. OR US-6696066-$.DID. OR US-6995169-$.DID. OR US-7144587-$.DID. OR US-7172767-$.DID. OR US-7384653-$.DID. OR US-7402591-$.DID. OR US-7419686-$.DID. OR US-7749542-$.DID. OR US-20020010127-$.DID. OR US-20020013301-$.DID. OR US-20020058673-$.DID. OR US-20030004178-$.DID. OR US-20030031712-$.DID. OR US-20030044458-$.DID. OR US-20030068392-$.DID. OR US-20030124185-$.DID. OR US-20030191147-$.DID. OR US-20030211157-$.DID. OR US-20040086561-$.DID. OR US-20050048115-$.DID. OR US-20050063909-$.DID. OR US-20050191340-$.DID. OR US-20050192309-$.DID. OR US-20060058332-$.DID. OR US-20060058333-$.DID. OR US-20060069113-$.DID. OR US-20070122348-$.DID.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/08/22 11:04
S12	1566	(myers-g$ or hilbert-s$ or boone-b$ or bogue-b$ or sanghvi-P$ or hariharan-M$).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 11:12
S13	1332	(matrix or liposome or polymeric or carrier) and (buprenorphine) and naloxone and buffer	US-PGPUB; USPAT; USOCR; FPRS;	OR	ON	2011/08/22 11:13

			EPO; JPO; DERWENT; IBM_TDB			
S14	5	S13 and S12	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 11:13
S17	918	(matrix or liposome or polymeric or carrier) and (buprenorphine) and naloxone and buffer and absorption	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 14:10
S18	17	naloxone adj25 absorption	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 14:11
S19	5	S17 and S18	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 14:11
S20	1332	(matrix or liposome or polymeric or carrier) and (buprenorphine) and naloxone and buffer	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/08/22 16:34
S21	70	US-20070148097-$.DID. OR US-6228863-$.DID. OR US-6310072-$.DID. OR US-6375957-$.DID. OR US-6469170-$.DID. OR US-4582835-$.DID. OR US-4464378-$.DID. OR US-4990617-$.DID. OR US-5272149-$.DID. OR US-4154932-$.DID. OR US-5512578-$.DID. OR US-5512593-$.DID. OR US-5552406-$.DID. OR US-5817665-$.DID. OR US-5834480-$.DID. OR US-5856332-$.DID. OR US-6034091-$.DID. OR US-6277384-$.DID. OR US-6291675-$.DID. OR US-6475494-$.DID. OR US-6696066-$.DID. OR US-6995169-$.DID. OR US-7144587-$.DID. OR US-7172767-$.DID. OR US-7384653-$.DID. OR US-7402591-$.DID. OR US-7419686-$.DID. OR US-7749542-$.DID. OR US-20020010127-$.DID. OR US-20020013301-$.DID. OR US-20020058673-$.DID. OR US-20030004178-$.DID. OR US-20030031712-$.DID. OR US-20030044458-$.DID. OR US-20030068392-$.DID. OR US-	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/08/22 16:39

		20030124185-$.DID. OR US-20030191147-$.DID. OR US-20030211157-$.DID. OR US-20040086561-$.DID. OR US-20050048115-$.DID. OR US-20050063909-$.DID. OR US-20050191340-$.DID. OR US-20050192309-$.DID. OR US-20060058332-$.DID. OR US-20060058333-$.DID. OR US-20060069113-$.DID. OR US-20070122348-$.DID.				
S22	5	S21 and (film adj50 dosage)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/08/22 16:39
S23	5	S21 and (film adj50 dosage)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2011/08/22 16:40

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Filing Date	2009-08-07
First Named Inventor	Garry L. Myers
Art Unit	1633
Examiner Name	Janet L. Epps-Smith
Attorney Docket Number	1199-82

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	US307537	A	1884-11-04	Foulks	
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	9	3598122		1971-08-10	Zaffaroni	
	10	3632740		1972-01-04	Robinson et al.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12537571
	Filing Date	2009-08-07
	First Named Inventor	Garry L. Myers
	Art Unit	1633
	Examiner Name	Janet L. Epps-Smith
	Attorney Docket Number	1199-82

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.E./

TEVA EXHIBIT 1008
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/537,571	MYERS ET AL.	
	Examiner	Art Unit	
	JANET L. EPPS -SMITH	1633	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Inventor name search	8-22-11	JLE
Plus search	8-22-11	JLE
East-see attached	8-29-11	JLE

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PLUS Search Results for S/N 12537571, Searched Mon Aug 22 08:39:31 EDT 2011

The Patent Linguistics Utility System (PLUS) is a USPTO automated search system for U.S. Patents from 1971 to the present PLUS is a query-by-example search system which produces a list of patents that are most closely related linguistically to the application searched. This search was prepared by the staff of the Scientific and Technical Information Center, SIRA.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12537571
Filing Date	2009-08-07
First Named Inventor	Garry L. Myers
Art Unit	1633
Examiner Name	Janet L. Epps-Smith
Attorney Docket Number	1199-82

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12537571
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	First Named Inventor	Garry L. Myers
	Art Unit	1633
	Examiner Name	Janet L. Epps-Smith
	Attorney Docket Number	1199-82

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Jon A. Chiodo, Reg. No. 52,739/	Date (YYYY-MM-DD)	2011-06-21
Name/Print	Jon A. Chiodo	Registration Number	52739

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(54) Bezeichnung: Folienförmige Arzneimittel bzw. Placebos

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(56) Für die Beurteilung der Patentfähigkeit in Betracht gezogene Druckschriften:

DE-OS 20 06 696
DE-OS 19 31 080
DE-OS 18 00 580
AT 2 79 035
US 38 03 300

Fiedler: Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Aulendorf 1971, S. 24, 110, 111, 308, 376-378, 608, 609

In Betracht gezogene ältere Patente:
DE-PS 24 59 391

DE 24 32 925 B 2

● 12 80 030 163/123

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Patentansprüche:

1. Folienförmige Arzneimittel mit gleichmäßiger Wirkstoffverteilung bzw. folienförmige Placebos auf Basis filmbildender Celluloseäther, dadurch gekennzeichnet, daß sie bis zu 60% Wirkstoffe, ein Trennmittel und als Folienbildner einen nichtionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose enthalten.

2. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß sie Füllstoffe und/oder als Folienbildner Hydroxypropylcellulose, Hydroxyäthylcellulose und/oder Methylhydroxypropylcellulose enthalten.

3. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß sie als Trennmittel ein Polyoxyäthylenpolyoxypropylenpolymeres, Polyoxyäthylenstearate oder alkyl- bzw. acylsubstituierte Polyadditionsprodukte des Äthylenoxids enthalten.

4. Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, daß sie als Füllstoffe Cellulose, Zucker, Stärken, Mannit, Calciumcarbonat, Calciumphosphat oder Talkum enthalten.

5. Verfahren zur Herstellung von folienförmigen Arzneimitteln mit gleichmäßiger Wirkstoffverteilung bzw. von folienförmigen Placebos auf Basis filmbildender Celluloseäther durch Ausziehen einer Lösung bzw. Suspension auf einer Folienziehmaschine, durch nachträgliches Trocknen des nassen Ausstrichs und Teilen der Folie in Abschnitte, dadurch gekennzeichnet, daß man bis zu 60% Wirkstoffe, bezogen auf getrocknete Arzneimittel, und das Trennmittel in einer Flüssigkeit löst bzw. suspendiert, als Folienbildner einen nichtionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose einträgt und, im Falle der Herstellung transparenter, glatter Folien, gegebenenfalls lösliche Füllstoffe und, im Falle der Herstellung papierartiger Folien, unlösliche Füllstoffe zusetzt.

6. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß man den Folienbildner in Mengen von 6 – 20 Gewichtsprozent, Füllstoffe in Mengen von 0 – 30 Gewichtsprozent und das Trennmittel in Mengen 0,01 – 2 Gewichtsprozent, jeweils bezogen auf die Lösung bzw. Suspension, einsetzt.

7. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß die zum Lösen bzw. Suspendieren dienende Flüssigkeit aus Wasser und/oder einem oder mehreren organischen Lösungsmitteln besteht.

8. Verfahren nach Anspruch 5 und 7, dadurch gekennzeichnet, daß 48 – 84 Gewichtsprozent Flüssigkeit in der Lösung bzw. Suspension enthalten sind.

9. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß die Schichtdicke des nassen Ausstrichs 0,1 – 2 mm beträgt und die der trockenen Folie 0,05 – 1 mm beträgt.

10. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß die getrocknete Folie durch Schneiden bzw. Perforieren in Einzeldosen geteilt wird.

Die Erfindung betrifft den in den Ansprüchen gekennzeichneten Gegenstand.

Aus der belgischen Patentschrift Nr. 6 37 363 sind Papierfolien bekannt, die mit Wirkstoff beschichtet zur oralen Anwendung geeignet sind. Die Folien bestehen aus in Wasser unlöslichen Cellulosefasern und einem wasserlöslichen Bindemittel. Als wasserlösliche Bindemittel wird vorzugsweise Carboxymethylcellulose-Natrium verwendet. Nach den Beispielen der belgischen Patentschrift wird der Wirkstoff durch Auftropfen des gelösten Wirkstoffes, durch Aufstreuen des festen Wirkstoffes oder durch Durchziehen der Folie durch die Wirkstofflösung auf die Papierfolie gebracht. Das diskontinuierliche Verfahren der gesonderten Herstellung der Folie und Aufbringung des Wirkstoffes hat den Nachteil, daß die Dosierungsgenauigkeit nicht sehr gut ist, was bei den heute niedrig dosierten Wirkstoffen jedoch von großer Wichtigkeit ist. Ungenauigkeiten entstehen aber nicht nur bei dem Aufbringen des Wirkstoffes, sondern auch bei der Herstellung und Vorbehandlung des Trägers und durch Veränderungen bei der Lagerung des Trägermaterials. So hat es sich zum Beispiel gezeigt, daß nach der Rezeptur der belgischen Patentschrift bei Verwendung von Folienziehmaschinen keine gleichmäßige Folienschicht entsteht und daß die Folie bei der Trocknung schrumpft.

Aus den deutschen Offenlegungsschriften DE-OS 18 00 580 und DE-OS 19 31 080 sind Arzneimittelzubereitungen in flüssiger und salbenartiger Form bekannt, die erst nach der Applikation auf der Haut einen festen Film bilden.

Die deutsche Offenlegungsschrift DE-OS 20 06 696 bezieht sich auf ein medizinisches Pflaster oder einen Haftverband mit verschiedenen Ausnehmungen oder Hohlräumen, die mit einer Tablette, mit Puder, Salbe, Creme oder ähnlichen Substanzen gefüllt sind und zur Verabreichung von empfängnisverhütenden Substanzen mit Systemwirkung auf dem Wege durch die Haut geeignet sind. Das Pflaster kann auch aus einem Träger und einem Klebeteil bestehen, wobei die empfängnisverhütenden Stoffe durch Aufsprühen oder Dispergieren der Wirkstofflösung in den Klebeteil eingearbeitet sein können. Die erfindungsgemäßen folienförmigen Arzneimittel bestehen dagegen aus einer einheitlichen Phase mit inkorporiertem Wirkstoff.

Aus der amerikanischen Patentschrift US-PS 38 03 300 sind salbenartige Folien (getrocknete Öl-in-Wasser-Emulsionen) bekannt. Im Gegensatz zu den gelartigen erfindungsgemäßen Arzneimitteln und Placebos enthalten die Folien gemäß US-PS 38 03 300 Öle oder Fette und Emulgatoren.

Ferner ist es bekannt, feste oral applizierbare Arzneimittel mit Überzügen zu versehen, die als Bindemittel sogenannte Filmbildner wie Harze oder Celluloseäther enthalten. Die wirkstofffreien Überzüge schützen das Arzneimittel vor Abrieb, vor Licht und Feuchtigkeit, sie wirken außerdem geruchs- und geschmackshemmend (Fiedler: »Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete«).

In der österreichischen Patentschrift AT-PS 2 79 035 werden Folien zur Erzeugung lokaler Anästhesie beschrieben. Aus einer großen Zahl genannter Folienbildner, die auch Celluloseäther einschließt, werden Polyvinylalkohol, Polyvinylpyrrolidon und Alkalimetallcarboxymethylcellulose besonders herausgestellt. Es hat sich gezeigt, daß die nach der österreichischen Patentschrift bevorzugten Folienbildner für unsere Zwecke wenig geeignet sind, da diese Folienbildner die Wirkstoffe teilweise einschließen und nur verzögert

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oder überhaupt nicht freigeben. Bei der Verwendung von Polyvinylalkohol als Folienbildner wird die Folie bei Temperaturen um 100°C gegossen und getrocknet; nach dem Abkühlen tritt eine Kristallisation des Wirkstoffes ein, wodurch eine gleichmäßige Wirkstoffverteilung in der Folie nicht mehr gewährleistet ist.

Es ist die Aufgabe der Erfindung, folienförmige Arzneimittel bzw. Placebos bereitzustellen, in denen bis zu 60% Wirkstoffe gleichmäßig verteilt sind bzw. in denen eine Kristallisation der Wirkstoffe verhindert wird. Die Aktivität der Wirkstoffe muß in der Folie erhalten bleiben, und die Folie darf sich beim Lagern nicht verändern. Das Folienmaterial darf die Wirkstoffe nicht einschließen und muß sie bei Anwendung wieder vollständig freigeben.

Die Aufgabe wird dadurch gelöst, daß man ein Trennmittel einsetzt und als Folienbildner einen nichtionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose verwendet.

Als nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose seien beispielsweise Hydroxypropylcellulose, Hydroxyäthylcellulose und Methylhydroxypropylcellulose genannt.

Geeignete Trennmittel sind u. a. Polyoxyäthylenpolyoxypropylenpolymeres, Polyoxyäthylenstearate, alkyl- bzw. acylsubstituierte Polyadditionsprodukte des Äthylenoxids, z. B. das Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid), Silikone, Silikontrennemulsionen und Metallseifen.

Außer Trennmittel und Folienbildner können die erfindungsgemäßen Folien Füllstoffe und Wirkstoffe enthalten.

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

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

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

Zur Herstellung der erfindungsgemäßen folienförmigen Arzneimittel bzw. Placebos werden bis zu 60% Wirkstoffe, bezogen auf getrocknete Arzneimittel, und das Trennmittel gelöst bzw. suspendiert, der Folienbildner und gegebenenfalls der Füllstoff eingetragen, gegebenenfalls homogenisiert und die Lösung bzw. Suspension auf einer Folienziehmaschine zu einem Ausstrich ausgezogen. Die durch Trocknung des Ausstrichs erhaltene Folie wird durch Schneiden bzw. Perforieren in Einzeldosen geteilt.

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

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

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

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

Beispiel 1

Herstellung für 1000 Einheiten:

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

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

Zusammensetzung für eine Einheit:

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

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Eine Einheit entspricht einer Fläche von ca. 3 cm². Aussehen der Folie: weiß, papierartig. Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 2

Herstellung für 1000 Einheiten:

1,10 g Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid) werden in
152,00 g Wasser gelöst. In dieser Lösung werden
0,25 g mikronisiertes D-Norgestrel und
0,05 g mikronisiertes Äthinylöstradiol suspendiert und evtl. homogenisiert. In diese Suspension werden
22,10 g Hydroxypropylcellulose und
16,50 g Cellulose eingetragen.

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

Zusammensetzung für eine Einheit:

0,25 mg D-Norgestrel
0,05 mg Äthinylöstradiol
1,10 mg Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 ml Äthylenoxid auf 1 Mol Glycerid)
22,10 mg Hydroxypropylcellulose
16,50 mg Cellulose
40,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm². Aussehen der Folie: weiß, papierartig. Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 3

Herstellung für 1000 Einheiten:

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

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

Zusammensetzung für eine Einheit:

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

Eine Einheit entspricht einer Fläche von ca. 3 cm². Aussehen der Folie: weiß, papierartig. Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 4

Herstellung für 1000 Einheiten:

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

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

Zusammensetzung für eine Einheit:

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

Eine Einheit entspricht einer Fläche von ca. 3 cm². Aussehen der Folie: weiß, papierartig. Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 5

Herstellung für 1000 Einheiten:

10,00 g 7-Chlor-2-methylamino-5-phenyl-3H-1,4-benzo-diazepin-4-oxid und
0,84 g Polyoxyäthylenpolyoxypropylenpolymeres werden in
95,00 g Äthylalkohol gelöst.
In diese Lösung wird ein Pulvergemisch aus
16,93 g Hydroxypropylcellulose und
7,23 g Cellulose eingetragen.

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

Zusammensetzung für eine Einheit:

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

Eine Einheit entspricht einer Fläche von ca. 3 cm². Aussehen der Folie: gelb, papierartig. Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 6

Herstellung für 1000 Einheiten:

1,00 g Norethisteronacetat
0,03 g Äthinylöstradiol und
0,84 g Polyoxyäthylenpolyoxypropylenpolymeres werden in

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95,00 g Äthylalkohol gelöst.
In diese Lösung wird ein Pulvergemisch aus
16,93 g Hydroxypropylcellulose und
16,20 g Cellulose eingetragen.

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

Zusammensetzung für eine Einheit:

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

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 7

Herstellung für 1000 Einheiten:

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

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

Zusammensetzung für eine Einheit:

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

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 8

Herstellung für 1000 Einheiten:

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

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

Zusammensetzung für eine Einheit:

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

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 9

Herstellung für 1000 Einheiten:

25,0 g 5-Morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl)-methylenamino-2-oxazolidinon · HCl
werden in
2,1 g Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid) gelöst in
152,0 g Alkohol und Wasser 1 : 1 suspendiert. In diese Suspension werden
42,3 g Methylhydroxypropylcellulose und
18,1 g Cellulose eingetragen.

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

Zusammensetzung für eine Einheit:

25,0 mg 5-Morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl)-methylenamino-2-oxazolidinon · HCl
2,1 mg Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid)
42,3 mg Methylhydroxypropylcellulose
18,1 mg Cellulose

87,5 mg

Eine Einheit entspricht einer Fläche von ca. 8 cm².
Aussehen der Folie: hellgelb, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 10

Herstellung für 1000 Einheiten:

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

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

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Zusammensetzung für eine Einheit:

4,00 mg Glisoxepid
0,90 mg Polyoxyäthylenmonostearat-40
15,00 mg Hydroxyäthylcellulose
15,10 mg Calciumcarbonat

35,00 mg

Eine Einheit entspricht einer Fläche von ca. 3 cm².
Aussehen der Folie: weiß, papierartig.
Die trockene Folie hat eine Dicke von ca. 170 µm.

Beispiel 11

Herstellung für 1000 Einheiten:

0,84 g Polyoxyäthylenpolyoxypropylenpolymeres werden in

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

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

Zusammensetzung für eine Einheit:

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

35,00 mg

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(19) BUNDESREPUBLIK DEUTSCHLAND

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(54) Folienförmiges Arzneimittel

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Patentansprüche:

1. Folienförmiges Arzneimittel auf Basis filmbildender Celluloseäther gemäß Patentanmeldung P 24 32 925.7-41, dadurch gekennzeichnet, daß die Folie nebeneinander Dosierungseinheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff aufweist.

2. Verfahren zur Herstellung eines folienförmigen Arzneimittels auf Basis filmbildender Celluloseäther durch Ausziehen von Lösungen bzw. Suspensionen auf einer Folienziehmaschine, durch nachträgliches Trocknen des nassen Ausstrichs und Teilen der Folie in Abschnitte gemäß Patentanmeldung P 24 32 925.7-41, dadurch gekennzeichnet, daß man zwei oder mehrere unterschiedliche Lösungen bzw. Suspensionen aus Trennmittel, Folienbildner und gegebenenfalls Füllstoffen und/oder Wirkstoffen herstellt, die unterschiedlichen Lösungen bzw. Suspensionen mit Hilfe eines Spezialrakels, das aus zwei oder mehreren Kammern besteht, zu einem Ausstrich auszieht und die durch Trocknung des Ausstrichs erhaltene Folie in Einheiten mit unterschiedlichen Wirkstoffen und/oder verschiedenen Wirkstoffkonzentrationen bzw. Einheiten ohne Wirkstoff teilt.

Gegenstand der Patentanmeldung P 24 32 925.7-41 sind folienförmige Arzneimittel mit gleichmäßiger Wirkstoffverteilung bzw. folienförmige Placebos auf Basis filmbildender Celluloseäther, dadurch gekennzeichnet, daß sie bis zu 60% Wirkstoffe, ein Trennmittel und als Folienbildner einen nicht-ionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose enthalten sowie ein Verfahren zu deren Herstellung.

In Weiterentwicklung des Gegenstandes der Patentanmeldung P 24 32 925.7-41 betrifft die vorliegende Erfindung das in den Ansprüchen näher gekennzeichnete folienförmige Arzneimittel und dessen Herstellung.

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

Herstellung von Präparaten zur Konzeptionsverhütung.

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

Das folienförmige Arzneimittel enthält ein Trennmittel und als Folienbildner einen nichtionogenen, wasserlöslichen Hydroxyalkyläther der Cellulose, Methylcellulose oder Äthylcellulose.

Als nichtionogene, wasserlösliche Hydroxyalkyläther der Cellulose seien beispielsweise Hydroxypropylcellulose, Hydroxyäthylcellulose und Methylhydroxypropylcellulose genannt.

Geeignete Trennmittel sind u. a. Polyoxyäthylenpolyoxypropylenpolymeres, Polyoxyäthylenstearate, alkyl- bzw. acylsubstituierte Polyadditionsprodukte des Äthylenoxids, zum Beispiel das Polyadditionsprodukt aus Äthylenoxid und Rizinusöl (40 Mol Äthylenoxid auf 1 Mol Glycerid), Silikone, Silikontrennemulsionen und Metallseifen.

Außer Trennmittel und Folienbildner können die erfindungsgemäßen Folien Füllstoffe und Wirkstoffe enthalten.

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

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

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

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

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

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

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

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

Beispiel 1

Zweiphasenpräparat

Teil 1: 21 Einheiten mit Wirkstoff
Teil 2: 7 Einheiten ohne Wirkstoff

Herstellung für 3000 Einheiten Teil 1

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

Herstellung für 1000 Einheiten Teil 2

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

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

Zusammensetzung für je eine Einheit:

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

Fläche pro Einheit: ca.3 cm^2.
Aussehen: weiß.

Beispiel 2

Dreiphasenpräparat (Zweiwirkstoffstufenpräparat)

Teil 1: 11 Einheiten mit 0,05 mg D-Norgestrel
0,05 mg Äthinylöstradiol
Teil 2: 10 Einheiten mit 0,125 mg D-Norgestrel
0,050 mg Äthinylöstradiol
Teil 3: 7 Einheiten ohne Wirkstoff

Herstellung für 1100 Einheiten Teil 1:

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

Herstellung für 1000 Einheiten Teil 2:

0,125 g D-Norgestrel,
0,050 g Äthinylöstradiol und
0,180 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
79,000 g Äthylalkohol und
4,000 g Wasser gelöst. In diese Lösung werden
14,823 g Hydroxypropylcellulose und
14,822 g Cellulose eingetragen und gegebenenfalls homogenisiert.

Herstellung für 700 Einheiten Teil 3:

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

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

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Zusammensetzung pro Einheit:

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

Beispiel 3

Dreiphasenpräparat

Teil 1: 11 Einheiten mit 0,05 mg D-Norgestrel
0,05 mg Äthinylöstradiol
Teil 2: 10 Einheiten mit 0,125 mg D-Norgestrel
0,050 mg Äthinylöstradiol
Teil 3: 7 Einheiten mit 50,00 mg Eisen(II)fumarat

Herstellung für 1100 Einheiten Teil 1:

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

Herstellung für 1000 Einheiten Teil 2:

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

Herstellung für 700 Einheiten Teil 3:

0,042 g Saccharin,
0,042 g Sahne-Essenz und
0,406 g Polyoxyäthylenpolyoxypropylenpolymeres werden in einer Mischung aus
55,300 gÄthylalkohol und
2,800 g Wasser gelöst. In diese Lösung werden
35,000 g Eisen(II)fumarat,
17,500 g Hydroxypropylcellulose,
5,950 g Kakao und
4,060 g Cellulose eingetragen und gegebenenfalls homogenisiert.

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

Zusammensetzung pro Einheit:

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

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Espacenet

Bibliographic data: DE 3630603 (A1)

Dosage and administration forms for medicines, reagents or the like, and process for their preparation.

Publication date:	1988-03-10
Inventor(s):	SCHMIDT WOLFGANG [DE] ±
Applicant(s):	DESITIN ARZNEIMITTEL GMBH [DE] ±
Classification:	**- international:** ***A61K9/20; A61K9/70;*** (IPC1-7): A61J3/00; A61K9/00; A61K9/70; C08J5/18; C08J7/04; D21H5/00 **- European:** A61K9/20K4; A61K9/70
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Priority number (s):	DE19863630603 19860909
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Cited documents:	DE2449865 (A1) CH624846 (A5) View all

Abstract not available for DE 3630603 (A1)
Abstract of corresponding document: EP 0259749 (A1)

The dosage and administration form consists of a carrier material in the form of a release paper, a release film or a release foil which is provided on one side with a coating which contains active substance and which can, after previous division into dose units, be pulled off dosewise from the carrier material. The sections containing active substance which have been pulled off are particularly suitable as oral medicines.

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DE-OS 24 49 865
CH 6 24 846

(54) Dosierungsform für Wirkstoffe sowie Verfahren zu deren Herstellung

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Beschreibung

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

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

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekannt geworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-PS 6 37 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Aus den deutschen Offenlegungsschriften 24 32 925 und 24 49 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Auch die so erhaltenen wirkstoffhaltigen Folien lassen sich durch Perforation in einzelne Abschnitte zur Dosierung aufteilen. In der CH-PS 6 24 846 wird vorgeschlagen, eine Einheitsdosierungsform dadurch zu schaffen, daß ein Arzneimittelwirkstoff zwischen mehreren Lagen aus eßbarem Trägermaterial angeordnet wird, um den Wirkstoff gegen Einflüsse von außen zu schützen. Darüber hinaus ermöglicht die Ausbildung in mehreren Lagen die Einbringung verschiedener Wirkstoffe in voneinander getrennten Schichten. Wie die Betonung der Eßbarkeit der Trägermaterialien verdeutlicht, soll die gesamte auf diese Weise erhaltene schichtförmige Dosierungsform zur oralen Applikation dienen.

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

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

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

Gegenstand der Erfindung ist eine Dosierungsform für Wirkstoffe aus einem flächigen Trägermaterial mit einer wirkstoffhaltigen Beschichtung, wobei diese Dosierungsform dadurch gekennzeichnet ist, daß das Trägermaterial ein Trennpapier, ein Trennfilm oder eine Trennfolie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

Die erfindungsgemäße Dosierungsform weist mehrere wesentliche Vorteile auf:

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

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und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

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

Als Trägermaterialien eignen sich die verschiedensten Materialien, beispielsweise Papiere mit einem Gewicht von etwa 80 bis 120, vorzugsweise 100 g/m², Kunststoffilme bzw. -folien auf Basis von Polyethylen, Polyvinylchlorid, Polyvinylidenchlorid, Polyester und anderen indifferenten Polymeren oder dünne Metallfolien, beispielsweise solche aus Aluminium. Bevorzugt werden siliconisierte Papiere, welche in unterschiedlichen Qualitäten im Handel erhältlich sind, und welche insbesondere zur Abdeckung von selbstklebenden Produkten wie Pflastern, Klebebändern oder Haftetiketten Verwendung finden. Die an sich auch geeigneten, mit Wachs oder Paraffin beschichteten Trennpapiere sind dagegen in der Praxis weitgehend durch die mit inerten Siliconen beschichteten Papiere ersetzt worden. Bei einem Auftrag der wirkstoffhaltigen Beschichtung auf nur eine Seite der Trägerfolie reicht es aus, wenn nur diese mit einer nicht haftenden Beschichtung versehen ist. Die Rückseite sollte dagegen vorzugsweise so beschaffen sein, daß sie mit Informationen unterschiedlicher Art gut und dauerhaft bedruckbar ist.

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

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

Beschichtungsmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10 000 mpa · s haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

Folgende Rahmenrezeptur hat sich bewährt:

Gelatine	8 bis 10 g
Stärke	3 bis 8 g
Glycerin	1 bis 2 g
Wasser	30 bis 50 g

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

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

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

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

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

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Farbstoffe bzw. Pigmente lichtundurchlässig sein.

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

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

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

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

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

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

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

Zur näheren Erläuterung der Erfindung sollen die nachfolgenden Ausführungsbeispiele dienen.

Beispiel 1

Herstellung eines Cardiakum

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

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

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

Beispiel 2

Herstellung eines Contrazeptivum

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

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

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

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

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Patentansprüche

1. Dosierungsform für Wirkstoffe aus einem flächigen Trägermaterial mit einer wirkstoffhaltigen Beschichtung, **dadurch gekennzeichnet,** daß das Trägermaterial ein Trennpapier, ein Trennfilm oder eine Trennfolie ist und daß das Trägermaterial einseitig mit der wirkstoffhaltigen Beschichtung versehen ist, welche nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

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

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

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

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

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

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

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

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

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

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

12. Verfahren zur Herstellung der Dosierungsform der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß man eine wirkstoffhaltige Zusammensetzung mit Hilfe von Walzen auf die nichthaftend ausgerüstete Seite eines Trennpapiers, eines Trennfilms oder einer Trennfolie bringt.

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Beschreibung

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

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

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

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

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

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

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

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

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

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

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

Die erfindungsgemäß hergestellte Darreichungsform weist eine Reihe wesentlicher Vorteile auf:

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

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

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

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

– falls eine Sterilisierung erforderlich ist, kann diese wegen der geringen Schichtdicke problemlos mittels Strahlenbehandlung erreicht werden,

– der Träger läßt sich auf der Vorder- und insbesondere der Rückseite unter Verwendung physiologisch verträglicher Druckfarben mit verschiedenen Informationen bedrucken,

– aufgrund der relativ großen Fläche von beispielsweise 4 bis 10 cm^2 lassen sich ausführliche Informationen für den Benutzer auf das unbeschichtete Trägermaterial oder auch nachträglich aufdrucken,

– die Dosiereinheiten lassen sich durch entsprechende Vorzerteilung, z.B. eine Perforierung, flexibel gestalten, so daß für verschiedene Dosierungen (z.B. für Erwachsene und Kinder) nur ein Produkt hergestellt werden muß; die Vorzerteilung kann ggf. auch erst in der Apotheke oder im Krankenhaus nach ärztlichen Angaben vorgenommen werden.

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

Die Herstellung der Trägerfolie erfolgt in an sich bekannter Weise mit einer kontinuierlich arbeitenden Folienmaschine auf Rollenbasis. Das Streichverfahren zur Herstellung der Trägerfolie arbeitet nach dem Walzenprinzip, d.h. die wasserhaltige Zusammensetzung für die Trägerfolie wird mittels Rollen und Rakel angetragen und zu dünnen Bahnen ausgestrichen, auf der Rolle vorgetrocknet und im Haupttrockengang auf die gewünschte Endfeuchte nachgetrocknet. Das erhaltene Endprodukt ist so fest und elastisch, daß es auf Rollen gewickelt werden kann und lagerfähig ist, wenn die Restfeuchtigkeit nicht zu hoch ist (Gefahr der Schimmelbildung).

Die Folienbreite kann beliebig sein und wird günstigerweise auf die Breite der Beschichtungsmaschine zugeschnitten. Es bietet sich jedoch an, bereits bei der Herstellung beide Breiten aufeinander abzustimmen.

Es ist technisch auch möglich, die Folienherstellung und die Beschichtung zeitlich nacheinander auf derselben Anlage vorzunehmen, wodurch die Wirtschaftlichkeit wesentlich erhöht werden kann.

Die verwendete Zusammensetzung wird unter Umpumpen bei der gewünschten Temperatur, Viskosität und Homogenität gehalten. Die Trocknung der Folie erfolgt anschließend in einem Wärmetunnel. Die so gewonnene Trägerfolie stellt den indifferenten Träger für die spätere Beschichtung mit verschiedene Wirkstoffe enthaltenden Beschichtungsmassen dar.

Zur Herstellung der wasserlöslichen Trägerfolie dient eine physiologisch unbedenkliche Zusammensetzung. Die "Wasserlöslichkeit" soll dabei so definiert sein, daß die Herstellung der Folie aus einer wäßrigen Zusammensetzung erfolgt und daß sich die fertige Folie später bei der Anwendung wiederum in Wasser bzw. im Magensaftmilieu löst oder darin quillt.

Als Folienbildner kommen insbesondere Gelatinen sowie Stärken (Kartoffelstärke, Weizenstärke, Maisstärke) sowie ferner Poly-N-vinylpyrrolidon (PVP), Methyl- und Ethylzellulose sowie Polyvinylalkohol (PVA) infrage. Ferner können wässerlösliche Acrylharzdispersionen Verwendung finden. Geeignete Weichmacher sind insbesondere polyfunktionelle Alkohole wie Glycerin und Sorbit (Karion®).

Die Komponenten werden in geeigneter Weise mit Wasser kalt angemischt und unter leichtem Erwärmen und ständigem Rühren zu einem streichfähigen Schleim verarbeitet. Das Einrühren von Luft muß soweit wie möglich vermieden werden, um eine klare, allenfalls leicht opaleszierende Masse zu erhalten.

Die Stärke der Trägerfolie beträgt vorzugsweise zwischen etwa 50 und 250 µm. Sie ist in weitem Maße steuerbar. Auch die Eigenschaften der Trägerfolie lassen sich durch entsprechende Kombination der Folienbildner und Weichmacher qualitativ stark beeinflussen. Die Trägerfolie soll eine möglichst gleichmäßige Stärke aufweisen (vorzugsweise z.B. 100 µm), leicht elastisch und knickfähig sein, ohne zu brechen. Dabei sollte der Stärkeanteil ausreichend hoch sein, damit beim Aufbringen der Beschichtungsmasse Feuchtigkeit aufgenommen wird, ohne daß es zu einem Kleben der Oberfläche oder zum Erweichen der ganzen Folie kommt.

Folgende Rahmenrezeptur hat sich für die Trägerfolie bewährt:

Gelatine 8 bis 10 g
Stärke 4 bis 8 g
Glycerin 1 bis 2 g

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Polyvinyl-pyrrolidon 1 bis 2 g
Wasser 30 bis 50 g

Wasserlösliche natürliche und/oder synthetische Harze, z.B. Acrylharze, und Gumme sind ebenfalls geeignet. Ggf. können der Masse noch übliche weitere Stoffe zugefügt werden, z.B. Konservierungsmittel wie p-Hydroxybenzoesäure-Ester, inerte lösliche oder unlösliche Füllstoffe, Geschmackstoffe, Zucker oder andere Süßungsmittel, weitere Weichmacher, insbesondere Polyole, Wachse oder Farbstoffe.

Die Möglichkeit der vorder- und rückseitigen Bedruckung der Trägerfolie ist ein besonderer Vorteil der erfindungsgemäßen Darreichungsform. Beispielsweise können die Kennzeichnung, Angaben über die Inhaltsstoffe sowie Dosierungsangaben aufgedruckt werden. Gegebenenfalls läßt sich sogar der ganze Inhalt eines Beipackzettels rückseitig aufdrucken mit der Folge, daß ein separater Beipackzettel, der auch häufig verlorengeht, überflüssig wird. Bei Arzneimitteln, welche regelmäßig genommen werden müssen, beispielsweise bei hormonalen Contrazeptiva, kann der gesamte Verabreichungsplan so angebracht werden, daß eine einfache Einnahmekontrolle gewährleistet ist. Zur Bedruckung müssen physiologisch verträgliche Farben (Lebensmittelfarben) verwendet werden, da die Trägerfolie einen Teil der oral verabreichten Darreichungsformen bildet.

Für die wirkstoffhaltige Beschichtungsmasse findet eine wäßrige Zusammensetzung Verwendung, die physiologisch inert ist und deren Einzelkomponenten für Arzneimittel bzw. Lebensmittel geeignet sind. Wesentlich ist die gegenseitige physikalisch-chemische Affinität und Verträglichkeit zwischen Beschichtungsmasse und Trägerfolie, welche besonders gut ist, weil die verwendeten Komponenten gleich sind bzw. sehr ähnliche Eigenschaften besitzen. Unter Berücksichtigung des zugeführten Wirkstoffes entspricht die Rezeptur der Beschichtungsmasse demgemäß der oben für die Trägerfolie genannten, wobei die genaue Einstellung auf Feststoffgehalt und Viskosität mittels indifferenter Quell- und Füllstoffe erfolgt.

Die Masse enthält somit einmal polymere Filmbildner, vorzugsweise Gelatine und quellende oder lösliche Stärken sowie ggf. Zellulosen oder Hemizellulosen. Ferner werden Weichmacher zugesetzt, insbesondere mehrwertige Alkohole wie Glycerin oder Sorbit. Zur Einstellung der erwünschten Viskosität der Beschichtungsmasse, welche die Konsistenz eines Schleimes aufweist, finden polymere Quellstoffe Verwendung, vorzugsweise Alginate, Pectine, Chitine, Lecithine oder Polyethylenglykole. Diese letzteren Stoffe können gleichzeitig als Haftvermittler dienen. Andererseits können auch wasserlösliche synthetische oder natürliche Harze oder Gumme oder Gummi arabicum zugesetzt werden, um die Haftung der Beschichtung auf dem Trägermaterial zu verbessern. Schließlich können noch Konservierungsmittel wie z.B. p-Hydroxybenzoesäureester, Farbstoffe (Lebensmittelfarbstoffe), Pigmente wie Titandioxid oder Aroma- und Süßstoffe zugesetzt werden.

Coatingmassen mit einem Wassergehalt von ungefähr 50% und einer Viskosität von etwa 30 bis zu 10 000 cPs haben sich als besonders geeignet erwiesen. Die Rezeptur und Herstellung ähnelt derjenigen eines Arzneimittelsaftes, in welchem der Wirkstoff bzw. die Wirkstoffkombination gelöst oder gleichmäßig dispergiert wird. Die Beschichtungsmasse muß ausreichende Homogenität und galenische Stabilität aufweisen, damit ein gleichmäßiger Wirkstoffgehalt der fertigen Beschichtung sichergestellt ist.

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

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

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

In einem Beschichtungsgang lassen sich ca. 4 bis 20 g Wirkstoff je m^2 (= 10.000 cm^2) Trägerfolie aufbringen, so daß 10 cm^2 (= 2 übliche Briefmarken) bis zu 20 mg Wirkstoff aufnehmen können.

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

Weiterhin kann durch entsprechenden Aufbau der Beschichtung die Wirkstoffabgabe nach Verabreichung des Arzneimittels gesteuert werden. Beispielsweise ist es möglich, eine Wirkstoffschicht zwischen mindestens zwei weiteren Schichten anzuordnen, welche die Wirkstoffresorption im Magen/Darmtrakt in an sich bekannter Weise steuern.

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Dabei kann die Wirkstoffschicht z.B. zwischen zwei säureunlöslichen Schichten angeordnet werden, so daß bei Verabreichung der Magen passiert wird und die Resorption erst im Darmtrakt erfolgt. In ähnlicher Weise können unterschiedliche Wirkstoffe in verschiedenen Schichten übereinander auf die Trägerfolie aufgebracht werden, damit die Resorption nacheinander und/oder verzögert erfolgt.

Ähnliche pharmakokinetische Effekte lassen sich durch das Einarbeiten (z.B. Suspendieren) von unterschiedlich vorbehandelten mikroverkapselten Wirkstoffen erzielen.

Die Beschichtung des Trägermaterials mit der wirkstoffhaltigen Beschichtungsmasse erfolgt mittels eines Walzenauftragverfahrens. Dieses für die quantitative Beschichtung besonders geeignete Verfahren arbeitet nach einem dem Tiefdruck ähnlichen Verfahren, welches als "Akkugravur" bezeichnet wird. Hierfür geeignete Maschinen sind im Handel (Fa. Pagendarm, Hamburg) und erlauben Auftragsgewichte bis zu 80 g/m² bei Bahngeschwindigkeiten von mehreren 100 m/min. Die reproduzierbare Gewichtskonstanz liegt für 20 g/m² bei nur +/- 2,5% für 1 g/m² und für ca. +/- 10% über die gesamte Fläche. Der Auftrag der Beschichtungsmasse erfolgt kontinuierlich über Walzen mit spezieller Feingravur, wobei die eingravierten Rillen zur Laufrichtung der Trägerfolie vorzugsweise einen Winkel von 30 bis 60, insbesondere 45° bilden. In die Walzen können 27 bis 80 Rillen/cm eingeätzt sein. Entsprechend ihrer Form und Tiefe kann die Gravur eine definierte Menge der Beschichtungsmasse aufnehmen und anschließend an die Trägerfolie weitergeben. Durch Variation der Vorlaufgeschwindigkeit, der Laufrichtung und der Gravur sowie durch indirektes Auftragen über eine weitere geschwindigkeitsvariable Walze lassen sich die Beschichtungsmengen sehr exakt einstellen.

Eine zweiseitige Beschichtung ergibt häufig Vorteile, da Probleme durch Verwerfen des Trägermaterials und durch unterschiedliche Hygroskopizität ausgeglichen werden. Mehrfach- und auch Streifenbeschichtungen, ja sogar Druckbildbeschichtungen, sind möglich und bieten bei der Verarbeitung von inkompatiblen Wirkstoffen eine große Variabilität.

Ein anderes geeignetes Auftragverfahren entspricht dem Streichen von Papier oder von Folien. Dabei werden Rohpapiere dadurch verbessert, daß sie ein- oder zweiseitig mit Coatingmaterialien beschichtet werden. Die wässrigen Beschichtungsmassen gelangen zunächst auf ein Walzwerk, welches sie mittels einer rotierenden Walze aufnimmt, mit einen Rakel bestimmten Abstandes auf eine definierte Schichtdicke abstreift, worauf die Walze die Beschichtungsmasse auf den Träger abgibt. Die Trägerfolie, welche 0,30 bis 7,50 m breit sein kann, durchläuft anschließend einen Trockentunnel und wird dann auf Rollen aufgewickelt. Dieser Vorgang ist in einem oder mehreren Schritten ein- oder zweiseitig wiederholbar, wobei auch eine bereits beschichtete Fläche nochmals beschichtet werden kann. Das Gewicht des Trägermaterials nimmt um das der Trockenmasse zu. Die Genauigkeit des Auftragverfahrens mittels dieses Rakel-Verfahrens liegt reproduzierbar bei +/- 5%. Sie ist abhängig von der jeweiligen Schichtdicke, die variabel zwischen 4 und 40 g/m² betragen kann. Innerhalb der einzelnen Fertigungen kann eine Gewichtstoleranz pro Flächeneinheit bis unter +/- 1 % erreicht werden.

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

Die wirkstoffbeschichtete Trägerfolie wird anschließend in Dosiseinheiten vorzerteilt, welche ähnlich wie Briefmarken abtrennbar sind. Normalerweise wird diese Vorzerteilung beim Arzneimittelhersteller erfolgen, es ist jedoch auch denkbar, das beschichtete Material beispeilsweise an Krankenhäuser oder Apotheken auszuliefern, wo dann die Vorzerteilung dosisabhängig oder auch individuell nach ärztlicher Vorgabe durchgeführt werden kann.

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

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

Da als Grundstoffe für die Herstellung der erfindungsgemäßen Darreichungsform überwiegend Naturstoffe wie Stärken und Gelatine verwendet werden, erhält man insgesamt Produkte, welche den bekannten Oblaten ähneln und deren orale Einnahme keinerlei Schwierigkeiten bereitet. Wichtig ist, daß das Fertigprodukt weitgehend von Wasser befreit ist, d.h. einen Wassergehalt von wengier als 10 und vorszugsweise von weniger als 2% aufweist, da sonst Schimmelbildung auftreten kann.

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

Zur näheren Erläuterung der Erfindung soll das nachfolgende Ausführungsbeispiele dienen.

Beispiel

Herstellung einer Arzneimittel-Darreichungsform in Form einer beschichteten Folie.

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Zur Herstellung einer wasserlöslichen Trägerfolie wurde von folgender Zusammensetzung ausgegangen:
Gelatine 10,0 Gew.-Teile = 25%
Kartoffelstärke 8,0 Gew.-Teile = 20%
Glycerin 1,5 Gew.-Teile = 3,75%
gereinigtes Wasser 20,5 Gew.-Teile = 51,25%

Die Viskosität der schleimartigen Zusammensetzung betrug bei 50°C ca. 3000 cPs. Mit Hilfe des Streichverfahrens wurde die Masse zu einer Folie verarbeitet, welche nach dem Trocknen noch 9,3% Restwasser enthielt.

Unter Verwendung derselben Grundstoffe wie für die Trägerfolie wurde die Beschichtungsmasse gemäß folgender Rezeptur hergestellt:
Gelatine 10,0 Gew.-Teile = 18,2%
Kartoffelstärke 5,0 Gew.-Teile = 9,1%
Glycerin 1,0 Gew.-Teile = 1,8%
Wirkstoff 5,0 Gew.-Teile = 9,1%
gereinigtes Wasser 34,0 Gew.-Teile = 61,8%

Die Viskosität der schleimartigen Zusammensetzung betrug temperatur- und wirkstoffabhängig zwischen 4.000 und 10.000 cPs. Zur Herstellung der Beschichtungsmasse wurde zunächst die Gelatine in einer ausreichenden Menge Wasser gelöst. Dazu wurde Wasser von 90 bis 95°C vorgelegt, in das die Gelatine unter Rühren eingetragen wurde. In einem getrennten Ansatz wurde der Wirkstoff zusammen mit dem Glycerin in Wasser gelöst. Schließlich wurde die Kartoffelstärke bei 50 bis 60°C unter Rühren in einer ausreichenden Menge Wasser angerührt. Die Gelatinelösung und die Kartoffelstärkesuspension wurden zusammengegeben und die Wirkstoffsuspension wurde in die Mischung langsam eingerührt, wobei Lufteinschlüsse vermieden wurden. Die Temperatur wurde auf 55 bis 60°C gehalten. Zuletzt wurde der gewünschte Wassergehalt durch Zugabe von weiterem Wasser eingestellt.

Die Beschichtungsmasse wurde mittels Akkugravur mit einem Naßbeschichtungsgewicht von 55 g/m² auf die Trägerfolie aufgebracht. Nach dem Trocknen betrug das Beschichtungsgewicht 23 g/m² entsprechend einem Wirkstoffgehalt von 5 g/m². Die wirkstoffbeschichtete Folie wurde anschließend kastenartig perforiert, so daß die einzelnen Abschnitte bei Abmessungen von 2 x 2,5 cm eine Fläche von 5 cm² aufwiesen. Ein solcher Abschnitt enthielt 2.5 mg Wirkstoff.

Nach dem Trocknen lag die Restfeuchtigkeit des Produktes bei 8,6%.

Es wurde eine Darreichungsform erhalten, welche bei oraler Einnahme im Mund rasch quillt und zergeht und sich demgemäß leicht schlucken läßt.

Patentansprüche

1. Verfahren zur Herstellung einer Darreichungs- und Dosierungsform für Arzneimittelwirkstoffe, Reagentien oder andere Wirkstoffe in Form einer wasserlöslichen Folie auf Basis von Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen, dadurch gekennzeichnet daß man
a) eine wässrige Zusammensetzung, deren Rezeptur derjenigen der Trägerfolie entspricht, aus dem Wirkstoff sowie Stärken, Gelatinen, Glycerin und/oder Sorbit sowie gegebenenfalls natürlichen und/oder synthetischen Harzen und Gummen herstellt, und
b) diese Beschichtungsmasse kontinuierlich mittels eines Walzenauftragsverfahrens in genau vorbestimmter Menge (Schichtdicke) auf mindestens eine Seite der wasserlöslichen wirkstofffreien Folie aufbringt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man der Zusammensetzung für die Trägerfolie und die Beschichtung zusätzlich inerte lösliche und/oder unlösliche Füllstoffe, Zucker und/oder andere Süßungsmittel, weitere Weichmacher, insbesondere Polyole, Wachse, Farbstoffe, Geschmacksstoffe und/oder Konservierungsmittel zusetzt.

3. Verfahren nach einem der Ansprüche 1 oder 2, dadurch gekennzeichnet, daß man für die Herstellung der Trägerfolie und der Beschichtungsmasse eine Zusammensetzung verwendet, die 8 bis 10 Gew.-Teile Gelatine, 4 bis 8 Gew.-Teile Stärke, 1 bis 2 Gew.-Teile Glycerin und 20 bis 50 Gew.Teile Wasser enthält.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß man eine Beschichtungsmasse einsetzt, die bis zu 10 Gew.-Teile des Wirkstoffes enthält.

5. Verfahren nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß man der Beschichtungsmasse zur Einstellung der Viskosität indifferente Quell- und Füllstoffe zusetzt.

6. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß man die Beschichtungsmasse kontinuierlich mittels Rasterwalzen, welche eine genau definierte Menge der Beschichtungsmasse aufnehmen und wieder abgeben, auf die Trägerfolie aufbringt.

7. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß man die Beschichtungsmasse kontinuierlich mittels glatter Walzenpaare, welche in geschwindigkeitsversetztem Gleichlauf die Masse aufnehmen und in definierter Menge abgeben, auf die Trägerfolie aufbringt.

8. Verfahren nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß man zur Herstellung eines Kombinationspräparates auf die Ober- und die Unterseite der Trägerfolie unterschiedliche Wirkstoffe aufbringt.

Claims

1. Process for the manufacture of a presentation and dosage form for pharmaceutical active substances, reagents or other active substances in the form of a water-soluble foil based on starches, gelatines, glycerin and/or sorbite and also in some cases on natural and/or synthetic resins and gums, characterized in that
a) an aqueous composition, the formulation of which corresponds to that of the carrier foil, is manufactured from the active substance and from starches, gelatines, glycerin and/or sorbite and also in some cases from natural and/or synthetic resins and gums, and that

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b) this coating substance is applied continuously in a precise pre-determined quantity (layer thickness) to at least one side of the active-substance-free-water-soluble foil by means of a roller coating process.

2. Process according to claim 1, characterized in that inert, soluble and/or insoluble fillers, sugars and/or other sweeteners, other softeners, particularly polyols, waxes, colorants, flavouring agents and/or preservatives are also added to the composition for the carrier foil and the coating.

3. Process according to one of claims 1 or 2, characterized in that, for the manufacture of the carrier foil and the coating substance, a composition is used which contains 8 to 10 parts by weight of gelatine, 4 to 8 parts by weight of starch, 1 to 2 parts by weight of glycerin and 20 to 50 parts by weight of water.

4. Process according to claim 3, characterized in that a coating substance is used which contains up to 10 parts by weight of the active substance.

5. Process according to one of claims 1 to 4, characterized in that inert swelling agents and fillers are added to the coating substance to regulate the viscosity.

6. Process according to one of claims 1 to 5, characterized in that the coating substance is continuously applied by means of grid rollers which take up and then release a precisely defined quantity of the coating substance.

7. Process according to one of claims 1 to 5, characterized in that the coating substance is applied to the carrier foil continuously by means of smooth pairs of rollers synchronized but out of phase which take up the substance and release a pre-defined quantity.

8. Process according to one of claims 1 to 7, characterized in that different active substances are applied to the top and bottom of the carrier foil for the manufacture of a compound preparation.

Revendications

1. Procédé de fabrication d'une forme d'administration et de dosage pour des principes actifs de médicaments, des réactifs ou d'autres substances actives, sous forme d'une feuille hydrosoluble à base d'amidons, de gélatines, de glycérol et/ou de sorbitol, et éventuellement de résines et gommes naturelles et/ou synthétiques, procédé caractérisé en ce que l'on

a) fabrique une composition aqueuse, dont la formulation correspond à celle de la feuille support, à partir de la substance active ainsi que d'amidons, de gélatines, de glycérol et/ou de sorbitol, et éventuellement de résines et gommes naturelles et/ou synthétiques, et

b) dépose en continu, à l'aide d'un cylindre d'enduction, cette masse, en quantité exactement prédéterminée (épaisseur de couche), sur au moins une des faces de la feuille hydrosoluble dépourvue de substance active.

2. Procédé selon la revendication 1, caractérisé en ce que l'on ajoute en plus, à la composition pour la feuille support et le revêtement, des charges inertes solubles et/ou insolubles, des sucres et/ou d'autres édulcorants, en outre des plastifiants, en particulier des polyols, des cires, des colorants, des aromatisants et/ou des conservateurs.

3. Procédé selon l'une des revendications 1 ou 2, caractérisé en ce que, pour la fabrication de la feuille support et du revêtement, on utilise une composition qui renferme de 8 à 10 parties en poids de gélatine, 4 à 8 parties en poids d'amidon, 1 à 2 parties en poids de glycérol et 20 à 50 parties en poids d'eau.

4. Procédé selon la revendication 3, caractérisé en ce que l'on met en œuvre une masse d'enduction qui renferme jusqu'à 10 parties en poids de la substance active.

5. Procédé selon l'une des revendications 1 à 4, caractérisé en ce que l'on ajoute des agents gonflants et charges inertes à la masse d'enduction, pour ajuster la viscosité.

6. Procédé selon l'une des revendications 1 à 5, caractérisé en ce que l'on dépose en continu la masse d'enduction sur la feuille support, à l'aide de cylindres à trame, qui prennent puis rétrocèdent une quantité exactement définie de la masse d'enduction.

7. Procédé selon l'une des revendications 1 à 5, caractérisé en ce que l'on dépose en continu la masse d'enduction sur la feuille support, à l'aide de paires de cylindres lisses, qui prennent la masse avec un syndrome décalé de la vitesse et la rétrocèdent en quantité définie.

8. Procédé selon l'une des revendications 1 à 7, caractérisé en ce que, pour fabriquer une préparation combinée, on dépose différentes substances actives sur la face supérieure et sur la face inférieure de la feuille support.

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(54) Title: ORAL AND DENTAL HYGIENE PREPARATION

(54) Bezeichnung: MUND- UND ZAHNPFLEGEMITTEL

(57) Abstract

An oral and dental hygiene preparation consists of tensides, polishing agents, flavourings and other usual additives, incorporated in a binder or mixture of binders in the form of water-soluble or water-dilatable, physiologically acceptable foil-forming substances. The mixture is processed to a foil, which is predivided into dosage units.

(57) Zusammenfassung

Ein Mund- und Zahnpflegemittel besteht aus Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen welche in ein Bindemittel oder eine Bindemittelmischung aus wasserlöslichen oder -quellenbaren, physiologisch unbedenklichen Folienbildnern eingearbeitet sind. Die Mischung ist zu einer Folie verarbeitet, welche in Dosiseinheiten vorzerteilt ist.

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Mund- und Zahnpflegemittel

Zahnpflegemittel werden seit vielen Jahren als Pasten, sogenannte Zahnpasten hergestellt. Dabei ist der wesentliche Ausgangsstoff eine Schlämmkreide, die mit Wasser, Glycerin, waschaktiven Stoffen und Verdickungsmitteln zu einer Paste verarbeitet und in Tuben oder Spendern abgefüllt wird. Die Zahnpasta hat den Markt erobert, während andere Zahnpflegemittel wie Tropfen, Zahnseifen und -pulver oder Granulate kaum noch eine Rolle spielen. Mit den Mitteln soll der bakterielle Zahnbelag entfernt, Kariesprophylaxe betrieben sowie die Reinigung der Zähne schonend und durch die Bürstenbehandlung wesentlich unterstützt durchgeführt und der Mundraum gründlich gereinigt und angenehm erfrischt werden.

In neuerer Zeit hat sich das Bild der Zahnpasten nicht wesentlich verändert, obwohl die Rezepturen in vielerlei Hinsicht abgewandelt wurden. Die Verwendung einer recht groben Kreideform zum mechanischen Reinigen der Zähne wich mehr und mehr modernen, feineren Poliermitteln auf Basis von Aluminiumoxid oder Siliciumdioxid (Kieselgele). Neben Tensiden finden strukturbildende Komponenten und ausgefeilte Geschmackskorrigentien Verwendung. Oft werden Wirkstoffe wie insbesondere verschiedene Fluorderivate oder Mineralsalze zugefügt. Das Volumen konnte teilweise

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reduziert werden; sicherlich hat die Einführung und allgemeine Verwendung elektrischer Zahnbürsten hierbei einen starken Einfluß gehabt.

Die Handhabung von Zahnpasten ist jedoch mit einer Reihe von Nachteilen verbunden. Weil die Dosierung aus einfachen Tuben Schwierigkeiten bereitet, hat man in neuerer Zeit Zahnpastaspender entwickelt, welche jeweils eine vorbestimmte Menge Zahnpasta abgeben. Diese Spender sind jedoch verhältnismäßig groß und daher zur Mitnahme auf Reisen wenig geeignet. Tuben sind druckempfindlich und daher auf Reisen ebenfalls nicht ideal. Sowohl in Spendern als auch in Tuben kann Zahnpasta bei längeren Gebrauchsunterbrechungen austrocknen, so daß die angebrauchten Behälter dann weggeworfen werden müssen. Ferner lassen sich sowohl Tuben als auch Spender nicht vollständig entleeren. Nach Verbrauch bleiben die aus Metall oder Plastik hergestellten Behälter zurück und verursachen Umweltprobleme.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine neue Verabreichungs- und Dosierungsform für Mund- und Zahnpflegemittel zu entwickeln, welche die vorstehend genannten Nachteile nicht aufweist. Insbesondere soll eine genaue Dosierung für die einzelne Zahnreinigung ermöglicht und sichergestellt werden, daß das Mittel vollständig aufgebraucht werden kann, ohne daß Reste in der Packung zurückbleiben.

Das erfindungsgemäße Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen ist dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittelmischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildern bestehen, und daß diese Mischung zu einer Folie verarbeitet ist, wobei die so gebildete Folie in

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Dosiseinheiten vorzerteilt ist.

Als Bestandteile des Mund- und Zahnpflegemittels kommen die Komponenten in Frage, welche üblicherweise zur Herstellung von Zahnpasten Verwendung finden, wobei natürliche Rohstoffe besonders bevorzugt sind. Wichtig ist darüber hinaus, daß alle Bestandteile völlig ungiftig und physiologisch unbedenklich sind, was selbstverständlich auch für die verwendeten Folienbildner gilt. Als wesentliche Bestandteile von Zahnpflegemitteln sind zu nennen:

- Schleifmittel wie Kreide (Calciumcarbonat), Calcium- und Natriumphosphate, Aluminiumoxid oder Siliciumdioxid, insbesondere Kieselgele
- Tenside (Schaummittel) wie Natriumlaurylsulfat, Natriumlaurylsulfoacetat, Sarcoside, Monoglyceridsulfate und andere
- Aromastoffe wie Pfefferminzöl, Krauseminzöl, Anisöl, Zimtöl, Nelkenöl, Menthol und ähnliche
- Süßstoffe wie Saccharin, Cyclamat, Aspartam und ähnliche.

Die in Zahnpasten üblicherweise enthaltenen flüssigen Komponenten wie Glycerin, Propylenglykol oder Sorbitsirup müssen den erfindungsgemäßen Mitteln in Folienform nicht in den üblichen Mengen zugesetzt werden, da hier die für Tuben oder Spender erforderliche Plastizität keine Rolle spielt. Weitere übliche Zusätze wie Fluorverbindungen, Mittel gegen Zahnsteinbildung, antibakterielle Wirkstoffe und ähnliche, wie sie in Mund- und Zahnpflegemitteln üblicherweise Verwendung finden, können auch erfindungsgemäß eingesetzt werden.

Als wasserlösliche bzw. -quellbare Folienbildner eignen sich vor allem Stärken, Gelatinen, Glycerin und/oder Sorbit sowie ferner natürliche oder synthetische Harze und

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Gumme. Folgende Rahmenrezeptur hat sich bewährt:

Gelatine	8 - 10 g
Stärke	3 - 8 g
Glycerin	1 - 2 g
Wasser	30 - 50 g.

In dieser Grundmasse werden die Bestandteile des Mund- und Zahnpflegemittels gelöst bzw. dispergiert, um eine gleichmäßige Verteilung der Stoffe zu erreichen. Die so erhaltene Mischung kann erfindungsgemäß in verschiedener Weise zu einem folienförmigen Mund- und Zahnpflegemittel verarbeitet werden:

a) Es ist einmal möglich, die Masse direkt zu einer Folie zu verarbeiten, welche im allgemeinen eine Dicke zwischen 0,1 und etwa 3 mm aufweist. Durch Sollbruchstellen mittels Stanzung oder Perforierung kann diese Folie in Dosiseinheiten vorzerteilt werden, wobei die Streifenbreite und -länge vorzugsweise etwa der Zahnbürstengröße, d.h. der von den freien Borstenenden gebildeten Fläche des Borstenblocks oder der Längsquerschnittfläche des Borstenblocks in der Borstenebene entsprechen sollte.

b) Alternativ kann die Masse auf eine Trägerfolie aufgebracht werden, deren Zusammensetzung derjenigen des Bindemittels der Masse entspricht, wie dies in der EP-OS 219 762 im einzelnen offenbart ist. Auch die auf diese Weise erhaltenen Folien können wie oben angegeben vorzerteilt werden.

c) Es ist ferner möglich, die Masse auf eine Releasefolie oder ein Releasepapier aufzubringen, wie dies aus der DE-PS 36 30 603 bekannt ist. In diesem Fall wird die Beschichtung in einzelne Abschnitte der oben

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angegebenen Größe vorzerteilt, welche sich ähnlich wie Haftetiketten von der Trägerfolie vor Gebrauch abziehen lassen.

In allen Fällen erhält man eine Darreichungs- und Dosierungsform, deren Anwendung besonders leicht ist, da die jeweils zu verwendende Menge gleichmäßig vorgegeben ist. Eine Dosis wird in Form eines Folienabschnittes abgetrennt bzw. abgezogen und auf die angefeuchtete Zahnbürste bzw. zwischen die Borsten gelegt, wo sie durch die Feuchtigkeitsberührung haftet und anquillt. Durch das Einführen in die Mundhöhle und in Verbindung mit dem Speichel und der intensiven Zahnbürstenbewegung wird der Streifen an- und aufgelöst, so daß die Inhaltsstoffe zur vollen Wirkung gelangen. Nach der Anwendung und der anschließenden Mundspülung mit Wasser verbleiben keinerlei Rückstände im Mund.

Gewünschtenfalls können die Folien in unterschiedlicher Weise bedruckt, geprägt oder gestanzt werden, wobei beispielsweise für Kinder auch bildliche Darstellungen möglich sind. Es entfällt das Öffnen und Schließen von Tubenverschlüssen, es wird keine Zahnpasta vergeudet und die erfindungsgemäße Darreichungsform läßt sich auch besondes gut auf Reisen einsetzen, da sie leicht ist, ein Auslaufen nicht befürchtet werden muß und sie äußerst wenig Platz beansprucht. Die Verpackung ist umweltfreundlich in Pappschachteln ohne Verwendung von Metallen oder Kunststoff möglich.

Die Mittel der Erfindung eignen sich nicht nur zur Zahnpflege im Mund, sondern bei geeigneter Zusammensetzung auch zur Reinigung und Pflege von künstlichen Zähnen und Gebissen. Für diesen letzteren Einsatzzweck ist eine Mehrfachbeschichtung besonders günstig, bei der sich in einer Schicht die reinigenden, desinfizierenden und sauren

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Komponenten befinden, während sich, ggf. getrennt durch eine ebenfalls wasserlösliche Sperrschicht, in einer zweiten Schicht die CO_2 bzw. O_2 abgebenden Substanzen enthalten sind.

Beispiel

Ein erfindungsgemäßes Zahnpflegemittel hat folgende Zusammensetzung:

Amylogum	57,0 g
Honig	25,0 g
Zitronensäure	2,0 g
Titandioxid	1,0 g
Aroma	1,0 g
Siliciumdioxid	3,0 g
Ca-Hydrog-phos.	10,0 g
Na-Laurylsulfat	1,0 g

Mit der erforderlichen Menge Wasser wird ein Brei hergestellt, der zu einer Folie verarbeitet wird, die ca. 0,5 mm dick ist. Durch Perforation wird die Folie in Abschnitte von 8 x 35 mm unterteilt.

Gegebenenfalls kann die Masse auch als Beschichtung auf ein Releasepapier als Träger aufgebracht und durch Stanzung in Abschnitte der angegebenen Größe vorzerteilt werden.

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Patentansprüche

1. Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen, dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittel-Mischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildnern bestehen, und daß diese Mischung zu einer Folie verarbeitet ist, wobei die so gebildete Folie in Dosiseinheiten vorzerteilt ist.

2. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Stärken, Gelatinen, Glycerin und/oder Sorbitol oder natürliche und/oder synthetische Harze und Gumme enthält.

3. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Amylogum enthält.

4. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß es als Folienbildner eine Mischung aus 8 bis 10 Gewichtsteilen Gelatine, 4 bis 8 Gewichtsteilen Stärke und 1 bis 2 Gewichtsteilen Glycerin enthält.

5. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß es aus einer Trägerfolie aus dem Bindemittel oder der Bindemittel-Mischung besteht, auf welche eine Schicht aufgebracht ist, welche die Bestandteile des Pflegemittels zusammen mit Bindemittel oder der Bindemittel-Mischung enthält, wobei das Bindemittel oder die Bindemittel-Mischung in der Trägerfolie und in der Beschichtung im wesentlichen die gleiche qualitative

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Zusammensetzung aufweisen.

6. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß eine Beschichtung aus den Bestandteilen des Pflegemittels und dem Bindemittel oder der Bindemittel-Mischung auf eine Trägerfolie in Form eines Trennpapiers, eines Trennfilms oder einer Trennfolie aufgebracht ist, wobei die Beschichtung nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 90/01936

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[5] A61K 7/16

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[5]	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category * [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0219762 (DESITIN ARZNEIMITTEL GmbH) 29 April 1987 see the whole document (cited in the application)	1,2,5,6
A	GB, A, 2186190 (COLGATE-PALMOLIVE COMPANY) 12 August 1987 see claims 1,2,4,8	1,2,5,6
A	EP, A, 0259749 (DESITIN ARZNEIMITTEL GmbH) 16 March 1988 see the whole document (cited in the application)	1,2,5,6
A	GB, A, 2163348 (DENTAB UK LTD) 26 February 1986 see claims 1,4,9,14	1
A	GB, A, 1476057 (UNICLIFFE LTD) 10 June 1977 see pages 1-3	1,3

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* Special categories of cited documents: [10]

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 March 1991 (15.03.91)	11 April 1991 (11.04.91)

International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	

Form PCT/ISA/210 (second sheet) (January 1985)

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9001936 SA 41110

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/04/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0219762	29-04-87	AU-A-	6541786	05-05-87
		CA-A-	1275046	09-10-90
		WO-A-	8702241	23-04-87
		EP-A-	0283474	28-09-88
		JP-T-	63501794	21-07-88
		US-A-	4849246	18-07-89
GB-A- 2186190	12-08-87	US-A-	4705680	10-11-87
		US-A-	4765984	23-08-88
		AT-B-	390370	25-04-90
		AT-B-	389812	12-02-90
		AU-B-	598220	21-06-90
		AU-A-	6712887	23-07-87
		AU-B-	598512	28-06-90
		AU-A-	6790387	23-07-87
		BE-A-	1000635	28-02-89
		BE-A-	1000488	27-12-88
		CH-A-	676082	14-12-90
		CH-A-	672250	15-11-89
		DE-A-	3701122	23-07-87
		DE-A-	3701123	23-07-87
		FR-A-	2593063	24-07-87
		FR-A-	2593064	24-07-87
		GB-A,B	2185399	22-07-87
		JP-A-	62223109	01-10-87
		NL-A-	8700152	17-08-87
		NL-A-	8700153	17-08-87
		OA-A-	8467	29-07-88
		SE-A-	8700220	23-07-87
		SE-A-	8700221	23-07-87
EP-A- 0259749	16-03-88	DE-A-	3630603	10-03-88
		AU-B-	601478	13-09-90
		AU-A-	7792987	17-03-88
		JP-A-	63077816	08-04-88
		US-A-	4925670	15-05-90
GB-A- 2163348	26-02-86	US-A-	4753792	28-06-88

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9001936 SA 41110

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/04/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 1476057	10-06-77	None	

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen PCT/EP 90/01936

I. KLASSIFIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben)[6]

Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC

Int.Cl.[5] A 61 K 7/16

II. RECHERCHIERTE SACHGEBIETE

Recherchierter Mindestprüfstoff[7]

Klassifikationssystem	Klassifikationssymbole
Int.Cl.[5]	A 61 K

Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen[8]

III. EINSCHLÄGIGE VERÖFFENTLICHUNGEN[9]

Art*	Kennzeichnung der Veröffentlichung[11], soweit erforderlich unter Angabe der maßgeblichen Teile[12]	Betr. Anspruch Nr.[13]
A	EP, A, 0219762 (DESITIN ARZNEIMITTEL GmbH) 29. April 1987 siehe das ganze Dokument in der Anmeldung erwähnt ---	1,2,5,6
A	GB, A, 2186190 (COLGATE-PALMOLIVE COMPANY) 12. August 1987 siehe Patentansprüche 1,2,4,8 ---	1,2,5,6
A	EP, A, 0259749 (DESITIN ARZNEIMITTEL GmbH) 16. März 1988 siehe das ganze Dokument in der Anmeldung erwähnt ---	1,2,5,6
A	GB, A, 2163348 (DENTAB UK LTD) 26. Februar 1986 siehe Patentansprüche 1,4,9,14 --- ./.	1

* Besondere Kategorien von angegebenen Veröffentlichungen[10]:

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist

"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

IV. BESCHEINIGUNG

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
15. März 1991	11 APR 1991
Internationale Recherchenbehörde	**Unterschrift des bevollmächtigten Bediensteten**
Europäisches Patentamt	Mme N. KUIPER

Formblatt PCT/ISA/210 (Blatt 2) (Januar 1985)

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

III. EINSCHLÄGIGE VERÖFFENTLICHUNGEN (Fortsetzung von Blatt 2)

Art *	Kennzeichnung der Veröffentlichung, soweit erforderlich unter Angabe der maßgeblichen Teile	Betr. Anspruch Nr.
A	GB, A, 1476057 (UNICLIFFE LTD) 10. Juni 1977 siehe Seiten 1-3	1,3

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ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

EP 9001936
SA 41110

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 03/04/91
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
EP-A- 0219762	29-04-87	AU-A-	6541786	05-05-87
		CA-A-	1275046	09-10-90
		WO-A-	8702241	23-04-87
		EP-A-	0283474	28-09-88
		JP-T-	63501794	21-07-88
		US-A-	4849246	18-07-89
GB-A- 2186190	12-08-87	US-A-	4705680	10-11-87
		US-A-	4765984	23-08-88
		AT-B-	390370	25-04-90
		AT-B-	389812	12-02-90
		AU-B-	598220	21-06-90
		AU-A-	6712887	23-07-87
		AU-B-	598512	28-06-90
		AU-A-	6790387	23-07-87
		BE-A-	1000635	28-02-89
		BE-A-	1000488	27-12-88
		CH-A-	676082	14-12-90
		CH-A-	672250	15-11-89
		DE-A-	3701122	23-07-87
		DE-A-	3701123	23-07-87
		FR-A-	2593063	24-07-87
		FR-A-	2593064	24-07-87
		GB-A,B	2185399	22-07-87
		JP-A-	62223109	01-10-87
		NL-A-	8700152	17-08-87
		NL-A-	8700153	17-08-87
		OA-A-	8467	29-07-88
		SE-A-	8700220	23-07-87
		SE-A-	8700221	23-07-87
EP-A- 0259749	16-03-88	DE-A-	3630603	10-03-88
		AU-B-	601478	13-09-90
		AU-A-	7792987	17-03-88
		JP-A-	63077816	08-04-88
		US-A-	4925670	15-05-90
GB-A- 2163348	26-02-86	US-A-	4753792	28-06-88

EPO FORM P0473

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

EP 9001936
SA 41110

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 03/04/91
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
GB-A- 1476057	10-06-77	Keine	

EPO FORM P0473

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82

TEVA EXHIBIT 1002
TEVA PHARMACEUTICALS USA, INC. V. RB PHARMACEUTICALS LTD.

Espacenet

Bibliographic data: EP 0259749 (A1)

Dosage and administration forms for medicines, reagents or the like, and process for their preparation.

Publication date:	1988-03-16
Inventor(s):	SCHMIDT WOLFGANG [DE] +
Applicant(s):	DESITIN ARZNEIMITTEL GMBH [DE] +
Classification:	**- international:** ***A61K9/20; A61K9/70;*** (IPC1-7): A61K9/20; A61K9/70 **- European:** A61K9/20K4; A61K9/70
Application number:	EP19870112712 19870901
Priority number(s):	DE19863630603 19860909
Also published as:	• EP 0259749 (B1) • US 4925670 (A) • JP 63077816 (A) • GR 3003083 (T3) • DE 3630603 (A1) • more
Cited documents:	DE2746414 (A1) EP0019929 (A2) FR1382158 (A) DE1947684 (A1) View all

Abstract of EP 0259749 (A1)

The dosage and administration form consists of a carrier material in the form of a release paper, a release film or a release foil which is provided on one side with a coating which contains active substance and which can, after previous division into dose units, be pulled off dosewise from the carrier material. The sections containing active substance which have been pulled off are particularly suitable as oral medicines.

Last updated: 26.04.2011 Worldwide Database 5.7.22; 92p

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

(11) Veröffentlichungsnummer: **0 259 749 B1**

(12) # EUROPÄISCHE PATENTSCHRIFT

(45) Veröffentlichungstag der Patentschrift: **14.08.91**

(51) Int. Cl.5: **A61K 9/20**, A61K 9/70

(21) Anmeldenummer: **87112712.2**

(22) Anmeldetag: **01.09.87**

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

(30) Priorität: **09.09.86 DE 3630603**

(43) Veröffentlichungstag der Anmeldung:
16.03.88 Patentblatt 88/11

(45) Bekanntmachung des Hinweises auf die Patenterteilung:
14.08.91 Patentblatt 91/33

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

(56) Entgegenhaltungen:
EP-A- 0 019 929
EP-A- 0 219 762
DE-A- 1 947 684
DE-A- 2 746 414
FR-A- 1 382 158
GB-A- 2 022 999

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

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

(74) Vertreter: **UEXKÜLL & STOLBERG Patentanwälte**
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W-2000 Hamburg 52(DE)

EP 0 259 749 B1

Anmerkung: Innerhalb von neun Monaten nach der Bekanntmachung des Hinweises auf die Erteilung des europäischen Patents kann jedermann beim Europäischen Patentamt gegen das erteilte europäische Patent Einspruch einlegen. Der Einspruch ist schriftlich einzureichen und zu begründen. Er gilt erst als eingelegt, wenn die Einspruchsgebühr entrichtet worden ist (Art. 99(1) Europäisches Patentübereinkommen).

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Beschreibung

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

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

Es sind bereits Versuche zur Schaffung einer neuen Darreichungsform für die orale Verabreichung von Arzneimitteln bekannt geworden, welche aus wirkstoffhaltigen Folien bestehen. Gemäß der BE-PS 637 363 wird ein papierartiges Trägermaterial aus unlöslichen Zellulosefasern mit einer Wirkstofflösung getränkt bzw. beschichtet und eine Dosierung durch Perforation der Trägerfolie nach Art eines Briefmarkenbogens erreicht. Aus den DE-OS 24 32 925 und 24 49 865 ist es bekannt, Arzneimittelwirkstoffe in Folienbildner einzuarbeiten, bei denen es sich vorzugsweise um wasserlösliche Verbindungen wie Methyl- und Ethylzellulose, insbesondere aber Hydroxypropylzellulose, Hydroxyethylzellulose oder Methylhydroxypropylzellulose handelt. Auch die so erhaltenen wirkstoffhaltigen Folien lassen sich zur Dosierung durch Perforation in einzelne Abschnitte aufteilen. Aus DE-A-2746414 ist es ferner bekannt, derartige Dosierfolien mit weiteren Wirkstoffhaltigen oder- freien folien zu Dosierlaminaten zu vereinigen. Dadurch lassen sich inkompatible Wirkstoffe verarbeiten oder die Lösungsgeschwindigkeit bereinflussen. Diese Laminate insgesamt werden in form von Dosiereinheiten verwendet. Diese Vorschläge haben keinen Eingang in die Praxis gefunden und in dem neuesten Lehrbuch der "Arzneiformenlehre" von P.H. List, 4. Auflage, Stuttgart, 1985, finden sie keine Erwähnung. Dies beruht ersichtlich darauf, daß die bislang bekanntgewordenen Vorschläge es nicht ermöglichen, die geforderte Gewichtskonstanz und gleichmäßige Wirkstoffverteilung zu erreichen, welche heute gefordert werden. Die Ph. Eur. setzt zum Beispiel Maßstäbe für die Gleichförmigkeit des Gewichtes einzeldosierter Arzneiformen, wobei diese dem jeweiligen Durchschnittsgewicht entsprechend nach höchstzulässigen Abweichungen in % gestaffelt sind. Die Forderung liegt im allgemeinen bei +/- 5 bis max. 10%. Entsprechende Werte für feste Arzneiformen bestehen auch hinsichtlich anderer Parameter wie Zerfallzeit und Lösungsgeschwindigkeit.

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

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

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

Die erfindungsgemäße Darreichungsform weist mehrere wesentliche Vorteile auf:

- Da der Träger im Gegensatz zu den vorbekannten Ausführungsformen keinen Teil der Darreichungsform bildet, kann er die erforderliche Festigkeit aufweisen, ohne die Akzeptanz des Arzneimittels

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durch Patienten zu beeinträchtigen,

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

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

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

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

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

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

Folgende Rahmenrezeptur hat sich bewährt:

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Gelatine	8 bis 10 g
Stärke	3 bis 8 g
Glycerin	1 bis 2 g
Wasser	30 bis 50 g

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

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

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

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

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

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

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

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

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

Die Vorzerteilung erfolgt in besonders einfacher Weise durch Stanzung, wobei es möglich ist, diesen

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Schritt mit der Bedruckung des Trägermaterials zu kombinieren. In vielen Fällen wird es allerdings günstiger sein, die Bedruckung des Trägermaterials vor der Beschichtung vorzunehmen.

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

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

Zur näheren Erläuterung der Erfindung sollen die nachfolgenden Ausführungsbeispiele dienen.

Beispiel 1
Herstellung eines Cardiakum

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

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

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

Beispiel 2
Herstellung eines Contrazeptivum

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

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

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

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

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Patentansprüche

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

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

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

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

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

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

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

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

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

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

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

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

Claims

1. Presentation and dosage form for pharmaceutical active substances, reagents, aromas or the like in the form of a foil-like carrier material with an active-substance-containing coating, characterized in that the carrier material is a release paper, a release film or a release foil and that the carrier material is provided on one side with the active-substance-containing coating, which can be removed dosewise from the carrier material following prior division into dosage units.

2. Presentation form according to claim 1, characterized in that the carrier material is a silicone or wax-coated release paper.

3. Presentation form according to claims 1 or 2, characterized in that the active-substance-containing coating substance is pre-divided into dosage units by punching.

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4. Presentation form according to one of claims 1 to 3, characterized in that the coating contains one or more pharmaceutical active substances.

5. Presentation form according to one of claims 1 to 4, characterized in that the coating contains water-soluble swelling substances as polymeric foil formers and optionally softeners.

6. Presentation form according to one of claims 1 to 5, characterized in that it contains, to set the viscosity, polymeric swelling substances, which can simultaneously serve as adhesion promoters.

7. Presentation form according to one of claims 1 to 6, characterized in that the coating is applied in the form of several layers having differing composition.

8. Presentation form according to claim 7, characterized in that incompatible active substances are applied one after the other as separate layers to the carrier material.

9. Presentation form according to claim 7, characterized in that an active substance layer is arranged between at least two other layers which control the absorption of the active substance in the gastro-intestinal tract in a manner known per se.

10. Presentation form according to claim 7, characterized in that a further layer is applied onto the active substance layer, said layer protecting the active substance against contact with the atmosphere and/or against light.

11. Presentation form according to one of claims 1 to 10, characterized in that the back of the carrier material can be printed with the active substance composition and/or information concerning the intake thereof.

12. Process for preparing the pharmaceutical presentation form according to claims 1 to 11, characterized in that an active-substance-containingcomposition is applied with the aid of rollers to the non-adhesively finished side of a release paper, a release film or a release foil.

Revendications

1. Forme de présentation ou de dosage de principes actifs médicamenteux, réactifs, substances aromatisantes ou similaires, sous la forme d'un matériau support en forme de feuille muni d'un revêtement contenant le principe actif, caractérisée en ce que le matériau support est un papier détachable, un film détachable ou une feuille détachable et, le matériau support est muni d'un côté du revêtement contenant le principe actif, que l'on peut détacher par doses du matériau support après l'avoir préalablement divisé en doses unitaires.

2. Forme de présentation selon la revendication 1, caractérisée en ce que le matériau support est un papier détachable revêtu de silicone ou de cire.

3. Forme de présentation selon la revendication 1 ou 2, caractérisée en ce que le revêtement contenant le principe actif est préalablement divisé en doses unitaires par poinçonnage.

4. Forme de présentation selon l'une quelconque des revendications 1 à 3, caractérisée en ce que le revêtement contient un ou plusieurs principe(s) actif(s) médicamenteux.

5. Forme de présentation selon l'une quelconque des revendications 1 à 4, caractérisée en ce que le revêtement contient des substances épaississantes, comme des agents filmogènes polymères et, le cas échéant, des plastifiants.

6. Forme de présentation selon l'une quelconque des revendications 1 à 5, caractérisée en ce qu'elle contient des substances épaississantes polymères pour ajustement de la viscosité, celles-ci pouvant servir en même temps d'agents adhésifs.

7. Forme de présentation selon l'une quelconque des revendications 1 à 6, caractérisée en ce que le

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revêtement est constitué de plusieurs couches de compositions différentes.

8. Forme de présentation selon la revendication 7, caractérisée en ce que des principes actifs incompatibles entre eux sont appliqués successivement sur le matériau support, dans des couches séparées.

9. Forme de présentation selon la revendication 7, caractérisée en ce qu'une couche de principe actif est placée entre au moins deux autres couches qui règlent, par des moyens connus par eux-mêmes, la résorption du principe actif dans l'estomac/le tractus intestinal.

10. Forme de présentation selon la revendication 7, caractérisée en ce que l'on étale, sur la couche de principe actif, une couche supplémentaire qui préserve le principe actif, une couche supplémentaire qui préserve le lumière.

11. Forme de présentation selon l'une quelconque des revendications 1 à 10, caractérisée en ce que l'on peut imprimer au verso du matériau support la composition du principe actif et/ou des informations concernant sa prise.

12. Procédé pour préparer la forme de présentation de médicament des revendications 1 à 11, caractérisé en ce que l'on étale, à l'aide de cylindres, une composition contenant le principe actif sur le côté laissé non adhésif d'un papier détachable, d'un film détachable ou d'une feuille détachable.

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Description

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In the accompanying drawing:

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

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

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

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

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

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

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

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

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

Method of determing Dissolution Ratio:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EXAMPLE 1

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

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

COMPARATIVE EXAMPLE 1

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

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

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

COMPARATIVE EXAMPLE 2

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

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

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

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

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

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

TABLE 1

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

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

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

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

Adhesion Test:

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

Peel Test:

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

The results obtained are shown in Table 2 below.

TABLE 2

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

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

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duration.

EXAMPLE 2

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

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

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

TABLE 3

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

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

EXAMPLE 3

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

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

EXAMPLE 4

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

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

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

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

EXAMPLE 5

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

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

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

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

EXAMPLE 6

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

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

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

EXAMPLE 7

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

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

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

COMPARATIVE EXAMPLE 3

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

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

COMPARATIVE EXAMPLE 4

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

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

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

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TABLE 4

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

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

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

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

COMPARATIVE EXAMPLE 5

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

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

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

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

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

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

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

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

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

TABLE 5

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

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

EXAMPLE 8

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

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

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

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

EXAMPLE 9

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

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

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

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

EXAMPLE 10

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

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

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

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

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EXAMPLE 11

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

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

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

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

EXAMPLE 12

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

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

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

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

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

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

EXAMPLE 13

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

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

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

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

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

EXAMPLES 14 to 19

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

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TABLE 6

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

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

EXAMPLES 20 to 37

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

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TABLE 7

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

* Dried at 70°C for 15 minutes

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TABLE 7 (cont'd)

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

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

CLINICAL EXAMPLE 1

Effect on Stomatitis

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

CLINICAL EXAMPLE 2

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Effect on Stomatitis

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

CLINICAL EXAMPLE 3

Effect on the injured site by toothbrushing

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

CLINICAL EXAMPLE 4

Effect on Halitosis

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

CLINICAL EXAMPLE 5

Prophylactic Effect on Infection

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

CLINICAL EXAMPLE 6

Effect on Periodontal Disense

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

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

CLINICAL EXAMPLE 7

Effect on Dentin Hyperesthesia

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

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

CLINICAL EXAMPLE 8

Effect on dentin hyperesthesia

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

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

CLINICAL EXAMPLE 9

Local Anesthetic Effect

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

Claims

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

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

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

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

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

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

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

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

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

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

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

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polymers (a).

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

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

Revendications

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

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

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

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

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

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

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

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

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

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

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

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

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

Patentansprüche

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

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

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

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

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

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

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

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

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

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

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

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

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

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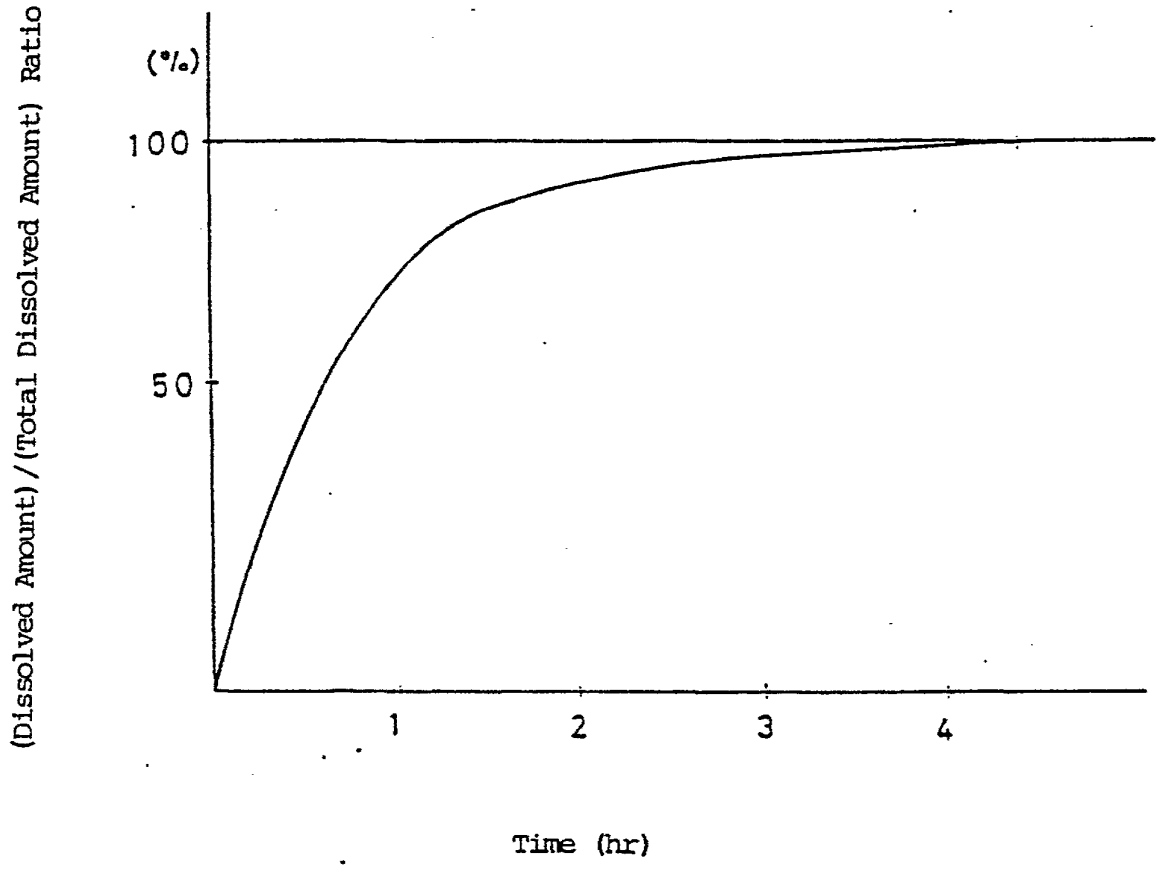
(Dissolved Amount)/(Total Dissolved Amount) Ratio
(%)
100
50
1
2
3
4
Time (hr)

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Description

This invention relates to a pharmaceutical composition which is applied to a periodontal pocket or paradentium for the purpose of treating periodontal diseases. The pharmaceutical composition may be provided in the form of gel, sheet, film or bar-like formulation to release a controlled and effective amount of an active ingredient at the periodontal pocket or paradentium.

The "periodontal diseases" is a general term of various inflammatory diseases of paradentium. The diseases include a series of diseases exhibiting various syndromes which vary from each other according to the stage or situation of the diseases or the age of the patient, and have not been definitely subclassified. Since, however, the term "periodontal diseases" is given to any inflammatory disease which initially occurs at a marginal gingiva area and finally reaches an alveolar bone, the diseases can be roughly divided, on the basis of the degree of the inflammation, into "gingivitis" in which the inflammation is limited to the gingiva tissue, and "paradentitis" in which the inflammation is chronic and found even in an alveolar bone. However, peculiar diseases such as "juvenile paradentitis" and "acute necrotizing ulcerative gingivitis" are also included in the periodontal diseases.

The paradentitis, which was once called "alveolar pyorrhea", is characterized by remarkable symptoms such as inflammation of gingiva, formation of periodontal pockets, bleeding and pus discharge from said periodontal pockets, and it brings about resorption of alveolar bone, loose teeth, and shedding of teeth.

The consensus of most investigators is that periodontal diseases are caused by bacteria present in dental plaques formed in periodontal pockets. Efforts have been concentrated on the discovery of pathogenic bacteria responsible for said diseases. At the present time, an attributable major pathogen is recognized to be certain nigral pigment-producing bacteria, such as genus Bacteroides. However, other genera of bacteria including Actinobacillus, Capnocytophaga, Fusobacterium and Spirochetes may be included in the causative pathogens. In any case, it is an established theory that the periodontal diseases should not be attributed to all bacteria present in the dental plaque.

The periodontal diseases have previously been treated in several ways, such as exhaustive scaling of plaques in periodontal pockets, root planing, gingivectomy to eliminate the periodontal pocket, or surgical curettage to excise inflammatory tissues. These treatments have been effective to some extent but not satisfactory.

On the other hand, pharmacotherapy has also been conducted using drugs, for example germicides, antiinflammatory agents, plaque solubilizing agents, and hemostyptics. These drugs are used in the form of formulations suited for internal use or massotherapy (e.g., dentifrices and ointments). However, they are not satisfactory for the purpose of treatment of periodontal diseases because the internal use hardly permits the selective migration of the drug to the lesional region, and the massotherapy is not successful in solubilizing the plaques which are present beneath the gingival margin.

Recently, strips which comprise polymers and active ingredients for treatment of periodontal diseases have been developed. These strips are said to be useful for the treatment of plaques and inflammation beneath the gingival margin. The strips can be applied directly to the lesional region to be treated, and therefore, the active ingredient can be concentrated to the desired site selectively. This modified therapeutic method has been proved to be more effective than any conventional pharmacotherapy. For instance, J. M. Goodson et al. disclose the implantation of "hollow fiber", which contains germicides, into the gingival region (J. Clinical Periodontology, 1979: 6: 83-92). M. Addy et al. have reported the insertion of strips, which were prepared from a mixture of an insoluble polymer such as polyethylmethacrylate and germicides, into periodontal pockets (J. Periodontal, 693, Nov. 1982). In addition, insertion of the strips, prepared from a mixture of a soluble polymer and a drug, into the lesional region, such as periodontal pockets, is also reported (Japan Patent Publication No. 59-222406).

The formulations mentioned above comprise a mixture of an active ingredient and a homogeneous polymer base. Accordingly, where such formulation is designed to contain two or more active ingredients which differ from each other in terms of pharmacological activity and therapeutically effective dose, it has been impossible to prepare a formulation in which each of the plural ingredients may release independently and provide its suitable concentration as desired.

The use of the hollow fiber or insoluble polymer, as a base, causes irritation or pain to patients, and moreover, it necessitates the removal of the base after release of an active ingredient, which is often annoying. On the other hand, the strip which comprises a soluble polymer as a base or carrier permits a rapid release of an active ingredient. Accordingly, it does not afford a constant therapeutic effect and, therefore, has a poor practical use.

As the result of an extensive study for seeking a novel therapeutical composition for periodontal diseases, which suitably controls the release of one or more active ingredients and which does not give any uncomfortable feelings to patients, it has been

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found that the use of a two-phase carrier base, which consists of particles comprising a polymer having a limited solubility in water and a water soluble polymer used for dispersing such particles, meets the requirements just mentioned above.

DE-A-3 432 573 and US-A-4 693 887 disclose pharmaceutical composition having two polymeric phases, one hydrophobic and one hydrophilic, the combination being insoluble in water and thus suitable for water-insoluble implants. A drug partitions itself between the phases. The hydrophilic phase has a different composition from the discontinuous phase employed in the present

Thus the present invention provides:

a controlled-release pharmaceutical composition in the form of gel, sheet, film, or bar to be inserted or placed into a periodontal pocket for treating a periodontal disease, said composition comprising a therapeutically effective amount of at least one active ingredient effective for the treatment of the periodontal disease, said active ingredient being dispersed in a two-phase carrier consisting of

(a) a continuous phase consisting of a water-soluble polymer capable of dissolving in water at a concentration of more than 1% by weight irrespective of pH, and

(b) a discontinuous phase consisting of solid particles composed of a polymer capable of dissolving in water at a concentration of at least about 0.1% and not more than about 1.0% by weight; or solid particles composed of a polymer capable of dissolving in water at a concentration of more than 1% by weight only at a pH higher than 4 or lower than 6

said particles having an average size ranging from 1 μm to 500 μm and being dispersed in said water-soluble polymer, with the weight ratio of said particles to said water-soluble polymer ranging from 1:99 to 99:1 on a dry weight basis, said water-soluble polymer being selected from the

methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium alginate, propylene glycol alginate, pullulan, tragacanth, xanthan gum, chitosan, polyethylene oxide, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and salts thereof, and said solid particles being selected from

poly(glycolic acid), poly(lactic acid), polytetramethylglycolide, polydiethylglycolide, poly-ε-caprolactone, poly(DL-decalactone), poly(alkyleneadipate), methylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ octylacrylate copolymer, ethylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ methylmethacrylate copolymer, methylmethacrylate/ methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate maleate, starch acetate phthalate, amylose acetate phthalate, methyl cellulose phthalate, hydroxypropylmethyl cellulose phthalate, hydroxyethyl ethylcellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, polyvinylalcohol phthalate, polyvinyl acetate phthalate, polyvinylacetal phthalate, polyvinylbutylate phthalate, methylmethacrylate/ dimethylaminoethyl methacrylate copolymer, and polyvinylacetal/ dimethylamino acetate.

Brief Description of the Drawing

Fig. 1 shows the dissolution profile of two active ingredients contained in the pharmaceutical composition of the invention which is in the form of a film. Fig. 2 shows the dissolution profile of two active ingredients contained in a conventional composition.

"Water soluble polymer" or "soluble polymer" denotes any polymer which dissolves in an aqueous medium, particularly in water, in a concentration of more than 1% by weight, irrespective of pH.

For the purpose of simplicity, the polymers usable for the discontinuous phase are hereinafter referred to as "non-soluble polymer" as a whole.

The soluble polymer used in the present invention must be fabricated into a semi-solid or a solid material. The non-soluble polymer should have a property suitable for being fabricated into particles. Both soluble and non-soluble polymers employed in the present application should be, of course, physiologically acceptable.

The pharmaceutical composition of the present invention may be prepared by dispersing one or more of active ingredients into a non-soluble polymer, or both of a soluble polymer and a non-soluble polymer, and mixing these polymers, and finally forming the resultant mixture into a solid material of a film, sheet or bar-like shape, or into a semi-solid material such as gel or ointment.

In more detail, one or more non-soluble polymers is dissolved, as the first step, in an appropriate organic solvent. To the resultant solution is dissolved or dispersed one or more active ingredients, and the mixture is formed into film or sheet by casting method. The resultant solid material is ground into particles.

The particles are also obtainable by spray drying, Wuster coating, Coacervation, or Drying in liquid phase. The average particle size may range from 1μm to 500μm depending on the contemplated release pattern of the active ingredient. However, the size range between 1μm and 300μm is generally preferred.

On the other hand, one or more water soluble

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polymers are dissolved in a suitable solvent. The solvent may contain, if desired, one or more active ingredients. Subsequently, the pH of the mixture is adjusted, if necessary, and the particles obtained above are uniformly suspended in the mixture. The pharmaceutical composition of the invention in the form of gel is thus obtained.

The composition of the invention in the form of film or sheet is obtained by deaerating the just mentioned gel, and subjecting the same to the casting process. The film or sheet may also be prepared by compression molding, extrusion or calendering. The most suitable forming process among others is selected depending on the physico-chemical properties of the polymers employed.

The bar-like composition of the invention is prepared in the similar manner as the film or sheet, but through extrusion.

The weight ratio of the particles to the soluble polymer ranges from 1:99 to 99:1 on the basis of dry weight. The composition of the particles: soluble polymer in a ratio of 10:90-70:30 is preferred.

Therapeutically active ingredient or ingredients used for the preparation of the composition of the invention are selected from those effective for prevention or treatment of periodontal diseases, for example, germicides, such as chlorhexidine, Ag protein, glyceryl iodide, phenol, benzalkonium chloride, and cetylpyridinium chloride; antimicrobial agents, such as ampicillin, tetracycline, benzylpenicillin, clindamycin, cefalexin, erythromycin, chloramphenicol, and fragiomycin sulfate; anti-inflammatory agents, such as ibuprofen, indomethacin, ketoprofen, mefenamic acid, antipyrine, pranoprofen, ibufenac, tiaramide hydrochloride, prednisolon, dexamethasone, triamcinolone acetonide, and prostaglandine; plaque solubilizing agents, such as dextranase, protease, and amylase; collagenase inhibitors obtained from the extraction of crude drugs, such as gambir-catechu known by the name of "asenyaku"; local anesthetics, such as tetracaine hydrochloride and ethyl aminobenzoate; antihistaminic agents, such as chlorphenilamine maleate and diphenhydramine; and hemostatic agents such as tranexamic acids.

The solid composition of the invention in the form of film, sheet or bar can be prepared in different sizes. However, the convenient size of the film or sheet may be 0.1-0.5 mm in thickness, 0.5-3 mm in width, and 10-50 mm in length. The size of the bar may generally range from 0.5 to 1.5 mm in diameter and from 10 to 50 mm in length. Furthermore, the composition of the invention may be cut in suitable size by the user depending on several factors, such as severity of the disease, and the width and depth of the locus to be applied. The composition of the invention can be applied to the periodontal pocket or paradentium by insertion, injection, or rubbing according to the type of formulation.

The pharmaceutical composition of the invention exhibits a desirably controlled release pattern of the active ingredient(s). Such controlled release is attained by careful selection of a particular condition with respect to the following variables.

(1) Distribution ratio of an active ingredient between the particles and the soluble polymer.

(2) The particle size to be dispersed in the soluble polymer.

(3) Selection of non-soluble polymer or polymers which permits the modification of both the solubility of particles and diffusion velocity of an active ingredient in the particles in the manner as desired.

(4) The use of one or more kind(s) of particles which differ from each other in their solubilities.

(5) The ratio of the amounts of particles and soluble polymer to be combined.

(6) Selection of soluble polymer or polymers having desired viscosity.

By selection of suitable conditions in regard to the above variables, there is obtained the pharmaceutical composition of the invention which releases one or more of active ingredients in the manner as contemplated. Since the surface of the composition of the invention is mainly composed of water soluble polymer, it does not give any uncomfortable feeling to patients.

The following examples are presented by way of illustration of specific embodiments of the pharmaceutical composition of the invention. In examples, part or parts are represented by weight basis.

Example 1

Poly(lactic acid) (10 parts) and tetracycline hydrochloride (2 parts) are dissolved in methylene chloride (100 parts). Flow casting of the resultant mixture yields a sheet, which is ground into particles having an average size of 50μm.

The particles (10 parts) and hydroxypropyl cellulose (10 parts) are uniformly admixed. The mixture is blended with water, extruded with pressure, and dried. The bar-like shaped product of 1.0 mm diameter is thus obtained.

Example 2

Methacrylic acid / methyl methacrylate copolymer (1:2 molar ratio) (80 parts) is dissolved in ethanol (1000 parts). In the solution are suspended or dissolved indomethacin (5 parts) and triacetin (20 parts), and the mixture is cast into a sheet, which is then pulverized into particles having an average size of 80μm.

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Hydroxypropyl cellulose (10 parts) is dissolved in water (1000 parts), and tetracycline (25 parts) is added to the resultant solution, after adjusting to pH 6.0 by addition of hydrochloric acid. The resultant mixture (80 parts) is uniformly admixed with the particles obtained above (20 parts) to yield the product in a gel form.

Example 3

The particles produced in Example 2 (20 parts), methyl cellulose (80 parts) and tetracycline hydrochloride (5 parts) are uniformly admixed, and the resulting mixture is pressed to a sheet having a 500μm thickness.

Experiment 1

The controlled release of an active ingredient was evaluated for a pharmaceutical composition of the invention which contains two kinds of active ingredients.

Method and materials

(1) Preparation of Sample

Methacrylic acid / methyl methacrylate copolymer (1:2 molar ratio) (80 parts) was dissolved in ethanol (1000 parts). Triacetin (20 parts) and tetracycline hydrochloride (6 parts) were then mixed with the resultant solution. The mixture was cast on a Teflon tray and dried at 40°C. The resultant sheet was pulverized into particles of 105μm to 177μm in size.

On the other hand, hydroxypropyl cellulose (viscosity of 2% aqueous solution is 1000 to 4000 cp at 20°C) (one part) was dissolved in water (99 parts). In the solution was dissolved tetracaine hydrochloride (0.03 part).

The hydroxypropyl cellulose solution and the particles are uniformly admixed at a weight ratio of 100:0.5, and the mixture is deaerated, cast on a Teflon tray with care to ensure the constant thickness, and air-dried to yield a film having 300μm thickness.

In a solution of hydroxypropyl cellulose (1 part) dissolved in water (100 parts) were dissolved tetracycline hydrochloride (0.02 part) and tetracaine hydrochloride (0.02 parts), and the mixture was adjusted to pH 6, deaerated, cast on a Teflon tray, air-dried to obtain a film having 300μm thickness, which was employed as a reference.

(2) Evaluation of Dissolution Rate

The dissolution rates of the active ingredients released from the films obtained above were measured using a phosphate buffer (500ml), pH 7.2, at 37°C, in accordance with the Rotating Basket Method (100 rpm) of Japanese Pharmacopoeia (X).

Results

The dissolution profiles of the film of the invention and that of the reference are respectively shown in Fig. 1 and Fig. 2 of the accompanying drawing. The abscissa indicates immersion time and the ordinate indicates the dissolution rate. Fig. 1 shows that two active ingredients were released from the film with different release patterns while Fig. 2 shows the same and identical release pattern of the two active ingredients. Thus, this experiment illustrates that the composition of the invention permits separate control of the release patterns of two active ingredients. It also teaches that the composition of the invention in the form of a sustained release formulation may be obtained where a single active ingredient is employed rather than two active ingredients as employed in this experiment.

Claims

1. A controlled-released pharmaceutical composition in the form of gel, sheet, film, or bar to be inserted or placed into a periodontal pocket for treating a periodontal disease, said composition comprising a therapeutically effective amount of at least one active ingredient effective for the treatment or the periodontal disease, said active ingredient being dispersed in a two-phase carrier consisting of
   (a) a continuous phase consisting of a water-soluble polymer capable of dissolving in water at a concentration of more than 1% by weight irrespective of pH, and
   (b) a discontinuous phase consisting of solid particles composed of a polymer capable of dissolving in water at a concentration of at least about 0.1% and not more than about 1.0% by weight; or solid particles composed of a polymer capable of dissolving in water at a concentration of more than 1% by weight only at a pH higher than 4 or lower than 6.

   said particles having an average size ranging from 1 μm to 500 μm and being dispersed in said water-soluble polymer, with the weight ratio of said particles to said water-soluble polymer ranging from 1:99 to 99:1 on a dry weight basis, said water-soluble polymer being selected from the
   methyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium alginate, propylene glycol al-

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ginate, pullulan, tragacanth, xanthan gum, chitosan, polyethylene oxide, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and salts thereof, and said solid particles being selected from

poly(glycolic acid), poly(lactic acid), polytetramethylglycolide, polydiethylglycolide, poly-ε-caprolactone, poly(DL-decalactone), poly(alkyleneadipate), methylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ octylacrylate copolymer, ethylacrylate/ methacrylic acid copolymer, methylacrylate/ methacrylic acid/ methylmethacrylate copolymer, methylmethacrylate/ methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate maleate, starch acetate phthalate, amylose acetate phthalate, methyl cellulose phthalate, hydroxypropylmethyl cellulose phthalate, hydroxyethyl ethylcellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, polyvinylalcohol phthalate, polyvinyl acetate phthalate, polyvinylacetal phthalate, polyvinylbutylate phthalate, methylmethacrylate/ dimethylaminoethyl methacrylate copolymer, and polyvinylacetal/ dimethylamino acetate.

2. The composition of claim 1 wherein two active ingredients are dispersed in said carrier.

3. The composition of claim 1 having at least two active ingredients whereof one is in the continuous phase and one is in the discontinuous phase, whereby they have different release profiles.

4. Use of the two-phase carrier according to Claim 1 as a carrier for preparing a controlled-release pharmaceutical composition in the form of gel, sheet, film or bar to be inserted or placed into a periodontal pocket for treating a periodontal disease, a therapeutically effective amount of at least one active ingredient effective for tile treatment of the periodontal disease being dispersed in said two-phase carrier.

5. Use according to claim 4 wherein two active ingredients are dispearsed in said carrier.

6. Use according to claim 5 wherein one active ingredient is dispersed in the continuous phase and the other active ingredient is dispersed in the discontinuouse phase.

7. A process for preparing the controlled-released pharmaceutical composition of Claim 1, 2 or 3 which comprises the following steps:

(1) preparing polymer particles using a polymer capable of dissolving in water at a concentration of at least about 0.1% and not more than about 1.0% by weight or a polymer capable of dissolving in water only at a pH higher than 4 or a pH lower than 6 at a concentration of more than 1% by weight, said polymer being specified in Claim 1.

(2) uniformly admixing the particles and a polymer capable of dissolving in water at a concentration of more than 1% by weight irrespective of pH, said polymer being specified in Claim 1.

(3) processing the mixture to form a pharmaceutical composition in the form of gel, sheet, film or bar, wherein at least one active ingredient effective for the treatment of the periodontal disease is added in Step (1) and/or Step (2).

8. The process of Claim 7, wherein one active ingredient is added in Step (1) and another ingredient is added in Step (2).

Revendications

1. Composition pharmaceutique à libération contrôlée sous la forme de gel, feuille, pellicule ou barre à insérer ou placer dans une poche parodontale pour le traitement d'une parodontopathie, ladite composition comprenant une quantité thérapeutique efficace d'au moins un ingrédient actif efficace pour le traitement de la parodontopathie, ledit ingrédient actif étant dispersé dans un support à deux phases constitué de

(a) une phase continue formée d'un polymère hydrosoluble capable de se dissoudre dans l'eau à une concentration de plus de 1 % en poids quel que soit le pH, et

(b) une phase discontinue formée de particules solides constituées d'un polymère capable de se dissoudre dans l'eau à une concentration d'au moins environ 0,1 % et d'au plus environ 1,0 % en poids ; ou de particules solides constituées d'un polymère capable de se dissoudre dans l'eau à une concentration de plus de 1 % en poids uniquement à un pH supérieur à 4 ou inférieur à 6,

lesdites particules ayant une taille moyenne comprise entre 1 µm et 500 µm et étant dispersées dans ledit polymère hydrosoluble, le rapport en poids desdites particules audit polymère hydrosoluble étant compris entre 1:99 et 99:1 en poids sec, ledit polymère hydrosoluble étant choisi parmi ceux qui suivent : méthylcellulose, hydroxypropylcellulose, car-

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boxyméthylcellulose sodique, hydroxypropylméthylcellulose, hydroxyéthylcellulose, alginate de sodium, alginate de propylène-glycol, pullulane, gomme adragante, gomme de xanthane, chitosane, poly(oxyde d'éthylène), alcool polyvinylique, acide polyacrylique, acide polyméthacrylique et leurs sels, et lesdites particules solides étant choisies parmi ceux qui suivent : poly(acide glycolique), poly(acide lactique), polytétraméthylglycolide, polydiéthylglycolide, poly-ε-caprolactone, poly(DL-décalactone), poly(adipate d'alkylène), copolymère acrylate de méthyle/acide méthacrylique, copolymère acrylate de méthyle/acide méthacrylique/acrylate d'octyle, copolymère acrylate d'éthyle/acide méthacrylique, copolymère acrylate de méthyle/acide méthacrylique/méthacrylate de méthyle, copolymère méthacrylate de méthyle/acide méthacrylique, acétophtalate de cellulose, acétosuccinate de cellulose, acétomaléate de cellulose, acétophtalate d'amidon, acétophtalate d'amylose, phtalate de méthylcellulose, phtalate d'hydroxypropylméthylcellulose, phtalate d'hydroxyéthyléthylcellulose, acétosuccinate d'hydroxypropylméthylcellulose, carboxyméthyléthylcellulose, phtalate d'alcool polyvinylique, acétophtalate de polyvinyle, phtalate de polyvinylacétal, butyrophtalate de polyvinyle, copolymère méthacrylate de méthyle/méthacrylate de diméthylaminoéthyle et polyvinylacétal/diméthylaminoacétate.

2. Composition selon la revendication 1, dans laquelle deux ingrédients actifs sont dispersés dans ledit support.

3. Composition selon la revendication 1, contenant au moins deux ingrédients actifs dont l'un se trouve dans la phase continue et l'autre dans la phase discontinue, de sorte qu'ils aient des profils de libération différents.

4. Utilisation du support à deux phases selon la revendication 1 comme support pour préparer une composition pharmaceutique à libération contrôlée sous la forme de gel, feuille, pellicule ou barre à insérer ou placer dans une poche parodontale pour le traitement de parodontopathies, une quantité thérapeutique efficace d'au moins un ingrédient actif, efficace pour le traitement de la parodontopathie, étant dispersée dans ledit support à deux phases.

5. Utilisation selon la revendication 4, dans laquelle deux ingrédients actifs sont dispersés dans ledit support.

6. Utilisation selon la revendication 5, dans laquelle un ingrédient actif est dispersé dans la phase continue et l'autre ingrédient actif est dispersé dans la phase discontinue.

7. Procédé pour préparer la composition pharmaceutique à libération contrôlée de la revendication 1, 2 ou 3, qui comprend les étapes suivantes :
   (1) préparer des particules de polymère en utilisant un polymère capable de se dissoudre dans l'eau à une concentration d'au moins environ 0,1 % et d'au plus environ 1,0 % en poids ou un polymère capable de se dissoudre dans l'eau a une concentration de plus de 1 % en poids uniquement à un pH supérieur à 4 ou un pH inférieur à 6 ledit polymère étant spécifié dans la revendication 1 ;
   (2) mélanger uniformément les particules et un polymère capable de se dissoudre dans l'eau à une concentration de plus de 1 % en poids quel que soit le pH, ledit polymère étant spécifié dans la revendication 1 ;
   (3) transformer le mélange pour former une composition pharmaceutique sous la forme de gel, feuille, pellicule ou barre,
   dans lequel au moins un ingrédient actif, efficace pour le traitement de parodontopathies, est ajouté dans l'Etape (1) et/ou l'Etape (2).

8. Procédé selon la revendication 7, dans lequel un ingrédient actif est ajouté dans l'Etape (1) et un autre ingrédient est ajouté dans l'Etape (2).

Patentansprüche

1. Pharmazeutisches Präparat mit kontrollierter, verzögerter Freigabe in Form eines Gels, einer Folie bzw. Platte, eines Films oder eines Stabes, das in eine periodontale Tasche eingesetzt oder eingesetzt wird, für die Behandlung einer periodontalen Krankheit, dadurch **gekennzeichnet,** daß das Präparat eine therapeutisch wirksame Menge von mindestens einem aktiven Bestandteil, der für die Behandlung der periodontalen Krankheit wirksam ist, enthält, wobei der aktive Bestandteil in einem Zweiphasen-Träger dispergiert ist, der aus
   (a) einer kontinuierlichen Phase, die aus einem wasserlöslichen Polymeren, welches sich in Wasser in einer Konzentration von über 1 Gew.-%, unabhängig vom pH-Wert, lösen kann, besteht, und
   (b) einer diskontinuierlichen Phase, die aus festen Teilchen, die aus einem Polymeren,

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das sich in Wasser in einer Konzentration von mindestens etwa 0,1 Gew.-% und nicht mehr als etwa 1,0 Gew.-% lösen kann, bestehen, oder aus festen Teilchen, die aus einem Polymeren, das sich in Wasser in einer Konzentration von über 1 Gew.-% nur bei einem pH-Wert über 4 oder niedriger als 6 lösen kann, besteht,

besteht, wobei die Teilchen eine durchschnittliche Teilchengröße im Bereich von 1 µm bis 500 µm aufweisen und in dem genannten wasserlöslichen Polymeren dispergiert sind, das Gewichtsverhältnis der Teilchen zu dem wasserlöslichen Polymeren im Bereich von 1:99 bis 99:1 auf Trockengewichtsbasis liegt, das wasserlösliche Polymere ausgewählt wird aus der Gruppe:

Methylcellulose, Hydroxypropylcellulose, Natriumcarboxymethylcellulose, Hydroxypropylmethylcellulose, Hydroxyethylcellulose, Natriumalginat, Propylenglykolalginat, Pullulan, Traganthgummi, Xanthangummi, Chitosan, Polyethylenoxid, Polyvinylalkohol, Polyacrylsäure, Polymethacrylsäure und ihren Salzen, und daß die festen Teilchen ausgewählt werden aus:

Poly(glykolsäure), Poly(milchsäure), Polytetramethylglykolid, Polydiethylglykolid, Poly-ε-caprolacton, Poly-(DL-decalacton), Poly-(alkylenadipat), Methylacrylat/Methacrylsäure-Copolymeren, Methylacrylat/Methacrylsäure/Octylacrylat-Copolymeren, Ethylacrylat/Methacrylsäure-Copolymeren, Methylacrylat/Methacrylsäure/Methylmethacrylat-Copolymeren, Methylmethacrylat/Methacrylsäure-Copolymeren, Celluloseacetatphthalat, Celluloseacetatsuccinat, Celluloseacetatmaleat, Stärkeacetatphthalat, Amyloseacetatphthalat, Methyloellulosephthalat, Hydroxypropylmethylcellulosephthalat, Hydroxyethylethylcellulosephthalat, Hydroxypropylmethylcelluloseacetatsuccinat, Carboxymethylethylcellulose, Polyvinylalkoholphthalat, Polyvinylacetatphthalat, Polyvinylacetalphthalat, Polyvinylbutylatphthalat, Methylmethacrylat/Dimethylaminoethylmethacrylat-Copolymeren und Polyvinylacetal/Dimethylaminoacetat.

2. Präparat nach Anspruch 1, dadurch **gekennzeichnet,** daß zwei aktive Bestandteile in dem Träger dispergiert sind.

3. Präparat nach Anspruch 1, dadurch **gekennzeichnet,** daß es mindestens zwei aktive Bestandteile enthält, wovon einer in der kontinuierlichen Phase und einer in der diskontinuierlichen Phase vorliegt, wobei sie unterschiedliche Freigabeprofile aufweisen.

4. Verwendung eines Zweiphasen-Trägers nach Anspruch 1 als Träger für die Herstellung eines pharmazeutischen Präparats mit kontrollierter Freigabe in Form eines Gels, einer Folie bzw. Platte, eines Films oder eines Stabes, das in eine periodontale Tasche eingesetzt oder eingelegt wird, für die Behandlung einer periodontalen Krankheit, wobei das pharmazeutische Präpart eine therapeutisch wirksame Menge von mindestens einem aktiven Bestandteil, der für die Behandlung der periodontalen Krankheit wirksam ist und in dem Zweiphasen-Träger dispergiert ist, enthält.

5. Verwendung nach Anspruch 4, dadurch **gekennzeichnet,** daß zwei aktive Bestandteile in dem Träger dispergiert sind.

6. Verwendung nach Anspruch 5, dadurch **gekennzeichnet,** daß ein aktiver Bestandteil in der kontinuierlichen Phase dispergiert ist und der andere aktive Bestandteil in der diskontinuierlichen Phase dispergiert ist.

7. Verfahren zur Herstellung des pharmazeutischen Präparats mit kontrollierter Freigabe nach Anspruch 1, 2 oder 3, dadurch **gekennzeichnet,** daß die folgenden Stufen durchgeführt werden:

(1) Herstellung von Polymerteilchen unter Verwendung eines Polymeren, welches sich in Wasser in einer Konzentration von mindestens etwa 0,1 und nicht mehr als etwa 1,0 Gew.-% lösen kann, oder eines Polymeren, welches sich in Wasser nur bei einem pH-Wert über 4 oder einem pH-Wert unter 6 in einer Konzentration von nicht mehr als 1 Gew.-% lösen kann, wobei das Polymere das in Anspruch 1 definierte Polymere ist,

(2) einheitliches Vermischen der Teilchen und des Polymeren, welches sich in Wasser bei einer Konzentration von über 1 Gew.-%, unabhängig vom pH-Wert, lösen kann, wobei das Polymere in Anspruch 1 definiert wurde,

(3) Verarbeitung des Gemisches zu einem pharmazeutischen Präparat in Form eines Gels, einer Folie bzw. Platte, eines Films oder eines Stabes, wobei mindestens ein aktiver Bestandteil, der für die Behandlung der periodontalen Krankheit wirksam ist, bei der Stufe (1) und/oder der Stufe (2) zugegeben wird.

8. Verfahren nach Anspruch 7, dadurch **gekennzeichnet,** daß ein aktiver Bestandteil bei der

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Stufe (1) und ein weiterer Bestandteil bei der Stufe (2) zugegeben werden.

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Fig. 1

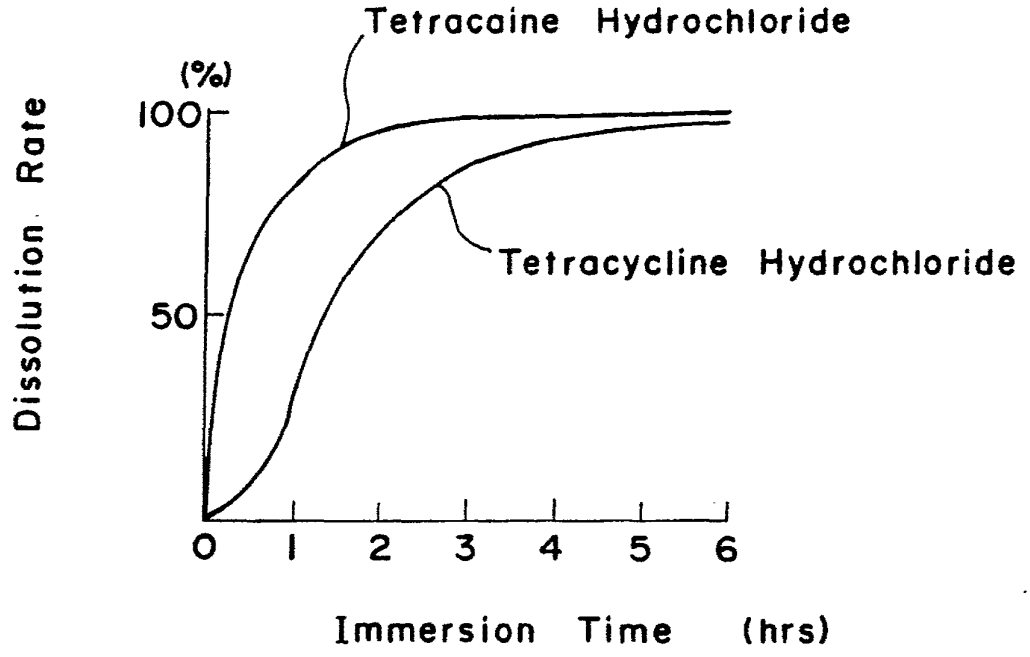
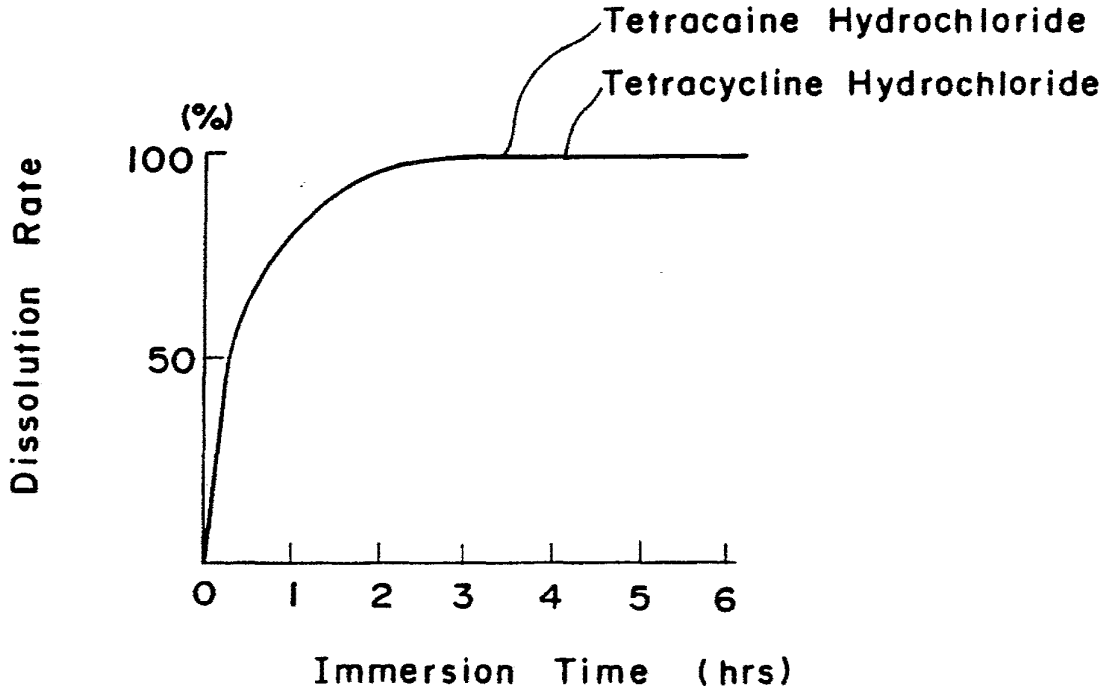

Tetracaine Hydrochloride
(%)
100
50
Dissolution Rate
Tetracycline Hydrochloride
0
1
2
3
4
5
6
Immersion Time (hrs)

Fig. 2


Tetracaine Hydrochloride
Tetracycline Hydrochloride
(%)
100
50
Dissolution Rate
0
1
2
3
4
5
6
Immersion Time (hrs)

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(54) Title: COMPOSITIONS AND METHODS FOR TOPICAL ADMINISTRATION OF PHARMACEUTICALLY ACTIVE AGENTS

(57) Abstract

A composition for topical application comprising a therapeutically effective amount of a pharmaceutical agent(s), a flexible, finite, pharmaceutically acceptable, adhesive, and a solvent for the pharmaceutical agent(s) in the adhesive and a method of administering the pharmaceutical agent to a mammal are disclosed.

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COMPOSITIONS AND METHODS FOR TOPICAL ADMINISTRATION OF PHARMACEUTICALLY ACTIVE AGENTS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. Patent Application Serial Number 07/661,827 filed February 27, 1991, and U.S. Serial Number 07/813,196 filed December 23, 1991, both of which applications are hereby incorporated by reference.

Field of the Invention

The present invention relates to compositions and methods for the topical administration of pharmaceutically active agents, namely those having a pharmacological or cosmetic effect, to a mammal in need thereof. The present invention is especially useful with local anesthetic agents for topical administration. In addition, the invention relates to a method for the topical administration of a pharmaceutical agent, especially an anesthetic agent or a combination of anesthetic agents, to prevent or ameliorate a disease or other medical or cosmetic condition, especially pain.

There is no limitation on the type of pharmaceutical agent that can be used in the present invention, provided that the agent can be absorbed percutaneously. Thus, the pharmaceutical agents can be drugs that can be topically applied for local effects and those which can be topically applied for systemic effects.

Background of the Invention

Anesthetic agents are pharmacologically active agents that block nerve conduction when applied in therapeutically effective amounts. They can be used for local or systemic effects. Anesthetic agents

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have been used extensively in the medical field to obtain topical anesthesia. Topical administration or application means the direct contact of the anesthetic with tissue to be anesthetized, such as skin or membrane, particularly the oral or buccal mucosa. Previous methods of applying topical anesthetic agents to the skin or mucosa have used "nonfinite" or semi-liquid carriers or spreading substances such as creams, gels or ointments, or "finite" carriers, non-spreading substances which retain their form, e.g. patches, dressings and bandages. The finite carriers are flexible in the sense that they can bend to conform to the configuration of the skin or mucosa where they are applied.

Local anesthetics generally are esters or amides of benzoic acid derivatives, administered either as the free base or the acid-addition salt. Free bases tend to be irritating at high concentrations. Acid-addition salts have low skin permeability.

To be effective, a topical, local anesthetic should contain sufficient concentration of the active agent to produce an anesthetic effect, it should penetrate intact skin or mucosa sufficiently to deliver a therapeutic dose, and it should exhibit rapid onset of anesthetic action and have a prolonged anesthetic effect. In achieving the foregoing, it is often desirable to have the anesthetic agent present in a high concentration in the dosage form to effect a rapid onset and, additionally or alternatively, in excess of the amount that can be immediately absorbed through the dermis at the site of application, so as to prolong the duration or effect of anesthesia. On the other hand, the presence of the anesthetic agent in crystalline form may irritate sensitive tissues such as mucosal tissues. This is particularly true

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with regard to lidocaine. The usefulness of topical anesthetics has been limited by the concentration of drug achievable in the dosage form. The same considerations also apply generally to other pharmaceutically active agents.

Anesthetic agents have been used in nonfinite form. United States Patent No. 4,894,232 to Reül, et al. discloses a base for mucosal or denture adhesive pastes and a process for the preparation thereof. A lidocaine salt is named as suitable for this paste.

Finite local anesthetic compositions are reported in the literature. Some compositions are solvent free. For instance, Swedish Patent Publication No. 352,239 published December 27, 1972 in the name of S.G. Davis et al., assigned to Astra Pharmaceutical Products, Inc., and based on Swedish patent application No. 17744/70 filed December 30, 1970, discloses a local anesthetic film containing up to 50% lidocaine in crystallized, microdispersed form. In its final form, this composition lacks a solvent for the anesthetic agent. The preparation is prepared by adding a solution of lidocaine in an organic solvent or an acid addition salt in water, under heat and agitation, to a solution or suspension of a film-forming material, namely carboxymethyl cellulose, polyvinyl alcohol, or a mixture of polyvinyl alcohol and polyvinyl pyrrolidone in water, followed by heating to remove any solvent present.

United States Patent No. 4,900,552 of Sanvordeker et al., disclose a trilaminate film suitable for prolonged and sustained delivery of an active ingredient in a buccal cavity. Specifically a hydratable mucoadhesive base layer, a non-adhesive reservoir layer containing the drug and a water-impermeable carrier film sandwiched between and bonded

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to the base layer and the reservoir layer form the trilaminate film.

Some finite anesthetic compositions contain polyhydric alcohol solvents. United States Patent Nos. 4,572,832 and 4,695,465 to Kigasawa and 3,249,109 to Maeth all describe the use of water soluble protein based systems which incorporate anesthetics, and which also contain a tackifier and a polyhydric alcohol.

Some finite anesthetic agent compositions have a separate adhesive. United States Patent No. 3,814,095 to Lubens describes an absorbent pad for topical application of an anesthetic agent having a peripheral adhesive.

Glycerol (glycerin) has been used as a plasticizer for karaya gum. United States Patent Nos. 4,307,717 and 4,675,009 to Hymes et. al., describe a drug in a solid phase formed of a synthetic polymer and/or a long chain natural or synthetic polysaccharide or a combination thereof and a liquid phase of water or an alcohol or a combination thereof. The amount of drug in the preparation (excluding solvent or carrier) is low. The cross-linked polysaccharide plasticized with water and/or a polyhydric alcohol is said to be not self-adhering. The formulations do not include both a solvent for the drug and a plasticizer for the polysaccharide.

It is also known to combine two local anesthetic free bases with different melting points. By mixing the two anesthetic bases, an eutectic mixture has been reported that is liquid at room temperature, making it possible to attain higher concentrations of the active bases. United States Patent No. 4,888,354 to Chang relates to a combination of the free base and an acid addition salt or a variety of drugs, typically in a liquid carrier, to increase skin penetration rates. Anesthetics, along

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with a list of other suitable drugs are mentioned. This reference specifically teaches that base and acid-addition forms of the same drug be used in carrier.

United States Patent No. 2,352,691 to Curtis teaches the use of salicylate salts of alkamine esters of aminobenzoic acid to enhance the water solubility of anesthetic agents. In one example, this reference discloses a solution of procaine acetyl salicylate containing insoluble anesthetics such as benzocaine, butesin, orthoform, or their salts, in certain glycols, which are combined with a volatile solvent, and then used to saturate gauze bandages or other suitable fabrics.

United States Patent No. 2,142,537 to Tisza describes an ointment containing isoamylhydrocupreine in combination with a quick acting local anesthetic to overcome the undesirable irritation caused by the prolonged acting anesthetic isoamylhydrocupreine or its salts. The preparation of Tisza combines short and long acting anesthetic agents.

United States Patent No. 2,277,038 to Curtis relates to preparations containing a mixture of two or more anesthetic agent salts having different pH values in solution, whereby the pH value of the combined mixture in solution may be adjusted to obtain a higher degree of stability of the solution, and at relatively higher pH, a more rapid onset of anesthetic action. The anesthetic agents in Curtis are not in highly dispersed form and are used in a liquid-soaked fabric.

Commonly, prolongation of anesthesia with topical anesthetics has been achieved by the addition of vasoconstrictors, such as the catecholamine, epinephrine, which caused constriction of blood vessels. Since catecolamines are not particularly effective when applied topically, such a prolongation

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is of minimal usefulness for topical anesthetics. The primary drawbacks of this approach are the potential adverse side effects of catecolamines, and the prolongation itself.

Although many local anesthetic compositions have been proposed, it has been discovered that the incorporation of one or more anesthetic agents in a solvent for the anesthetic agent or agents into a flexible, finite, pharmaceutically acceptable carrier, permits an exceptionally high loading of anesthetic agent in the carrier, permitting more rapid delivery of the anesthetic agent to the dermal membrane and a greater extent of anesthesia without crystallization of the anesthetic agent or agents which can limit absorption by the skin and which can cause irritation of the skin or other dermal membrane.

It has also surprisingly been found that concentrations of substantially dissolved anesthetic agent as high as 50% by weight of the total composition can be achieved in a system in which the adhesion of the adhesive is not hindered. Prolongation of anesthesia can thus be achieved by increasing the amount of time the composition is applied, without detrimental irritation.

The compositions of the present invention are in convenient form for topical application of the anesthetic agents, thereby enabling such anesthetics to penetrate the dermis, for example, intact skin or a mucous membrane. Moreover, the anesthetic action is highly localized. Because the drug is substantially microdispersed in the carrier, it is more readily available for permeation into the skin or dermal membrane.

It still further has surprisingly been found that the use of two different local anesthetic agents, the first in base form and the second in acid-addition

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salt form, in a finite, flexible, adhesive, pharmaceutically acceptable carrier, including a solvent for the anesthetic agents, permits the attainment of anesthetic agent concentrations in the final product of up to 50% by weight in microdispersed form, without crystallization of the anesthetic agents which can cause irritation of the skin or other dermal membrane.

Thus, in one embodiment, the present invention is in convenient form for topical application of the anesthetic agents, thereby enabling such anesthetics to penetrate intact skin or mucous membranes and have a highly localized effect. Furthermore, the combination of the salt and base forms, advantageously results in rapid onset of anesthetic action with prolonged anesthetic effect.

Summary of the Invention

The invention relates to a flexible, finite bioadhesive composition, for topical application comprising:

a therapeutically effective amount of at least one local anesthetic or other pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the anesthetic or other pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent based on the weight of the whole composition of a plasticizer for the bioadhesive;

in admixture with the anesthetic agent or other pharmaceutically active agent in the solvent, a flexible, finite, pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20

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to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is present in non-crystallized form in the composition.

In another embodiment, the flexible, finite composition of the invention is comprised of two anesthetic agents, that is:

a therapeutically effective amount of a first local anesthetic agent in base form;

a therapeutically effective amount of a different, second local anesthetic agent in acid-addition salt form;

a solvent for the first and second local anesthetic agents, preferably in an amount from about 5 to about 70 weight percent based on the weight of the whole composition; and

in an admixture with the anesthetic agents and the solvent, a pharmaceutically acceptable adhesive, preferably a bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is preferably substantially free of water, substantially water insoluble and self-adhesive; and wherein the anesthetic agents preferably are in non-crystallized form in the composition.

The compositions of the invention may be further include a backing material which conforms to the size and shape of a single dosage of the composition.

The present invention further relates to a method of administering one or more pharmaceutically active agents in a bioadhesive to a subject comprising the steps of:

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providing a composition comprising a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures; a pharmaceutically acceptable solvent for the pharmaceutically active agent, preferably in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent preferably including about 5 to about 50 weight percent of a plasticizer for the bioadhesive; and in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition; wherein said composition is substantially free of water, is substantially water insoluble and is self-adhesive; and wherein the pharmaceutically active agent is in non-crystallized form in the composition; and

contacting an area of skin or mucous membrane with the composition to administer the pharmaceutically active agent.

The invention further relates to a method of administering two local anesthetic agents to a subject comprising the steps of:

providing a composition comprising a therapeutically effective amount of a first local anesthetic agent in base form; a therapeutically effective amount of a different, second local anesthetic agent in acid-addition salt form; a pharmaceutically acceptable solvent for the anesthetic preferably in an amount which ranges from about 50 to about 70 weight percent based on the weight of the whole composition, said solvent preferably including about 5 to about 50 weight percent of a plasticizer for the bioadhesive carrier; and in admixture with the

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pharmaceutically active agent in the solvent, a pharmaceutically acceptable preferably polysaccharide bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition; wherein said composition is preferably substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is in non-crystallized form in the composition; and

contacting an area of skin or mucous membrane with the composition thereby administering the local anesthetic agent.

The compositions of this invention permit a far higher loading of drug than conventional dosage forms. This loading in the case of anesthetic agents can result in an extent (depth) of anesthesia which numbs the teeth when applied buccally, not a typical result for a topical anesthetic cream or ointment.

Detailed Description of the Invention

This invention provides a composition which adheres to an area of the skin or mucosa, and permits delivery at elevated levels of pharmaceutical agent or a combination of agents to produce a local or systemic effect over a prolonged period of time.

In accordance with one embodiment of the present invention, a local anesthetic in solution with a solvent for the anesthetic, containing a plasticizer for the adhesive, is in admixture with a pharmaceutically acceptable adhesive, which is preferably a bioadhesive, and more preferably a polysaccharide bioadhesive, is provided in a finite, flexible form for topical application to the skin or dermal membrane of a mammal.

In accordance with a further embodiment of the present invention, a combination of local anesthetic agents, a solvent for the anesthetic agents

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and a flexible, preferably adhesive pharmaceutically acceptable adhesive carrier is provided for topical application to the skin or mucosa of a mammal.

The anesthetic agents of this invention are those known, or of a type known, in the art. The local anesthetic bases encompassed by this invention are weak organic bases which are lipophilic in nature and thus poorly soluble in water. However, these bases will react with organic or inorganic acids to form acidic, water soluble acid-addition salts.

The base form and the salt form of the anesthetic agent incorporated in the combination composition of this invention must be different anesthetic agents, to achieve maximum duration of the anesthetic effect. By the term "different" is meant that the salt form in any combination is not a salt of the base form used in the given combination.

Local anesthetic agents suitable for use in the practice of this invention include amides and esters. Examples of the amides are lidocaine, prilocaine, mepivacaine, bupivacaine, dibucaine and etidocaine. Esters include procaine, tetracaine, propoxycaine, chloroprocaine, benzocaine, butamben picrate, cocaine, hexylcaine, piperocaine, oxyprocaine and proparacaine. Other suitable local anesthetics for use in the practice of this invention include cyclomethycaine, dimethisoquin, ketocaine, diperodon, dyclonine and pramoxine, all typically administered in the form of the acid addition hydro-chloride or sulfate salts.

The acid-addition salts of the present invention are any non-toxic, pharmaceutically acceptable organic or inorganic salts. Typical inorganic salts are the hydrogen halides, especially the hydrochlorides, carbonates, borates, phosphates, sulfates, hydrogen sulfates, hydrobromides, nitrates,

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sulfides, and arsenates. Typical organic salts are salts of mono- and polycarboxylic acids such as the citrate, tartrate, malate, cinnamate, oxalate, formate, succinate and phthalates.

The solvents for the anesthetic agents or other drugs are non-toxic, pharmaceutically acceptable substances, preferably liquids, which do not substantially negatively affect the adhesion properties of the system and in which the anesthetic agents or other drugs in the amounts employed are fully soluble. Preferably, the solvent is or is primarily a polyhydric alcohol or combination of polyhydric alcohols, particularly when the adhesive is a gum. The term polyhydric alcohol means any organic polyol. Other suitable solvents include carboxlyic acids and their derivatives and analogs such as fatty acids such as oleic acid, linoleic acid, capric acid and the like, as well as fatty esters or alcohols and ketones such as polyvinylpyrrolidone. Further suitable solvents include other non-toxic, non-volatile solvents commonly used in dermal or transdermal compositions for dissolving like compounds. As apparent to one skilled in the art what is a suitable solvent varies with the solubility of the drug in question.

The above mentioned polyhydric alcohols may include those having 2 to 6 alcoholic hydroxyl groups. Such polyhydric alcohols include glycols, triols and polyols having 4 to 6 alcoholic hydroxyl groups. Typical of said glycols are glycols containing 2 to 6 carbon atoms, e.g. ethylene glycol, propylene glycol, butylene glycol, polyethylene glycol (average molecular weight about 200 - 8,000, preferably about 200 to 6,000), dipropylene glycol, hexylene glycol, polyoxyethylene, polypropylene glycol, sorbitol, and the like. Examples of said triols include glycerin,

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trimethylolpropane. Said polyols are exemplified by cycloalkanepolyols such as polyols derived from monosaccharides such as sorbitol (sorbit). These polyhydric alcohols may be used either singly or in combination (preferably, of two or three). Thus, for example, glycerin alone or a mixture of glycerin and butylene glycol is employed. In general, when an anesthetic agent, especially an anesthetic base is used, there are limits to the amounts of lipophilic polyhydric alcohols containing more than two alcoholic hydroxyl groups that can be present in the solvent and yet not result in precipitation of the drug as crystals.

Among those polyhydric alcohols, those which satisfy the requirements relevant to the adjustment and maintenance of softness of the external drug of the invention, the compatibility or co-dispersibility with the other components, and provide a proper consistency of the composition, may be freely used. Those which are low in volatility and plastic, are generally preferred and, in this regard, dipropylene glycol, glycerin, propylene glycol, butylene glycol, and sorbitol are appropriate solvents, according to the invention. Since solvent is to remain, at least in part, in the composition, the solvent should include components that do not substantially volatilize under the drying conditions used in preparing the composition. In other words, the solvent for the drug should be non-volatile.

Solvent selection for a single anesthetic agent or a combination of anesthetic agents in either the free base form or in the acid-addition salt form, depends on the form of the anesthetic agent, namely whether it is in free base form or acid-addition salt form. Solvents for the salt form of anesthetic agent are polar organic solvents. Polar organic solvents

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are preferably polyhydric alcohols, as discussed above. Various other solvents suitable for either the base or acid-addition form of the anesthetic agent are those solvents known to dissolve either or both of these two types of forms including cyclic ketones such as 2-pyrrolidone; N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted alkyl-azacycloalkyl-2-ones (azones) dimethylformadide, and dimethylsulfoxide.

Other suitable solvents for the free base form of the anesthetic agent are cell envelope disordering compounds known to be useful in topical pharmaceutical preparation, which compounds are thought to assist in skin penetration by disordering the lipid structure of the stratum corneum cell-envelopes. Some of these compounds are generally encompassed by the formula:

R-X

wherein R is a straight-chain alkyl of about 7 to 16 carbon atoms, a non-terminal alkenyl of about 7 to 22 carbon atoms, or a branched-chain alkyl of from about 13 to 22 carbon atoms, and X is -OH, -$COOCH_3$, -$COOC_2H_5$, -$OCOCH_3$, -$SOCH_3$, -$P(CH_3)_2O$, -$COOCH_2H_4OC_2H_4OH$, -$COOCH(CHOH)_4CH_2OH$, -$COOCH_2CHOHCH3$, -$COOCH_2CH(OR")CH_2OR"$. -$(OCH_2CH_2)_mOH$, -COOR', or -$CONR'_2$ where R; is -H, -CH_3, -C_2H_5, -C_3H_7 OR -C_2H_4OH; R" is -H, or a non-terminal alkenyl of about 7 to 22 carbon atoms; and m is a positive integer from 2 to 6; provided that when R" is an alkenyl and X is -OH or -COOH, at least one double bond is in the cis-configuration.

Although the exact amount of the polyhydric alcohol or alcohols in the composition depends on the nature of other components, and therefore cannot be stated in specific terms, the proportion may range

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from about 5 to about 70 weight percent based on the whole composition.

The solvent includes from about 5% to about 50% and more preferably about 10% to about 30% of a polyhydric alcohol known to plasticize the bioadhesive carrier. A particularly useful plasticizer is glycerine.

The high concentrations of microdispersed drug, for example anesthetic agent, of this invention are achieved typically by mixing the anesthetic agents with the solvent, preferably at an elevated temperature, for example about 70° to 100°C, to obtain a mixture, preferably a solution, of the anesthetic agents which is then added to the pharmaceutically acceptable adhesive.

Preferably the anesthetic agent is substantially dissolved in the solvent so that when mixed with the adhesive, the anesthetic is microdispersed in the composition. The term "microdispersed" is intended to mean that in the solvent, and subsequently in the carrier, there is an intimate dispersion of the anesthetic agent at the molecular or ionic level, such that crystals of the anesthetic agent cannot be detected using a microscope having a magnification of roughly 25X. As such, the pharmaceutically active agent is in "non-crystallized" form when in the compositions of the present invention.

It has been discovered that high concentrations of a combination of microdispersed anesthetic agents, namely up to 50% by weight of the finite, flexible composition, require the use of a solvent as herein described. Omission of the solvent in the procedure of Example 1 below yields a product filled with crystals or crystalline mass.

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In particularly preferred embodiments of this invention, the free base local anesthetic agent is selected from the group comprising lidocaine, procaine, propoxycaine, mepivacaine, prilocaine, dyclonine, pramoxine, benzocaine and chloroprocaine. The salt form is preferably one selected from the group comprising prilocaine, tetracaine, bupivacaine, dyclonine, dibucaine, etidocaine and lidocaine salts. The aforementioned bases and salts can be used alone or in combination with other anesthetic bases and salts as needed to achieve therapeutically affective levels when administered transdermally.

The term "therapeutically effective amount" is intended to mean the amount of drug as a minimizer sufficient to produce a therapeutic effect, for example, an anesthetic effect when applied topically. These amounts are known in the art or may be determined by methods known in the art, and typically range from about 1 to 20,000 mg per human adult and preferably about 10 to 10,000 mg and most preferably range from about 20 to 5,000 mg of the anesthetic agent per application, depending upon the anesthetic agents chosen, and whether the skin or mucous membrane is the site of action. The only upper limit on the amount of anesthetic in the composition is that the preparation is substantially free of crystals of anesthetic agent or other drug and the amount of solvent used is not sufficient to undesirably affect the adhesive properties of the whole composition. Thus, the single ingredient anesthetic agent contains as a minimizer a therapeutically effective amount of anesthetic agent within the foregoing range.

The concentration as well as the quantity of anesthetic per square centimeter can be varied independently in order to achieve the desired effect. Higher concentrations of anesthetic base contained in

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a dosage form of decreased thickness will result in a anesthetic with fast onset and short duration. High concentrations of the anesthetic base contained in a dosage form of increased thickness (higher mg of anesthetic per square centimeter) will result in potent anesthesia with fast onset and long duration. Low concentrations of the anesthetic base in a dosage form of decreased thickness will result in mild anesthesia with longer onset and short duration. Low concentrations of the anesthetic base contained in a dosage form of increased thickness will have mild anesthesia with longer onset and longer duration. As shown in the above explanation, the ability to vary the concentration of anesthetic from very low (about 1%) to high (40% or higher) of the total composition, when combined with the ability to coat thin (about 0.001 inches) or thick (about 0.500 or more inches) enables the practitioner of the invention to vary the dosage of the system as needed for particular anatomical sites of interest.

As a general rule, in the case of mucosal application, the anesthetic drug selected, the concentration and thickness and the duration of the application is determined based upon the anesthetic's ability to penetrate the mucosa and to be at peak effectiveness within about 2 to 30 minutes. The duration of the effect of the anesthetic on the oral mucosa should range between about 2 to 240 minutes, depending on the anesthetic agent selected, the concentration of the anesthetic and the thickness of application. Longer or shorter durations can also be selected dependent on need, as will be apparent to one skilled in the art.

The ratio of the free base form to the salt form in the alternate composition of this invention will depend on several factors, namely: (1) the

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identity of the salt and base used; (2) the desired duration of action; and (3) the desired rapidity of anesthetic effect. As a general rule in the case of mucosal application, the ratios of base to salt are such that the free base form preferably should penetrate the mucosa and be at its peak effectiveness within about a 2 to 30 minute period, whereas, the salt form should preferably penetrate the mucosa and be at its peak effectiveness within a period of about 10 to 75 minutes. The duration of the effect of these on the oral mucosa will range between about 2 to 240 minutes depending on the base/salt combination selected and the length of application time.

The term "onset of anesthesia" is intended to mean the time to peak effect on the individual nerves. Onset of anesthesia principally depends upon the lipid solubility, molecular size, and quantity of available, un-ionized form of the local anesthetic. Thus, anesthetics with a high lipid solubility or a low pK_a, or both, have a more rapid onset of anesthesia.

The term "duration of anesthesia" as used herein means the period of time during which the local anesthetic measurably blocks nerve conduction. The foregoing depends upon all of the factors listed for onset of anesthesia, as well as on the extent of protein binding of the anesthetic agent.

The anesthetic agent free base can penetrate intact skin to a limited degree, and will more rapidly penetrate the skin if the keratin layers are abraded. In the case of the oral mucosa, the anesthetic base will penetrate much more readily due to the different keratin composition and the resulting difference in the hydrophilicity as compared to the stratum corneum of intact skin.

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As a general rule, the salt forms of the aforementioned anesthetics do not appreciably penetrate intact skin, but the un-ionized base form do penetrate to a limited degree. Both forms, salt and base, will penetrate abraded keratin layers. The salt as well as the base will penetrate, to a differing degree, the buccal mucosa due to the buccal mucosa's hydrophilicity, as compared to the stratum corneum of intact skin. Generally, the higher the lipid content of the mucosal membrane, the more rapidly the base form of the anesthetic agent will be absorbed. Therefore, when the composition is used for application to oral or buccal mucosa, the different lipid contents of the gum (gingiva) and the alveolar mucosa must be kept in mind in order to obtain the optimal penetration rate.

Although applicants do not intend to be bound by any theory or proposed mechanism of operation, it is believed that the base which is lipid soluble has a rapid onset of anesthesia since it enters the lipo-protein nerve membrane preventing the depolarization and ion exchange involved in stimulus conduction. On the other hand, the salt which is not lipid soluble, penetrates to the lipo-protein nerve membrane only after the buffering capacity of the skin or mucosal tissue converts the salt to the base, the final result being a delayed onset of anesthesia.

The salts of this invention in the combination composition are selected on the basis of onset of anesthesia and duration of anesthesia. Adjusting the ratio of base to salt affects the relative onset as well as the duration of anesthetic action. The greater the amount of anesthetic agent having a rapid onset of action, the shorter the onset of anesthesia. Similarly, the greater the amount of the anesthetic agent having a prolonged duration of

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anesthesia, the more prolonged the duration of anesthesia. More than two anesthetic agents may be used to have a broader spectrum of activity. Moreover, the composition can include other drugs used concomitantly.

Generally, the concentration of solubilized anesthetic agent can range, on a weight basis, between about 1 and about 50% or more, preferably between 2.5 and 40% and more preferably between 5 and 30% of the total weight of the composition. In a preferred embodiment of the combination of this invention, the concentration of dissolved base is 20% by weight of the total composition. The base used in the preferred embodiment for a single ingredient preparation is lidocaine.

Generally, for the hydrochloride salts the ratio by weight of base to salt is about 90:10 to about 60:40, preferably about 75:25 to about 60:40, and more preferably about 70:30 to about 60:40. For other salts, the ratios are comparable based on relative molar amounts. In a preferred embodiment of the invention, the ratio is about 2:1 base to salt, respectively. The base used in the preferred embodiment is lidocaine and the preferred salt is a salt of prilocaine, bupivacaine, dyclonine, mepivacaine, or tetracaine, preferably the hydrochloride salt.

Table 1 below summarizes the peak and duration of action of selected local anesthetics based primarily on application to skin or mucous membranes:

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TABLE 1

Local Anesthetic	Minimum Adult Dose	Maximum Adult Dose (mg)	Peak Effect (minutes)	Duration of Effect (minutes)
Dibucaine		25	< 15	120-240
Lidocaine		750	2-5	30-60
Benzocaine		5000	1	30-60
Cocaine		50	2-5	30-120
Tetracaine		50	3-8	30-60
Dyclonine		100	< 10	< 60
Pramoxine		200	3-5	NA

NA: Not Available.

Source: Drug Facts and Comparisons, 1990 edition, J.B. Lippincott Company, St. Louis, MO. Page 601.

In general, the relative speed of onset of anesthesia and duration of anesthesia for any given form of anesthetic agent is available in the literature or can be calculated by standard tests.

Onset time, as well as duration of anesthesia, will vary from individual to individual as well as on the basis of the site of application. When applying the composition to highly keratinized dermal tissues, the onset of anesthesia may take as long as 2 to 4 hours.

The composition of this invention can be manufactured by numerous methods known in the art which permit the achievement of a microdispersed anesthetic agent, including extruding, molding, solvent casting, coating, and all other methods which employ a solvent to disperse the drug in a carrier prior to shaping of the carrier.

Contrary to the typical method for manufacturing a drug in a solvent containing adhesive, the preparation is either not dried so as to force removal of the solvent from the adhesive or a solvent

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is used which is not substantially evaporated during the conditions of manufacture. The composition in question can then be applied to a flexible backing or a combination of backings which will serve to define the size and shape of a single dosage of the composition. Such backing may be a three dimensional material such as paper, a non-woven fabric or natural or synthetic polymer substance. Methods of coating backings are well-known in the art and include techniques involving Mayer rod, gravure, and knife-over roll. Further processing of backings may involve the use of converting equipment for die cutting.

The finished dosage form will be substantially occlusive to water permeation in in-vivo.

For example, the anesthetic agents are dissolved in a solvent, preferably a polyhydric alcohol, and then the resulting mixture is added to an adhesive prior to being placed onto the flexible form or backing. The final form in which the composition of the invention will be applied depends upon the anatomical site of application.

The phrase "flexible, finite" with reference to the pharmaceutically acceptable carrier, is intended to mean a solid capable of conforming to a surface with which it comes into contact and capable of maintaining the contact so as to facilitate topical application without any adverse physiological response, and which can be used to establish the compositions herein in their preferred solid form without being appreciably decomposed by aqueous contact during administration to a patient.

An important characteristic of the present invention relates to the substantially water-free and water-insoluble nature of the composition. By the term "substantially water-free" is meant that the

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preparation contains less than about 10% by weight water, and preferably less than 5%, and most preferably less than 3%. In general, it is desirable to avoid the addition of water entirely and to eliminate, as far as possible, the presence of water in the other ingredients of the composition. By the term "substantially water insoluble" is meant that the composition remains "finite" and does not generally detach from the skin or other dermal membrane at the site of application and under the conditions of regular, intended use for a period of at least 3 hours. The advantages to be derived from the substantially water-free and water-insoluble nature of the compositions of the present invention include achievement of higher concentrations of drug. Another advantage of these compositions is minimization of precipitation of drug into crystals, which precipitation affects processing of the composition, affects rate of delivery of the drugs and in certain cases can affect sensitivity of the subject to be treated to the drug.

Suitable adhesive carriers include any of the non-toxic polymers, particularly those of the type used to carry drugs for transdermal delivery including natural or synthetic elastomers, such as polyisobutylene, styrene, butadiene, styrene isoprene block copolymers, acrylics, urethanes, silicones, styrene butadiene copolymers, methyl acrylate copolymers, acrylic acid, polyacrylates, and polysacchrides such as, karaya gum, tragacanth gum, pectin, guar gum, cellulose, and cellulose derivatives such as methyl cellulose, propyl cellulose, cellulose acetate and the like, along with other substances known for use in transdermal preparations capable of forming a solid colloid that can adhere to skin and mucosa, used alone or in

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combination with other suitable carriers. A particularly preferred carrier is a bioadhesive and more preferably a polysaccharide bioadhesive for application to the dermis, preferably the mucosa. The adhesive can be modified so as to adhere to the skin or mucosal tissue, depending on the intended application site.

The term "adhesive" as used herein means a substance, inorganic or organic, natural or synthetic, that is capable of surface attachment to the intended application site.

The term "bioadhesive" as used herein means an adhesive which attaches and preferably strongly attaches to a live or freshly killed biological surface such as skin or mucosal tissue upon hydration. Indeed, to qualify as a bioadhesive, a substance must be capable of maintaining adhesion in moist or wet in *in-vivo* or *in-vitro* environments. The final composition of the present invention is "self-adhesive" in that it attaches to the site of interest without the need to reinforce its attachment by way of another adhesive which is applied to the composition.

The strength of adherence can be measured by standard tests for measuring the force, e.g. in dynes per square centimeter, as disclosed in U.S. 4,615,697. Suitable bioadhesives include those prepared from optionally partially esterified or etherified polyacrylic acid polymers, including but not limited to, polyacrylic acid polymers lightly cross-linked with a polyalkenyl polyether or other cross-linking agent such as those commercially available from B.F. Goodrich, Cincinnati, Ohio, under the trademarks Carbopol 934, 934P, 940 and 941.

Other suitable bioadhesives include natural or synthetic polysaccharides. The term "polysaccharide" as used herein means a carbohydrate

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decomposable by hydrolysis into two or more molecules of natural or synthetic monosaccharides or their analogs or derivatives. Suitable polysaccharides include cellulose derivatives such as methylcellulose, cellulose acetate, carboxymethylcellulose, hydroxyethylcellulose and the like. Other suitable bioadhesives are pectin, a mixture of sulfated sucrose and aluminum hydroxide, hydrophilic polysaccharide gums such as natural plant exudates, including karaya gum, ghatti gum, tragacanth gum, xanthan gum, jaraya gum and the like, as well as seed gums such as guar gum, locust bean gum, psillium seed gum and the like.

In addition to the above ingredients, there may also be incorporated other additives selected from among the various pharmaceutically acceptable additives available to those skilled in the art. These additives include binders, stabilizers, preservatives, penetration enhancers, flavorings and pigments. In the preferred embodiment, the compositions of the present invention also contain a binder or emulsifier such as lecithin which promotes dispersion of the other ingredients having differing solubilities, thereby enhancing the uniform consistency of the final composition.

The composition is administered in appropriate sizes, typically having a surface area of from about 0.1 to about 200 cm^2 or conveniently 0.2 to 100 cm^2. The anesthetic agent is loaded into the composition in as high a concentration as necessary to effect therapy, e.g., in a range from about 0.1 mg/cm^2 to about 50 or more mg/cm^2.

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In general, the composition can have the following types and amounts of ingredients:

Ingredient	Typical Range (% by weight)	Preferred Range (% by weight)	Optimum Range (% by weight)
Adhesive	15 to 60	20 to 50	20 to 35
Solvent	2 to 75	5 to 70	20 to 40
(plasticizer included in solvent)	1 to 50	5 to 50	10 to 30
Anesthetic agent (single ingredient)	1 to 50	5 to 40	10 to 30
Anesthetic agent (multiple ingredient)	1 to 50	5 to 40	10 to 30
(a) Anesthetic base	.7 to 50	5 to 40	7 to 20
(b) Anesthetic salt	.3 to 25	2 to 30	3 to 20

In one embodiment, the flexible, finite, bioadhesive composition for topical application comprises:

a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent of a plasticizer for the bioadhesive;

in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active

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agent is present in non-crystallized form in the composition.

In another embodiment, the flexible, finite composition of the invention comprises;

a composition for topical application comprising a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, second local anesthetic agent in salt form in a pharmaceutically acceptable, adhesive-containing carrier containing a solvent for the first and second local anesthetic agents.

wherein the composition is preferably substantially free of water, and substantially water insoluble and is self-adhesive; and wherein the anesthetic agents are in non-crystallized form in the composition.

Preferably, the pharmaceutically acceptable solvent is in an amount from about 20 to about 53 weight percent based on the weight of the whole composition of which the plasticizer represents about 10 to about 30 weight percent based on the weight of the whole composition, and the bioadhesive carrier is in an amount from about 20 to about 34 weight percent based on the weight of the whole composition. More preferably, the composition is comprised of 20 to 34 weight percent of karaya gum, about 20 to 53 weight percent of at least one glycol, and about 10 to 25 weight percent of lidocaine base and is further comprised of a binder in or emulsifier an amount sufficient to bind the other ingredients.

Another embodiment of the invention relates to a method of administering one or more local anesthetics to a subject in need of such local anesthetic. The term "administering" is intended to mean any mode of application which results in the physical contact of the composition with an anatomical

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site in need of anesthesia. The term "subject" is intended to include all warm-blooded mammals, including humans.

The following examples will further describe the instant invention, and are used for the purposes of illustration only, and should not be considered as limiting in any way the invention being disclosed herein. Percent (%) as used in these examples refer to percentage of the liquid formulation on a weight to weight basis and temperatures are given in degrees celsius (°C).

Example 1

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	11
Solvent (propylene glycol)	7
Solvent/plasticizer (glycerin)	19
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (prilocaine hydrochloride)	14

The final product is manufactured by first blending the lidocaine base, prilocaine hydrochloride, propylene glycol, lecithin and glycerin at about 70 to 90°C until all of the drug is dissolved. The solution is then cooled to 20 to 35°C prior to adding the karaya gum. Once the karaya gum is added, the final composition is applied to a suitable backing material such as a non-woven, polyester film (for example, the film sold under the trademark Sontara 8100, manufactured by DuPont de Nemours, E.I. and Co., Wilmington, DE) and warmed to about 100°C to accelerate the formation of the gel into its final, finite form.

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Example 2

Ingredient	% (w/w)
Adhesive (karaya gum)	30
Solvent/plasticizer (glycerin)	30
Solvent (propylene glycol)	39
Anesthetic agent base (lidocaine base)	0.7
Anesthetic agent salt (prilocaine hydrochloride)	0.3

The procedure set forth in Example 1 is used with appropriate substitutions of quantities to prepare this formulation.

Example 3

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	4
Solvent (propylene glycol)	3
Solvent (isocetyl alcohol)	7
Solvent/plasticizer (glycerin)	26
Anesthetic agent base (lidocaine base)	26
Anesthetic agent salt (tetracaine hydrochloride)	13

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 4

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Solvent (propylene glycol)	29
Solvent/plasticizer (glycerin)	4
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (dyclonine hydrochloride)	12

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

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Example 5

Ingredient	% (w/w)
Adhesive (karaya gum)	26
Binder (lecithin)	10
Solvent (propylene glycol)	7
Solvent (butylene glycol)	17
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (lidocaine base)	20
Anesthetic agent salt (dyclonine hydrochloride)	10

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 6

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Binder (lecithin)	12
Solvent (propylene glycol)	8
Solvent/plasticizer (glycerin)	13
Anesthetic agent base (lidocaine base)	27
Anesthetic agent salt (bupivacaine hydrochloride)	13

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 7

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Binder (lecithin)	12
Solvent (propylene glycol)	8
Solvent/plasticizer (glycerin)	13
Anesthetic agent base (lidocaine base)	13
Anesthetic agent salt (bupivacaine hydrochloride)	27

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

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Example 8

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	11
Solvent (propylene glycol)	7
Solvent/plasticizer (glycerin)	19
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (mepivacaine hydrochloride)	14

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 9

Ingredient	% (w/w)
Adhesive (Carbopol 934P, a polycarboxylic acid sold by B.F. Goodrich Chemical Company)	20
Solvent (propylene glycol)	15
Solvent/plasticizer (glycerin)	20
Anesthetic agent base (lidocaine base)	30
Anesthetic agent salt (bupivacaine hydrochloride)	15

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 10

Ingredient	% (w/w)
Adhesive (karaya gum)	24
Solvent (propylene glycol)	3
Solvent/plasticizer (glycerin)	14
Solvent (isocetyl alcohol)	7
Binder (lecithin)	4
Anesthetic agent base (lidocaine base)	32
Anesthetic agent salt (tetracaine hydrochloride)	16

The above formulation is prepared by a procedure which is analogous to that set forth in Example 1.

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The addition of up to 2% by weight water in this formulation did not result in precipitation of the anesthetic agent(s) prior to addition of the karaya gum. The addition of 3% to 10% water results in increased precipitation, which at 10% water results in a crystalline mass.

Example 11

Ingredient	% (w/w)
Adhesive (tragacanth gum)	24
Adhesive (pectin)	5
Solvent (propylene glycol)	12
Solvent/plasticizer (glycerin)	12
Anesthetic agent base (mepivacaine base)	35
Anesthetic agent salt (lidocaine hydrochloride)	12

The above formulation is prepared by a procedure analogous to that of Example 1.

Example 12

Ingredient	% (w/w)
Bioadhesive (karaya gum)	33
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The final product is manufactured by first blending the lidocaine base, lecithin, propylene glycol, dipropylene glycol and glycerine at about 70 to 90°C until all of the drug is dissolved. The solution is then chilled to about 20 to 40°C prior to adding the karaya gum. Once the karaya gum is added, the final composition is applied to a suitable backing material such as a non-woven polyester film (for example the film sold under the trademark Sontata 8100 manufactured by DuPont de Nemours, E.I. and Co., Wilmington, DE) and warmed at about 70 to 130°C to accelerate the formation of the gel into its final

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solid form. This gel can be directly applied to the oral mucosa or overlaid with a skin contact adhesive for skin adhesion.

Example 13

Ingredient	% (w/w)
Bioadhesive (karaya gum)	33
Binder (lecithin)	5
Solvent (propylene glycol)	7
Solvent (dipropylene glycol)	12
Solvent/plasticizer (glycerin)	33
Anesthetic agent base (lidocaine base)	10

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 14

Ingredient	% (w/w)
Bioadhesive (karaya gum)	35
Binder (lecithin)	5
Solvent (propylene glycol)	7
Solvent (dipropylene glycol)	12
Solvent/plasticizer (glycerin)	36
Anesthetic agent base (lidocaine base)	5

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 15

Ingredient	% (w/w)
Bioadhesive (karaya gum)	30
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	15
Anesthetic agent base (lidocaine base)	25

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

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Example 16

Ingredient	% (w/w)
Bioadhesive (karaya gum)	20
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	10
Solvent/plasticizer (glycerin)	10
Solvent (benzyl alcohol)	5
Anesthetic agent base (lidocaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 17

Ingredient	% (w/w)
Bioadhesive (karaya gum)	25
Binder (lecithin)	8
Solvent (isocetyl alcohol)	5
Solvent (propylene glycol)	12
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (prilocaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 18

Ingredient	% (w/w)
Bioadhesive (karaya gum)	25
Binder (lecithin)	4
Solvent (propylene glycol)	6
Solvent (benzyl alcohol)	10
Solvent (dipropylene glycol)	10
Solvent/plasticizer (glycerin)	5
Anesthetic agent base (tetracaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

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Example 19

Ingredient	% (w/w)
Bioadhesive (karaya gum)	30
Binder (lecithin)	8
Solvent (propylene glycol)	12
Solvent (dipropylene glycol)	25
Solvent (benzyl alcohol)	5
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (dibucaine base)	10

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 20

Ingredient	% (w/w)
Bioadhesive (karaya gum)	28
Bioadhesive (Carbopol 934 Trademark of B.F. Goodrich)	2
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	15
Binder (lecithin)	9
Anesthetic agent base (lidocaine base)	25

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation. The only difference is that the carbopol 934 is added to the original blend prior to heating it.

Example 21

Ingredient	% (w/w)
Bioadhesive (tragacanth gum)	27
Bioadhesive (pectin)	6
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The procedure of Example 12 is used with the solvents and anesthetic agent base added in the initial step followed later by the adhesives addition.

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Example 22

Ingredient	% (w/w)
Bioadhesive (cellulose acetate)	27
Solvent (dipropylene glycol)	33
Anesthetic agent base (prilocaine base)	20
Solvent/plasticizer (glycerin)	10

This formulation is prepared according to the procedure which is analogous to the procedure set forth in Example 1.

Example 23

Ingredient	% (w/w)
Bioadhesive (Xanthan gum)	27
Bioadhesive (Pectin)	6
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The procedure of Example 12 is followed with the appropriate substitution of ingredients.

Example 24

Ingredient	% (w/w)
Drug (miconazole nitrate)	2
Solvent (propylene glycol)	67
Thickener (hydroxymethylcellulose)	1
Adhesive (karaya gum)	30

This formulation is prepared by dispersing the hydroxymethylcellulose into the propylene glycol. Once the hydroxymethylcellulose is dispersed, the drug is added at a temperature between 50 and 80°C and mixed until dissolved. The sample is then cooled to approximately 20 to 35°C prior to adding the karaya gum. Once the karaya gum is added, the formulation is applied to a sheet of backing material, then the individual dosage forms are cut to the desirable shape to contain the desired amount of drug.

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Example 25

Ingredient	% (w/w)
Drug (miconazole base)	5.0
Solvent (dipropylene glycol)	32.5
Plasticizer (glycerin)	32.5
Adhesive (karaya gum)	30.0

Example #25 is prepared just as Example #24.

Example 26

Ingredient	% (w/w)
Drug (miconazole base)	5.0
Solvent (dipropylene glycol)	17.5
Plasticizer (glycerin)	30.0
Solvent (propylene glycol)	7.0
Binder (lecithin)	10.5
Adhesive (karaya gum)	30.0

Example #26 is prepared just as Example #24.

Example 27

Ingredient	% (w/w)
Drug (miconazole base)	10
Solvent (propylene glycol)	35
Plasticizer (glycerin)	25
Adhesive (karaya gum)	30

Example #27 is prepared just as Example #24.

Example 28

Ingredient	% (w/w)
Drug (clotrimazole)	1.0
Solvent (propylene glycol)	41.3
Plasticizer (glycerin)	24.7
Adhesive (karaya gum)	33.0

Example #28 is prepared just as Example #24.

Example 29

Buccal formulations containing, respectively, 5%, 10%, 20%, and 25% lidocaine were prepared according to the procedure of foregoing

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examples. A patch containing no drug (placebo patch) was also used.

The patches were tested on nine human subjects. The patch was applied to the buccal cavity of the mouth and removed after 15 minutes. The patch was placed on the gingival surface, since the gingival surface was found to be the best site to examine for a dose response relationship.

The extent of anesthesia at 5, 10, 15, 30, 45, and 60 minutes after application was determined by measurement of the extent of anesthesia. The exent of anesthesia was determined by a base line discomfort tolerance limit determined by application of a tip of a periodontal probe, to the treated surface. The patient was asked to determine the depth penetration they could tolerate at the various timed intervals.

Five minutes after initiation of treatment there was no statistical differences in pain toleration between the treatment groups, including the placebo and no-patch.

At ten minutes post application the 25% lidocaine patch produced the greatest mean change in response threshold followed by the 10 and 20% lidocaine patches. There was little difference between the 5% lidocaine and placebo patch. Lidocaine concentrations greater than 5% were necessary to produce a significant increase in pain threshold responses, and there was a distinct trend in dose proportionality in the range of 10% - 25% lidocaine.

The median change in response thresholds for the gingival surface group displayed the same relationship. The 25% lidocaine patch provided the greatest anesthetic effect followed by the 10% and 20% lidocaine patches.

When all the sites were combined into one group and the median change from baseline was plotted,

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the graph revealed a dose response profile where the doses appear in order of concentration from 10 to 30 minutes post application. The 25% lidocaine patch provided the greatest increase in response threshold. The 10% and 20% lidocaine patch responses were similar with the 20% lidocaine patch being slightly better.

There were no signs of inflammation, tissue damage, or other adverse effects associated with application of the patches.

Similar studies were conducted in which the patch was applied to the gingival sulcus and the interproximal sulcus.

Certain of the lidocaine preparations were distinguised in that they resulted in the numbness of the teeth, an effect not generally observed with topical anesthetics applied in fluid vehicles.

The foregoing examples are illustrative embodiments of the invention and are merely exemplary. A person skilled in the art may make variations and modification without departing from the spirit and scope of the invention. All such modifications and variations are intended to be included within the scope of the invention as described in this specification and the appended claims.

Indeed, the present invention is intended to encompass and be suitable for any pharmaceutically active agent, especially any of the following drugs as the pharmaceutically active agent in the composition:

1. Analgesic anti-inflammatory agents such as, acetaminophen, aspirin, salicylic acid, methyl salicylate, choline salicylate, glycol salicylate, l-menthol, camphor, mefenamic acid, fluphenamic acid, indomethacin, diclofenac, alclofenac, ibuprofen, ketoprofen, naproxene, pranoprofen, fenoprofen, sulindac, fenbufen, clidanac, flurbiprofen, indoprofen, protizidic acid, fentiazac, tolmetin,

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tiaprofenic acid, bendazac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, and the like;

2. Drugs having an action on the central nervous system, for example sedatives, hypnotics, antianxiety agents, analgesics and anesthetics, such as, chloral, buprenorphine, naloxone, haloperidol, fluphenazine, pentobarbital, phenobarbital, secobarbital, amobarbital, cydobarbital, codeine, lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine, benzocaine, fentanyl, nicotine, and the like;

3. Antihistaminics or antiallergic agents such as, diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine, tripelennamine, brompheniramine, hydroxyzine, cyclizine, meclizine, clorprenaline, terfenadine, chlorpheniramine, and the like;

4. Acetonide anti-inflammatory agents, such as hydrocortisone, cortisone, dexamethasone, fluocinolone, triamcinolone, medrysone, prednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, fludrocortisone, corticosterone, paramethasone, betamethasone, ibuprophen, naproxen, fenoprofen, fenbufen, flurbiprofen, indoprofen, ketoprofen, suprofen, indomethacin, piroxicam, aspirin, salicylic acid, diflunisal, methyl salicylate, phenylbutazone, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, and the like;

5. Steroids such as, androgenic steriods, such as, testosterone, methyltestosterone, fluoxymesterone, estrogens such as, conjugated estrogens, esterified estrogens, estropipate, 17β-estradiol, 17β-estradiol esters such as 17ß- estradiol

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valerate, equilin, mestranol, estrone, estriol, 17β-estradiol derivatives such as 17β-ethinyl estradiol, diethylstilbestrol, progestational agents, such as, progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α-hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, megestrol acetate, and the like;

6. Respiratory agents such as, theophylline and β_2-adrenergic agonists, such as, albuterol, terbutaline, metaproterenol, ritodrine, carbuterol, fenoterol, quinterenol, rimiterol, solmefamol, soterenol, tetroquinol, and the like;

7. Sympathomimetics such as, dopamine, norepinephrine, phenylpropanolamine, phenylephrine, pseudoephedrine, amphetamine, propylhexedrine, arecoline, and the like;

8. Antimicrobial agents including antibacterial agents, antifungal agents, antimycotic agents and antiviral agents; tetracyclines such as, oxytetracycline, penicillins, such as, ampicillin, cephalosporins such as, cefalotin, aminoglycosides, such as, kanamycin, macrolides such as, erythromycin, chloramphenicol, iodides, nitrofrantoin, anti fungals, such as, clotrimazole, miconazole, chloramphenicol, nystatin, amphotericin, fradiomycin, sulfonamides, purrolnitrin, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; clarithromycin; and other anti-infectives including nitrofurazone, and the like;

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9. Antihypertensive agents such as, clonidine, α-methyldopa, reserpine, syrosingopine, rescinnamine, cinnarizine, hydrazine, prazosin, and the like;

10. Antihypertensive diuretics such as, chlorothiazide, hydrochlorothrazide, bendoflumethazide, trichlormethiazide, furosemide, tripamide, methylclothiazide, penfluzide, hydrothiazide, spironolactone, metolazone, and the like;

11. Cardiotonics such as, digitalis, ubidecarenone, dopamine, and the like;

12. Coronary vasodilators such as, organic nitrates such as, nitroglycerine, isosorbitol dinitrate, erythritol tetranitrate, and pentaerythritol tetranitrate, dipyridamole, dilazep, trapidil, trimetazidine, and the like;

13. Vasoconstrictors such as, dihydroergotamine, dihydroergotoxine, and the like;

14. β-blockers or antiarrhythmic agents such as, timolol pindolol, propranolol, and the like;

15. Calcium antagonists and other circulatory organ agents, such as, aptopril, diltiazem, nifedipine, nicardipine, verapamil, bencyclane, ifenprodil tartarate, molsidomine, clonidine, prazosin, and the like;

16. Anti-convulsantants such as, nitrazepam, meprobamate, phenytoin, and the like;

17. Agents for dizziness such as, isoprenaline, betahistine, scopolamine, and the like;

18. Tranquilizers such as, reserprine, chlorpromazine, and antianxiety benzodiazepines such as, alprazolam, chlordiazepoxide, clorazeptate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam, diazepam, and the like;

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19. Antipsychotics such as, phenothiazines including thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperracetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, and other major tranqulizers such as, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine, and molindone, as well as, those agents used at lower doses in the treatment of nausea, vomiting, and the like;

20. Muscle relaxants such as, tolperisone, baclofen, dantrolene sodium, cyclobenzaprine;

21. Drugs for Parkinson's disease, spasticity, and acute muscle spasms such as levodopa, carbidopa, amantadine, apomorphine, bromocriptine, selegiline (deprenyl), trihexyphenidyl hydrochloride, benztropine mesylate, procyclidine hydrochloride, baclofen, diazepam, dantrolene, and the like;

22. Respiratory agents such as, codeine, ephedrine, isoproterenol, dextromethorphan, orciprenaline, ipratropium bromide, cromglycic acid, and the like;

23. Non-steroidal hormones or antihormones such as, corticotropin, oxytocin, vasopressin, salivary hormone, thyroid hormone, adrenal hormone, kallikrein, insulin, oxendolone, and the like;

24. Vitamins such as, vitamins A, B, C, D, E and K and derivatives thereof, calciferols, mecobalamin, and the like for dermatologically use;

25. Antitumor agents such as, 5-fluorouracil and derivatives thereof, krestin, picibanil, ancitabine, cytarabine, and the like;

26. Enzymes such as, lysozyme, urokinaze, and the like;

27. Herb medicines or crude extracts such as, glycyrrhiza, aloe, Sikon (Lithospermi radix), and the like;

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28. Miotics such as pilocarpine, and the like;

29. Cholinergic agonists such as, choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, arecoline, and the like;

30. Antimuscarinic or muscarinic cholinergic blocking agents such as, atropine, scopolamine, homatropine, methscopolamine, homatropine methylbromide, methantheline, cyclopentolate, tropicamide, propantheline, anisotropine, dicyclomine, eucatropine, and the like;

31. Mydriatics such as, atropine, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, hydroxyamphetamine, and the like;

32. Psychic energizers such as, 3-(2-aminopropy)indole, 3-(2-aminobutyl)indole, and the like;

33. Humoral agents such as, the prostaglandins, natural and synthetic, for example PGE_1, $PGE_{2\alpha}$, and $PGF_{2\alpha}$, and the PGE_1 analog misoprostol.

34. Antispasmodics such as, atropine, methantheline, papaverine, cinnamedrine, methscopolamine, and the like;

35. Antidepressant drugs such as, isocarboxazid, phenelzine, tranylcypromine, imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, maprotiline, trazodone, and the like;

36. Anti-diabetics such as, insulin, and anticancer drugs such as, tamoxifen, methotrexate, and the like;

37. Anorectic drugs such as, dextroamphetamine, methamphetamine, phenylpropanolamine, fenfluramine, diethylpropion, mazindol, phentermine, and the like;

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38. Anti-allergenics such as, antazoline, methapyrilene, chlorpheniramine, pyrilamine, pheniramine, and the like;

39. Decongestants such as, phenylephrine, ephedrine, naphazoline, tetrahydrozoline, and the like;

40. Antipyretics such as, aspirin, salicylamide, and the like;

41. Antimigrane agents such as, dihydroergotamine, pizotyline, and the like;

42. Anti-malarials such as, the 4-aminoquinolines, alphaaminoquinolines, chloroquine, pyrimethamine, and the like;

43. Anti-ulcer agents such as, misoprostol, omeprazole, enprostil, allantoin, aldioxa, alcloxa, N-methylscopolamine methylsuflate, and the like;

44. Peptides such as, growth releasing factor, and the like;

45. Anti-estrogen or anti-hormone agents such as, tamoxifen or human chorionic gonadotropin, and the like.

The drugs mentioned above can be used in combination as required. Moreover, the above drugs may be used either in the free form or, if capable of forming salts, in the form of a salt with a suitable acid or base. If the drugs have a carboxyl group, their esters can be employed.

All the drugs used are in solid form at ambient, namely room, temperatures and pressures. However liquid drugs can also be employed to the extent that such drugs, in the forms and amounts used do not undesirably affect the adhesive properties of the carrier.

The acid mentioned above may be an organic acid, for example, methanesulfonic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, acetic acid,

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or ann inorganic acid, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid. The base may be an organic base, for example, ammonia, triethylamine, or an inorganic base, for example, sodium hydroxide or potassium hydroxide. The esters mentioned above may be alkyl esters, aryl esters, aralkyl esters, and the like.

When a drug different than an anesthetic agent is used the solvent selected is one in which the drug is soluble. In generally the polyhydric alcohol can be used as a solvent for a wide variety of drugs. Other useful solvents are those known to solubilize the drugs in question.

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CLAIMS

1. A flexible, finite, bioadhesive composition for topical application comprising:

a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent of a plasticizer for the bioadhesive;

in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is present in non-crystallized form in the composition.

2. The composition of claim 1, wherein the pharmaceutically acceptable solvent is in an amount from about 20 to about 53 weight percent based on the weight of the whole composition, of which the plasticizer represents about 10 to about 30 weight percent based on the weight of the whole composition, and the bioadhesive is in an amount from about 20 to about 34 weight percent based on the weight of the whole composition.

3. The composition of claim 1, wherein the pharmaceutically active agent is at least one local anesthetic in an amount of about 10 to about 40 weight percent based on the weight of the total composition.

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4. The composition of claim 1, wherein the pharmaceutically active agent is from a class of drugs selected from the group consisting of analgesic anti-inflammatory drugs, central nervous system drugs, antihistaminic or antiallergic drugs, acitonide anti-inflammatory drugs, androgenic and estrogenic steroids, respiratory drugs, sympathomimetic drugs, antimicrobial drugs, antihypertensive drugs, cardiotonic drugs, coronary vasodilators, vasoconstrictors, beta blocking and antiarrhythemic drugs, calcium antagonistic and other circulatory anticonvulsants, anti-vertigo-tranquilizing drugs, antipsychotic drugs, muscle-reactants drugs, anti-Parkinson drugs, non-steroidal hormones, anti-hormones, vitamins, anti-tumor, enzymes, herb medicines or crude extracts, miotics, cholinergic agonists, antimuscarinic or muscarinic cholinergic blocking drugs, mydriatics, psychic energizers, humoral agents, antispasmodic drugs, antidepressants, antidiabetics, anorexic drugs, anti-allergic drugs, decongestants, antipyretics, anti-migraine drugs, antimalarial, antiulcer drugs, peptides, and anti-estrogens.

5. The composition of claim 4, wherein the antimicrobial drugs is an antifungal agent selected from the group consisting of chlotrimazole, miconazale and chloramphenicol

6. The composition of claim 4, in which the pharmaceutically active agent is one or more steroids selected from the group consisting of androgenic steroids, including testosterone; methyltestosterone; fluoxymesterone; estrogenic steroids, including conjugated estrogens, esterified estrogens, estropipate, 17ß-estradiol, 17ß-estradiol esters such as 17ß-estradiol valerate, equilin, mestranol, estrone, estriol; 17ß- estradiol derivatives such as

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17β-ethinyl estradiol; diethylstilbestrol, progestational agents, including progesterone and progesterone analogs such as 19-norprogesterone, hydroxyprogesterone caproate, 17α-hydroxyprogesterone, dydrogesterone, medroxyprogesterone acetate; and norethindrone, norethindrone acetate, melengestrol, chlormadinone; ethynodiol diacetate, norethynodrel, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, megestrol acetate, and anti-estrogen or anti-androgenic steroids.

7. The composition of claim 3, wherein the anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, chloroprocaine, tetracaine, bupivacaine, and etidocaine and is in the form of the base or an acid-addition salt or both forms.

8. The composition of claim 7, wherein the acid-addition salt is hydrochloride.

9. The composition of claim 1, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

10. The composition of claim 9, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum, guar gum, cellulose, and cellulose derivatives.

11. The composition of claim 1, wherein the solvent for the anesthetic agent is at least one polyhydric alcohol.

12. The composition of claim 11, wherein the polyhydric alcohol is a polyalkylene glycol.

13. The composition of claim 12, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol,

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polyethylene glycol, glycerin, butylene glycol, hexylene glycol, polypropylene glycol, and sorbitol.

14. The composition of claim 1, further comprising a backing material conforming to the size and shape of a single dosage of the composition.

15. The composition of claim 1 comprising about 20 to 34 weight percent of karaya gum, about 20 to 53 weight percent of at least one glycol, and about 10 to 25 weight percent of lidocaine base and further comprising a binder in an amount sufficient to bind the other ingredients.

16. The composition of claim 15 comprising about 30 weight percent of karaya gum, about 6 weight percent propylene glycol, about 15 weight percent of dipropylene glycol, about 15 weight percent of glycerine, about 25 weight percent of lidocaine base and about 9 weight percent of lecithin.

17. The composition of claim 15, comprising about 33 weight percent of karaya gum, about 7 weight percent of propylene glycol, about 12 weight percent of dipropylene glycol, 33 weight percent of glycerin, about 10 weight percent lidocaine base and about 5 weight percent lecithin.

18. The composition of claim 1 wherein the pharmaceutical agent comprises a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, local anesthetic agent in acid-addition salt form.

19. The composition of claim 18, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the local anesthetic agent in acid-addition salt form is selected from the group consisting of a dyclonine

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salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

20. The composition of claim 21, wherein the acid-addition salt is the hydrochloride.

21. The composition of claim 20, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

22. The composition of claim 21, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum and guar gum.

23. The composition of claim 22, wherein the solvent for the anesthetic agents is at least one polyhydric alcohol.

24. The composition of claim 23, wherein the polyhydric alcohol is a polyalkylene glycol.

25. The composition of claim 24, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol, polyethylene glycol, butylene glycol, hexylene glycol, polypropylene glycol, and sorbitol.

26. A method of administering one or more pharmaceutically active agent to a subject comprising the steps of:

providing the composition set forth in claim 1; and

contacting an area of skin or mucous membrane with the composition to administer the pharmaceutically active agent.

27. The method of claim 26, wherein the pharmaceutically active agent is an anesthetic agent selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine, chloroprocaine, tetracaine, bupivacaine, etidocaine, and dibucaine.

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28. The method of claim 27, wherein the anesthetic agent is administered in the form of a free base.

29. The method of claim 28, wherein the anesthetic agent is administered in the form of an acid-addition salt.

30. The method of claim 29, wherein the solvent is at least one polyhydric alcohol.

31. The method of claim 30, wherein the polyhydric alcohol is a glycol or cycloalkanepolyol.

32. The method of claim 31, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, polyethylene glycol, glycerin, butylene glycol, hexylene glycol, polypropylene glycol, sorbitol, and ethylene glycol.

33. The method of administering a pharmaceutically active agent of claim 26, wherein the pharmaceutically active agent is a combination of a therapeutically effective amount of a first local anesthetic agent in base form; and a therapeutically effective amount of a different, second local anesthetic agent in an acid-addition salt form.

34. The method of claim 33, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent in acid-addition salt form is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

35. The method of claim 34, wherein the acid-addition salt is hydrochloride.

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36. The method of claim 35, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

37. The method of claim 36, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum and guar gum.

38. The method of claim 37, wherein the solvent for the anesthetic agents is at least one polyhydric alcohol.

39. The method of claim 38, wherein the polyhydric alcohol is a polyalkylene glycol or cycloalkanepolyol.

40. The method of claim 39, wherein the glycol or polyol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol, polyethylene glycol, and sorbitol.

41. The composition of claim 1, wherein the pharmaceutically active agent is an anti-microbial agent.

42. The composition of claim 41, in which the anti-microbial agent in an antifungal agent.

43. The composition of claim 42 in which the anti-microbial agent is clotrimazole.

44. The composition of claim 43 in which the anti-microbial agent is miconazole.

45. A composition for topical application comprising a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, second local anesthetic agent in salt form in a flexible, finite, pharmaceutically acceptable adhesive-containing solvent for the first and second local anesthetic agents.

46. The composition of claim 45, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, lidocaine,

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prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine, and chloroprocaine.

47. The composition of claim 45, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt and a dibucaine salt.

48. The composition of claim 45, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent in salt form is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

49. The composition of claim 48, wherein the salt is the hydrochloride.

50. The composition of claim 45, wherein the adhesive is a bioadhesive.

51. The composition of claim 50, wherein the first local anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine and chloroprocaine.

52. The composition of claim 50, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

53. The composition of claim 50, wherein the bioadhesive is karaya gum.

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54. A method of delivering local anesthetic agents which comprises the topical administration to a mammal of a composition comprising:

a therapeutically effective amount of a first local anesthetic agent in base form and

a therapeutically effective amount of a different, second local anesthetic agent in salt form

in admixture with a flexible, finite, pharmaceutically acceptable, adhesive; and

a solvent in the adhesive for the first and second local anesthetic agents.

55. The method of claim 54, wherein the first local anesthetic agent is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

56. The method of claim 55, wherein the salt is a hydrochloride.

57. The method of claim 54, wherein the adhesive is a bioadhesive.

58. The method of claim 57, wherein the first local anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine and chloroprocaine.

59. The method of claim 57, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt and a dibucaine salt.

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60. The method of claim 57, wherein the bioadhesive is karaya gum.

61. The method of claim 59, wherein the salt is a hydrochloride.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/01730

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/70 A 61 L 15/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	DD,A, 217989 (ERNST MORITZ ARNDT UNIVERSITÄT GREIFSWALD) 30 January 1985, see the whole document	9
A	EP,A,0250187 (JOHNSON & JOHNSON PRODUCTS INC.) 23 December 1987, see page 3, line 1 - page 4, line 41; pages 7-9, examples 2-4; pages 11,12, examples 6,7	1-61
A	EP,A,0363224 (BLOCK DRUG CO. INC.) 11 April 1990, see pages 7,8, examples 1,2	1-61
A	WO,A,8910740 (INNOVATA BIOMED LTD) 16 November 1989	1-61

-/-

° Special categories of cited documents :[10]

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16-07-1992	11. 08. 92
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	LU,A, 52460 (ASTRA PHARMACEUTICAL PRODUCTS) 25 June 1968, see the whole document, in particular page 5, lines 17-23; page 18, example 7	1-61

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INTERNAT. NAL SEARCH REPORT

International application No.
PCT/US 92/01730

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.: please see remark
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-40 and 54-61 are directed to a method of treatment of the human/animal the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
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:

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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 searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] 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.:

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.

[ ] No protest accompanied the payment of additional search fees.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9201730 SA 58216

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/08/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DD-A- 217989		None	
EP-A- 0250187	23-12-87	US-A- 4713243	15-12-87
		AU-A- 7415587	17-12-87
		JP-A- 63019152	26-01-88
		US-E- RE33093	17-10-89
EP-A- 0363224	11-04-90	AU-A- 4265689	12-04-90
		CA-A- 2000277	07-04-90
		JP-A- 2196717	03-08-90
WO-A- 8910740	16-11-89	None	
LU-A- 52460	25-06-68	BE-A- 690383	29-05-67
		DE-A- 1617282	06-02-75
		FR-M- 6733	24-02-69
		GB-A- 1108837	
		NL-A- 6616878	31-05-67

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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

(11) Publication number: **0 273 069 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **14.10.92**

(51) Int. Cl.[5]: **C08B 37/14**, A22C 13/00, A61L 15/28, B01D 71/08

(21) Application number: **86118163.4**

(22) Date of filing: **30.12.86**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **Glucomannan/polyhydric alcohol composition and film prepared therefrom.**

(43) Date of publication of application:
06.07.88 Bulletin 88/27

(45) Publication of the grant of the patent:
14.10.92 Bulletin 92/42

(84) Designated Contracting States:
DE FR GB

(56) References cited:
EP-A- 0 109 269
DE-B- 2 148 159
GB-A- 853 378
GB-A- 2 048 642

CHEMICAL ABSTRACTS, vol. 97, 1982, page 487, abstract no. 4931e, Columbus, Ohio, US

CHEMICAL ABSTRACTS, vol. 100, 1984, page 530, abstract no. 137715q, Columbus, Ohio, US

PATENT ABSTRACTS OF JAPAN, vol. 6, no. 98 (C-106)[976], 8th June 1982

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Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

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Description

BACKGROUND OF THE INVENTION

The present invention relates to a composition having a complex network structure that is formed by mixing glucomannan and optionally another natural polysaccharide with a polyhydric alcohol such as glycerin or a concentrated solution thereof in the presence of absence of an alkali. The present invention also relates to a film prepared from this composition.

The composition of the present invention can be dissolved in water to form a viscous solution. A film formed of this composition is water-resistant and may be given greater strengthand heat-resisting property. The film finds utility in various applications such as edible films, semipermeable membranes for separating low-molecular weight materials from those having high molecular weights ; wound dressings, and the shells of soft capsules.

The principal use of glucomannan has been to produce konjak by reacting it with an alkali in an aqueous solution, then heating the reaction product to form a gel. The gel formed bythis method has an inhomogeneous structure and finds no utility other than as konjak. Other natural polysaccharides have been used in an aqueous solution as thickeners, gelling agents, water retainers, stabilizers, dispersants, emulsifiers, binders, etc.

Compounds having multiple hydroxyl groups as exemplified by polyhydric alcohols, sugar alcohols, monosaccharides, dissaccharides and oligosaccharides have been used solely as additives such as sweeteners, humectants, softening agents and plasticizers. Moreover, these compounds have been used singly and no attempt has been made to allow the natural polysaccharidesto react directly with polyhydric alcohols in the presence of a small amount of water.

Edible films currently available include starch-based waters, gelatin-based collagen film, and pullulan films. All of these films except those based on gelatin lack resistance to water. Even gelatin films lack high resistance to acid, alkalies and heat. Films formed of cyclodextrins or special proteins obtained by extracting nucleic acids, cell membranes, etc. from yeasts are expensive and their high cost is not justified by corresponding improvements in water resistance, heat resistance and strength.

In the production of smoked meat products such as hams and sausages, semipermeable membranes such as those made of animal guts, regenerated cellulose or cellulose derivatives are used to allow the fragrant and seasoning components in the smoke to penetrate into the meat. However, the supply of animal guts is not abundant and, in addition, they lack strength and are not uniform in size. The supply of regenerated cellulose and cellulose derivatives is also limited because strict regulations against pollution has rendered the construction of new plants practically impossible.

Gelatin has heretofore been used as the shell matereal of soft capsules for cunfining drugs, flavors or seasonings but the user of gelatin is limited to applications where oily substances are employed.

Electrolytes or low-molecular weight materials have been separated from high-molecular weight materials by such means as electrodialysis, reverse osmosis, and ion-exchange membrane technology. However, these methods use a large number of electrodes or require high pressures so that the equipment for practicing these methods is becoming more and more complex. In order to desalt foods by these methods, large-sized equipmentis necessary and it often occurs that other seasoning componentsare eliminated as well as the sodium salt with the result that the taste of the food is impaired.

In the treatment of skin losses due to burns or other external injuries, the affected area is temporarily covered to prevent loss of water or body fluids from the wound, or any exudate from the wound is desplaced to prevent bacterial infection so that the formation of granulations and the epidermis is promoted. The films which have been used or attempted to be used for these purposes are formed of such materials as silicone rubber, poly -E -caprolactone, poly (vinyl alcohol) , polyamino acids,fibrin membranes, collagen, polyurethane and pigskin.

However, freeze-dried pigskin and other polyamino acid based wound dressings are all made of polypeptides which are subject to biochemical decomposition. In order to avoid the adverse effects of the degradation products which are liberated, these wound dressings have to be replaced at short intervals, typically every other day. However, replacement of the wound dressing involves much pain for the patient. Furthermore, the film itself has insufficient strength to attain satisfactory coverage. Wound dressings made of synthetic resins such as polyurethane and silicone rubber do not have sufficient affinity for the wound surface to achieve satisfactory permeation to oxygen and water. Nomal skin generally allows water to be evaporated in an approximate amount of 350g/m^2 per day, but it has been difficult to prepare synthetic resin films that exhibit this amount of water evaporation and which yet has sufficient strength.

It has been proposed to prepare a composite wound dressing by laminating a polyamino acid based

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film with a synthetic resin film but this composite film still suffers from the defects of the respective film components.

SUMMARY OF THE INVENTION

The present inventors have found that if glucomannan, either independently or in combination with other natural polysaccharides, is mixed with a compound having multiple hydroxyl groups or with a concentrated solution thereof in the presence of absence ofan alkali, the respective components react with each other to form a composition having a dense three-dimensional structure. The present inventors have also found that a viscous solution formed by dissolving this composition in water has unique physicochemical properties that have been unattainable by glucomannan, other natural polysaccharides or polyhydric alcohols, and that various products having the characteristics shown below can be prepared from this composition. The present invention has been accomplished on the basis of these findings.

Firstly, edible films having desirable properties s such as water resistance, heat resistance and strength can be prepared from the above-described viscous aqueous solution either directly or after being mixed with other foods or food materials. The so prepared films may be eaten as such or used as edible food packages.

Secondly, the viscous aqueous solution may be dried into film form and the resulting film may be used in the production of processed meat products (e.g. hams and sausages) as semipermeable membranes having sufficient strength and heat resistance to withstand smoking condition.

Thirdly, the viscous aqueous solution may be processed to form a film that is suitable for use as the shell of a soft capsule, and using this film, soft capsules capable of confining non-oily drugs, health foods, seasonings or flavors can be prepared.

Fourthly, the film made from the viscous aqueous solution also serves as a high-performance filter medium that is capable of efficient separation of low-molecular weight substances from high-molecular weight substances at reasonably low pressures.

Fifthly, the membrane formed by drying the viscous aqueous solution into film form is a superior wound dressing that achieves close contact with the skin and exhibits superior vapor and oxygen permeation without undergoing any biodegradation during prolonged attachment to the skin.

Sixthly, the viscous aqueous solution cools to provide a gel-like or semifluid foodstuff having unique properties.

DETAILED DESCRIPTION OF THE INVENTION

The glucomannan used in the preparation of the composition of the present invention is the polysaccharide naturally occurring in Amorphophallus Koniac K. Koch which is the rhizome of a plane belonging to Colocasia antiquorum; it is composed of particles referred to as idioblasts which range from 0.5 to 1.05 mm in length and from 0.37 to 0.5 mm in breadth. The chemical structure of glucomannan is a chain of a 1 : 2 mixture of glucose and mannose with acetyl and phosphate groups forming pendant ester linkages.

Illustrative polyhydric alcohols that can be used in the present invention are polhydric alcohols in the narrow sense of the term such as propylene glycol and glycerin. These polyhydric alcohols are liquid and may be directly used; however, because of their high hygroscopicity they contain water and are in the form of concentrated aqueous solutions. Moreover they can be used as water solution of concentration in the range of 30 to 90 %. Illustrative sugar alcohols include sorbital, mannitol, maltitol, xylytol and saccharified products of reducing sugar. Illustrative monosaccharides include glucose, fructose, galactose and xylose. Illustrative disaccharides are saccharose, maltose and lactose. Starches such as sweet potato, potato and corn that have been decomposed with enzymes or acids are usable as oligosaccharides, and include di-, tri-, tetra-, penta- and hexasaccharides. The polyhydric alcohols listed above, both in the broad and narrow sense of the term, which are in a powder form at ordinary temperatures, are used as aqueous solutions having concentrations in the range of 30-90 wt %, preferably 50-80 wt %, more preferable 65-75wt%.

Other natural polysaccharides that may be used in the present invention include the following:

alginic acid which are intracellular polysaccharides in brown algae,

sodium alginate,

propylene glycol ester of alginic acid, and

agar;

carrageenan which is an intracellular polysaccharide in red algae and is hydrolyzed into D-galactose and D-galactose sulfate ester ;

locust bean gum which is a polysaccharide that is present in the seeds of leguminous locust bean and

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carob and which is chiefly composed of glucomannan;

guar gum that is a polysaccharide present in the seed of leguminous guar and which is hydrolyzed into galactose and mannose ;

tamarind seed polysaccharide which is a polysaccharide present in the seed of leguminous Tamarindus indica and which is hydrolyzed into glucose, xylose and galactose ;

pectin which is a generic term for a group of polysaccarides that are the materials of construction of the cell walls of plants such as fruit and vegitables and which are hydrolyzed in to galacturonic acid;

xanthan gum is a polysaccharide produced by the microorganism Xanthomonas campestris during fermantation in the present of glucose and other appropriate essential elements;

chitin which is one kind of mucopolysaccharides;

pullulan which has a repeating unit of α -1,6 linkage derived from maltotriose ; and

cellulose,

cyclodextrin and

starches.

These natural polysaccharides are optionally used in amounts of 0.05 - 20 parts by weight, preferably from 0.1 to 10 parts by weight, per part by weight of glucomannan.

In the present invention, reaction is preferably carried out in the presence of an alkali. Ordinary inorganic or organic alkaline substances may be employed and suitable ones inclueded: sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, ammonium carbonate, magnesium carbonate, sodium bicarbonate, ammonium bicarbonate, basic amino acids and amines. The addition of these alkalis is generally effective in providing films with improved strength and heat resistance.

Part of the glucomannan and optionally used natural polysaccharides may be replaced by proteins to provide composition which generally have improved heat resistance. Solutions of these compositions in warm water have good mouth feel and can be readily eaten. Illustrative proteins are soybeen protein, wheat protein, milk protein, egg white, collagen, decomposed collagen and microbial proteins. Decomposition products of these proteins, such as polypeptides and amino acids, may also be used.

The present invention is characterized by reacting glucomannan directly with at least one compound selected from among the polyhydric alcohols, sugar alcohols, monosaccharides, disaccharides and oligosaccharides. The component made of at least one compound selected from polyhydric alcohols, sugar alcohols, monosaccharides, disaccharides and oligosaccharides is used in an amount which ranges from 0.05 to 10 parts by weight, preferably from 0.10 to 5.0 parts by weight, more preferably from 0.15 to 1.0 part by weight, per part by weight of the powder component made of glucomannan and optionally of other natural polysaccharides and proteins. Generally, a higher content of the polyhydric alcohol renders it difficult for a three-dimensional network to develop.

The reactants are mixed at a temperature ranging from 5 to 150 °C, preferably from 10 to 100 °C, more preferably from 20 to 80 °C. Mixing at low temperatures will cause no problem because the intended reaction can be allowed to proceed satisfactorily by heating the mixture in a subsequent step such as drying. Generally, mixing at high temperatures provides a composition having a dense structure whereas a brittle composition having a coarse network results if low mixing temperatures are used.

The composition formed by mixing the starting materials described above is a powder that is usually moist to some extent. A solution of this composition in water is viscous and will solidify irreversibly when left to stand at ordinary temperatures, frozen, refrigerated or heated. The properties, in particular the strength, heat resistance and the temperature for dissolution in water, of the solidified product can be altered by proper adjustment of the combination of the starting materials used. Therefore, the solidified product can be used as a base for semifluid or gel-like foods such as jelly and jam. Films may be formed from the viscous solution by shaping it into a soldified form of a suitable thickness between 1 and 1,000 μm by any of the known techniques such as wet casting, freeze-drying and extrusion molding. Some of the films formed by these methods are heat-resistant and heat-sealable. If desired, the viscous solution may be coated or sprayed onto a foodstuff and dried to form an edible film on the food.

Films having thicknesses in the range of 1-1,000 μm, preferably 2- 300 μm, are useful as semipermeable membranes. In a more preferable embodiment, a thin and reinforced semipermeable membrane can be formed by preparing a thin fibrous product from an appropriate material such as paper, nonwoven fabric, woven fabric or net, then filling the voids in the fibrous product with the filter film of the present invention. Filling of the voids in the thin fibrous product may also be achieved by coating the film with the viscous solution or submerging the film in the solution, followed by drying of the film.

Filtration may be achieved by any known technique such as simple filtering under gravity, ultrafiltration or reverse osmosis. The filter medium may be an assembly of hollow fibers or a module of a spirally wound

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sheet.

In the simplest way, afoodstuff having high sodium chloride concentration is placed on top of the semipermeable membrane of the present invention which is in contact with an underlying water layer; in the absence of any applied pressure, sodium chloride and other low-molecular weight substances in the upper layer will permeate through the membrane to enter the underlying aqueous layer.

Soy sauce, miso and pickled products contain a large amount of sodium chloride in order to ensure that they can be transported long distances or to achieve various purposes such as storage, preservation or good manufacturing practice. The filter film of the present invention is capable of allowing the sodium chloride content of these food products to be lowered without impairing their taste.

In producing processed meat products such as hams and sausages, the meat wrapped in a semipermeable membrane must be smoked. Conventionally, the semipermeable membrane is formed of regenerated cellulose, cellulose derivatives, alginates, collagen, or sheep or bovine gut. However, as already mentioned, these materials have problems in terms of their physical strength and heat resistance, and in particular, sheep and bovine guts are not uniform in size and shape and suffer from instability in supply.

Fibrous products are usually porous and the films prepared by impregnating or coating them with the edible composition of the present invention serve as ideal casing materials wherein the semipermeable membrane formed of the edible material isreinforced with the fibrous product. Such casing materials may be prepared as follows: a fibrous product of a given width is shaped into a tubular base, which is continuously impregnated with an aqueous solution of the composition of the present invention and dried to form a strong fibrous casing.

The shell of conventional soft capsules is formed from an aqueous solution of gelatin and glycerin and is only capable of confining oily products. The soft capsules formed from an aqueous solution of the composition of the present invention are capable of confining not only oily products but also water-soluble substances and, hence, are applicable to enlarged areas of use, for instance: (1) water-soluble vitamins such as vitamins B_1, B_2, B_5, B_6, B_{12}, niacin folic acid and vitamin C; (2) nutrients such as liquid glycides, proteins and minerals; (3) diets formed of soft capsules that incorporate liquid seasonings or flavors and which are readily edible after cooking ; and (4) cosmetics in soft capsules that are to be punctured with a needle to allow the contents to be used.

Soft capsules may be prepared from the composition of the present invention as follows : the composition is dissolved in water and the solution is allowed to flow out of a spreader box to form a gel which is subsequently shaped into a film form, two sheets of the film thus obtained are passed through a pair of die rolls to adhere to each other ; a predetermined amount of the content (ie, fill) is forced with a pump to obtain a caplule form, which is subsequently dried to form a soft capsule.

The film prepared in accordance with the present invention is also useful as an ideal wound dressing. It swells readily upon absorbing body fluids from a wounded site of the human body but its three-dimensional network will remain intact. The film increases in thickness but its area remains the same so as to allow the absorbed moisture to be evaporated from its furface. The film supplies the wound surface not only with moisture but also with the drug applied onto the outer surface of the film ; at the same time, the film allows the unwanted exudate to be liberated on its surface. Therefore, the film does not have to be peeled off until after the wound has healed. The thickness of the film used as a wound dressing generally ranges from 1 to 1,000μm, preferably form 5 to 200 μm, more preferably from 7 to 50 μm.

When the composition of the present invention is dissolved in water, a vicous solution or slurry with a solids content of 2-10 % will form and this can be incorporated in a large amount in suitable food materials. The incorporated composition will solidify irreversibly be being left to stand at ordinary temperatures, frozen, refrigerated or heated. The properties, in particular the strength, heat resistance and the temperature for dissolution in water of the solidified product can be altered by properly adjusting the combination of starting materials used. Furthermore, the solidifed product retains the tast flavor of the food material present.

The food materials that can be mixed with the viscous solution or paste of the composition of the present invention are diverse and include: seaweeds ; marine products such as shrimp, cuttlefish, fish (e.g. bonito, tuna and salmon) , and fish roe; vegitables such as spinach, cabbage, carrot and pumpkin; fruits such as orange, grape, apple and pineapple ; meats such as beef, pork, chicken, and corned beef ; processed foods such as cheese, jam, mayonnaise and miso ; seasonings such as soy sauce and sodium glutamate ; as well as spices and flavors such as peanut, almond, mustard, pepper, curry, cocoa, coffee an chocolate.

These food materials may be mixed with the viscous solution or slurry of the composition of the present invention either directly, or after being conditioned for a given particle size or shape, or after being formed into a paste. The mixing ratio of these food material to the glucomannan /polyhydric alcohol composition of

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the present invention is not limited to any particular value because it largely depends on the type of food material used or the specific formulation of the composition. It should however be noted that a preferable mixing ratio is such that the mixture can be readily formed into a film, and that the shaped food is easy to handle and does not reveal the mouth feel of the composition.

The aqueous solution of the composition of the present invention is viscous and its properties, in particular its strength, heat resistance and temperature for dissolution in water, can be altered by allowing it to stand at ordinary temperatures, freezing, refrigerating or heating the same. Therefore, the aqueous solution, after being shaped into a gelled block of an appropriate hardness, may be mixed with a non-alcoholic beverage such as juice or yogurt or foods, and the resulting mixture can be safely heated without melting to thereby provide a composite dietary product that shows a desirable combination having the sort of mouth feed that is possessed by dissimilar components. There is no particular limitation on the size of the gel block and its hardness varies with the type of base used: if the base is a liquid material such as juice, the moisture content of the block is preferably increased to provide a soft texture, whereas if the base is jelly or any other material that has a certain amount of self-retaining property, its moisture content is decreased to provide a hardness slightly lower than that of the jelly. In either case, the resulting product is composed to two dissimilar materials and yet displays good palatability.

Glucomannan has a complex structure containing various side chains and reactive groups and, because of the presence of many hydroxyl groups at high concentrations, glucomannan enters into reaction to form a complex matrix even under a substantially water-free condition. The matrix forming reaction will be enhanced by the presence of an alkali and an even more complex compound will form. In the presence of both an alkali and water, the development of a three-dimensional network is further promoted to form an irreversibly solidified product, which can be processed to provide a characteristic gel-like base or a coating.

The present invention is hereinafter described in greater detail with reference to the following examples to which the scope of the invention is by no means limited and wherein all parts are on a weight basis.

EXAMPLE 1

Eight parts of glucomannan was mixed with 2 parts of glycerin for 15 minuites an 70 °C to form a sample of the composition of the present invention which was a somewhat moist powder. Two parts and a half of this composition were mixed with 97.5 parts of water to form a viscous aqueous solution. This solution was coated onto the peel of orange and dried at 50 °C for 1 hour to provide orange having an edible film coating on its peel. This orange and uncoated orange were stored at 25 °C for 10 days. Thereafter, the appearance of the two oranges and the mouth feel of their pulp were compared. Compared with the uncoated orange, the one having an edible film coat had undergone a smaller degree of water evaporation and oxidation, retained more luster and experienced less surface discoloration. The pulp of the coated orange was fresher and more palatable.

EXAMPLE 2

Three parts of the composition prepared in Example 1 was mixed with 0.04 parts of a vitamin E powder (70% natural vitamin E and 30 % emulsifier) and 97 parts of water to form an aqueous solution. An orange whose peel was coated with the resulting aqueous solution as in Example 1 was stored at 25 °C for 15 days together with an uncoated orange. The results of comparison of the two oranges were the same as in Example 1.

EXAMPLES 3 - 10

The components listed in Table 1 were mixed for 10 minutes at 80 °C in the amounts also shown in Table 1, so as to prepare eight additional samples of the composition of the present invention. Three parts of each of the samples was mixed with 97 parts of water and the resulting aqueous solutions were cast by the wet process to form translucent edible films having thicknesses ranging from 10 to 20 μm. The films prepared in Examples 3 to 6 were water-resistant and stable in the following solutions: aqueous solutions with NaCl concentrations of 5% or more ; acidic aqueous solutions with pH of 2.5 - 4.5; alkaline aqueous sloutions with pH of 9.0 - 12.0 ; aqueous solutions with ethanol concentrations of 10 % or more. The films prepared in Examples 7 - 10 were not only water-resistant; they were resistant to hot water and stable in aqueous solutions heated to 80 - 100 °C.

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Table 1

(unit in parts by weight)

Example No.		3	4	5	6	7	8	9	10
natural polysaccharide	glucomannan	5	5	5	5	5	5	5	5
	carrageenan	3			2		4		3
	agar		2					1	
	locust bean gum			2					1
	xanthan gum				1		0.5		
alkali	calcium carbonate							0.3	0.1
	calcium hydroxide					0.05			
	sodium bicarbonate						0.5		0.3
glycerin			1.5		1.5	1		1	
sorbitol (70% aq.sol.)		1.5					1		
saccharose (80% aq. sol.)				1.5					1

EXAMPLE 11

An edible package film 15 μm thick was formed from a composition having the same formulation as used in Example 3. Stripped lobster (150g) was wrapped with this film and stored at-25°C for 3 months. The frozen lobster as wrapped in the film was thawed in a microwave oven and cooked. The cooked lobster had the edible film on it but one did not sense any peculiar feel as a result of the presence of the film.

EXAMPLE 12

An edible film 15μm thick was formed from a composition having the same formulation as used in Example 8. Vegitable salad with dressing was sandwiched between two slices of bread. During subsequent storage, the dressing did not permeate into the bread at all. After the strage, the bread was eaten ; it tasted good and the taste of the edible film was not sensed.

EXAMPLE 13

Components	Amount (in parts)
Glucomannan	5
Sodium bicarbonate	0.1
Calcium Carbonate	0.02
Glycerin	1

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These components were mixed at 75 °C for 20 minutes. Three parts of the resulting composition were dissolved in 97 parts of water. The aqueous solution was applied continuously to form a uniform coating on the inner surface a fluoroethylen resin-coated cylindrical pipe having a diameter of 120 mm. The applied coat was dried to form a tubular casing.

Processed meat was packed into the casing at a pressure of up to 2 kg/cm^2 without causing its disruption. The packed meat was smoked and sterilized by heating in hot water (80 °C) for 2 hours to produce a satisfactory ham.

EXAMPLE 14

Components	Amount (in parts)
Glucomannan	5
Agar	0.5
Calcium carbonate	0.5
Sodium citrate	0.3
Sorbitol (70% aq. sol.)	1

These components were mixed at 80 °C for 10 minuites. Three parts and a half of the resulting composition were dissolved in 96.5 parts of water to form a viscous aqueous solution. A sheet of porous paper having a thickness of 100 μm was prepared, with wood pulp and cotton linter being used as chief components. The two side edges of the sheet were adhered together to form a tubular base. The wall of this base was impregnated with the previously prepared viscous aqueous solution and dried to form a casing that was formed of a sample of the film of the present invention that had a thickness of 120 -130 μm and which was reinforced with a fibrous product.

Processed meat was packed into the casing at a pressure of up to 6 kg/cm^2 without causing its disruption. The packed meat was smoked and sterilized by heating in hot water (80 °C) for 2 hours to produce a satisfactory sausage.

EXAMPLE 16

A mixture of gelatin (100 parts) and glycerin (30 parts) was dissolved in 60 parts of water at 75 °C with stirring and defoamed with a vacuum pump. The solution was shaped into a 450 μm thick film on an automatic rotary continuous soft capsule filling machine. A film 25 μm thick that was prepared asin Example 6 was stacked on the inside surface of the 450 μm thick film to form a double-layered film. Two units of this double-layered film were passed between a pair of die rolls to be adhered to each other and an aqueous solution of 30% L-ascorbic acid was forced in with a filling pump to form capsules each containing 500 mg of the fill. The capsules were dried to produce soft capsules.

EXAMPLE 16

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Components	Amount (in parts)
Glucomannan	5
Carrageenan	0.5
Calcium carbonate	0.12
Glycerin	1

These components were mixed at 70 °C for 30 minutes. Three parts of the resulting composition was dissolved in 97 parts of water to form a viscous aqueous solution. the solution was formed into an edible film 15 μm thick by the wet casting method. As in Example 15, a dual-layered capsule shell was formed by staking this film over a gelatin film. Using this shell, soft capsules each containing 5 g of seasonings for instant chicken soup were produced. On of these capsules was mixed well with 150 ml of hot water (90 °C) under agitation ; the capsule was disintegrated in the water to provide chicken soup.

EXAMPLE 17

A mixture of gelain (100 parts) and glycerin (30 parts) was dissolved in 10 parts of water at 75 °C with stirring. Thesolution was defoamed with a vacuum pump and designated A. In a separate step, 5 parts of glucomannan, 3.5 parts of carrageenan and 1.5 parts of glycerin were mixed at 70 °C to form a sample of the composition of the presnet invention ; 3 parts of the composition was dissolved in 97 parts of water to form an aqueous solution which was designated B. An intimate blend of solution A (60 parts) and solution B (40 parts) was fed into an automatic rotary continuous soft capsule filling machine to form soft No. 5 oval capsules by the known rotary die method, with each capsule having confined therein 290 mg of an astringent lotion. Just prior to use, each soft capsule was punctured with a needle to recover to lotion in an amount sufficient for single use.

EXAMPLE 18

Components	Amount (in parts)
Glucomannan	5
Carrageenan	3
Cellulose	1
Glycerin	2

These components were mixed at 80 °C for 10 minutes and 2.5 parts of the resulting composition was dissolved in 97 parts of water. The solution was formed into a circular film (thickness, 15 μm ; diameter, 29 mm) by the wet casting method. The film was set in a filtration vessel which was filled with 450 ml of tap water in its lower compartment and with 150 ml of soy sauce (18% NaCl) in its upper compartment. The vessel was left to stand at 20 °C for a given period and the contents of NaCl and amino acid nitrogen in the soy sauce were measured at predetermined intervals. The results are shown in Table 2.

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Table 2

(effective surface area of film: 960.6 m㎡)

Time (min)	NaCl (%)	Amino acid N_2	Increase in water content (%)
0	16.4	0.91	0
30	15.7	0.86	0.7
60	16.5	0.82	1.6
90	15.0	0.86	2.7
120	14.1	0.79	4.1
150	13.3	0.78	5.7

As Table 2 shows, the NaCl content of the soy sauce decreased with time and this was accompanied by gradual depletion of amino acids and increase in the moisture content. However, most of the amino acids that flowed out were those having low molecular weights such as glycin and alanine and their depletion did not cause any substantial deterioration of the taste of the soy sauce. The soy sauce prepared in accordance with the present invention had a generally mellow taste and its sodium chloride content was low.

EXAMPLE 19

An aqueous solution of the composition used in Example 18 was heated to 70 °C with stirring and applied to a thin sheet of paper (basis weight: 16g / m^2) to form a film having a thickness of 35μm. This fiber-reinforced film was tested as in Example 18. The results were substantially the same as those obtained in Example 18. The film prepared in this example was superior to that prepared in Example 18 in terms of self-retaining property and tensile strength.

EXAMPLE 20

Components	Amount (in parts)
Glucomannan	5
Xanthan gum	0.5
Calcium hydroxide	0.06
Glycerin	1

These components were mixed at 60 °C for 20 minuites to obtain a sample of the composition of the present invention. Three parts of this composition were dissolved in 97 parts of water and a thin layer of the solution was spread onto a fluoroethylen resin-coated sheet. The coating was freeze-dried by a conventional method to prepared a wound dressing in a film form having a thickness of 12 μm. The film was sterilized, coated with a drug layer and attached to the surface of a wound produced by a third-degree burn. The treatment that ensured consisted of delivering the drug daily onto the surface of the film. Formation of granulations continued steadily without suppuration and in 10 days normal skin tissue was restored,

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whereupon the film separated from the skin spontaneously.

EXAMPLE 21

An aqueous solution of the composition used in Example 20 was coated onto a nonwoven polyester fabric (basis weight : 10g / m^2) and freeze-dried by a known method so as to make a film having a thickness of 30μm. This film was used as a wound dressing to cure a burn in accordance with the same regimen as employed Example 20. The results were substantially the same as those obtained in Example 20.

EXAMPLE 22

Components	Amount (in parts)
Glucomannan	5
Alginic acid	1
Guar gum	0.5
Glycerin	1

These components were mixed at 65°C for 20 minutes to form a sample of the composition of the present invention. Three partsof this composition were dissolved in 97 parts of water. Seventyfive parts of the solution were mixed with 25 parts of a beef fillet and the blend was shaped into an edible film (thickness : 25μm) by the wet casting method. The film was laid down on a slice of bread ; the product had a characteristic flavor originating from the blending of the taste of beef with the bread.

EXAMPLE 23

Components	Amount (in parts)
Glucomannan	5
Tamarind seed polysaccharide	1
Gelatin	1
Glucose (80% aq. sol.)	1

These components were mixed at 60°C for 40 minuites to form a sample of the composition of the present invention. Three parts of this composition were dissolved in 97 parts of water to form a viscous aqueous solution. Eighty parts of this solution were blended with 20 parts of a dried spinach powder (particle size : 100-Tylermesh pass) and the blend was shaped into an edible film (15μm thick) by a known freeze-drying technique. This film was rolled around a bar of cooked rice so as to provide a low-calorie dietary product.

EXAMPLE 24

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Components	Amount (in parts)
Glucomannan	5
Carrageenan	5
Calcium carbonate	0.2
Glycerin	1.5

These components were mixed at 70 °C for 30 minutes to form a sample of the composition of the present invention. Five parts of this composition were mixed and kneaded with 95 parts of cocoa paste and the necessary seasonings to make a chocolate mass, which was refined and molded into a sheet. Although conventional chocolate products are soften at 35 °C or higher, the chocolate sheet of the Example 24 did not soften until it was heated to 50 °C.

Claims

1. A glucomannan/polyhydric alcohol composition prepared by uniformly mixing at 5 to 150 °C 1 part by weight of a glucomannan powder with 0,05 to 10 parts by weight of an aqueous solution of 30-100 wt.-% of at least one polyhydric alcohol selected from the group consisting of propylene glycol, glycerin, sugar alcohols, monosaccharides, disaccharides and oligosaccharides.

2. A composition according to claim 1, characterized in that the components are mixed in the presence of an alkali.

3. A composition according to claim 1 or 2 wherein part of the glucomannan is replaced by another natural polysaccharide.

4. A composition according to claim 3, wherein the other natural polysaccharide is carrageenan.

5. A film prepared by a process comprising the steps of: dissolving a glucomannan/polyhydric alcohol composition according to anyone of the claims 1 to 4 in water, forming the solution into a film by shaping it into a solidified form of a suitable thickness between 1 and 1000 µm by any of the known techniques, and drying the film.

6. A film according to claim 5, characterized in that it is edible.

7. A film according to claim 5 or 6 which is reinforced with a thin fibrous product.

8. The use of a film according to anyone of the claims 5 to 7 as a food packaging.

9. The use of a film according to anyone of the claims 5 to 7 as a casing in the manufacture of smoked food products.

10. The use of a film according to anyone of the claims 5 to 7 as a shell of a soft capsule.

11. The use of a film according to anyone of the claims 5 to 7 as a semipermeable membrane for separating a high-molecular weight substance from a low-molecular weight substance.

12. The use of a film according to anyone of the claims 5 to 7 as a wound dressing.

Patentansprüche

1. Glucomannan/mehrwertiger Alkohol-Zusammensetzung, erhalten durch gleichförmiges Vermischen bei

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5 bis 150 °C von 1 Gew.-Teil eines Glucomannanpulvers mit 0,05 bis 10 Gew.-Teilen einer wäßrigen Lösung von 30 bis 100 Gew.-% mindestens eines mehrwertigen Alkohols, ausgewählt aus der aus Propylenglykol, Glycerin, Zuckeralkoholen, Monosacchariden, Disacchariden und Oligosacchariden bestehenden Gruppe.

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß die Komponenten in Gegenwart von Alkali vermischt werden.

3. Zusammensetzung nach Anspruch 1 oder 2, bei der ein Teil des Glucomannans durch ein anderes, natürliches Polysaccharid ersetzt ist.

4. Zusammensetzung nach Anspruch 3, bei der das andere natürliche Polysaccharid Carrageen ist.

5. Film bzw. Folie, erhalten durch ein Verfahren, das die Schritte umfaßt:
Auflösen einer Glucomannan/mehrwertiger Alkohol-Zusammensetzung gemäß einem beliebigen der Ansprüche 1 bis 4 in Wasser,
Überführung der Lösung in einen Film bzw. eine Folie durch Überführen derselben in eine verfestigte Form mit einer geeigneten Dicke zwischen 1 und 1000 µm durch eine beliebige, bekannte Arbeitsweise,
und
Trocknen des Films bzw. der Folie.

6. Film bzw. Folie nach Anspruch 5, dadurch gekennzeichnet, daß er bzw. sie eßbar ist.

7. Film bzw. Folie nach Anspruch 5 oder 6, der bzw. die mit einem dünnen, faserförmigen Produkt verstärkt ist.

8. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Verpackung für Lebensmittel.

9. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Umhüllung bei der Herstellung von geräucherten Lebensmitteln.

10. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Hülle einer Weichkapsel.

11. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als semipermeable Membran zur Abtrennung einer Substanz mit hohem Molekulargewicht von einer Substanz mit niedrigem Molekulargewicht.

12. Verwendung eines Films bzw. einer Folie gemäß einem beliebigen der Ansprüche 5 bis 7 als Wundverband bzw. Wundabdeckung.

Revendications

1. Composition à base de glucomannan et d'alcool polyhydrique, préparée en mélangeant uniformément à la température de 5 à 150 °C, une partie en poids de poudre de glucomannan avec 0,05 à 10 parties en poids d'une solution aqueuse de 30-100% en poids d'au moins un alcool polyhydrique, choisi parmi le groupe comportant propylène glycol, glycérine, alcools de sucres, monosaccharides, disaccharides et oligosaccharides.

2. Composition selon la revendication 1, caractérisée en ce que les composants sont mélangés en présence d'un alcali.

3. Composition selon la revendication 1 ou 2, dans laquelle une partie du glucomannan est remplacée par un autre polysaccharide naturel.

4. Composition selon la revendication 3, dans laquelle l'autre polysaccharide naturel est le carrageenan.

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5. Film préparé par un procédé comprenant les étapes de :
dissoudre une composition à base de glucomannan et d'alcool polyhydrique selon l'une quelconque des revendications 1 à 4, dans l'eau, former avec solution un film en la traitant dans une forme solidifiée, d'une épaisseur convenable, entre 1 et 1000 µm par n'importe quelle technique connue, et sécher le film.

6. Film selon la revendication 5, caractérisé en ce qu'il est comestible.

7. Film selon la revendication 5 ou 6, qui est renforcé avec un produit fibreux mince.

8. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme emballage de nourriture.

9. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme emballage dans la fabrication des produits alimentaires fumés.

10. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme enveloppe d'une capsule molle.

11. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme membrane semiperméable pour séparer une substance de poids moléculaire élevé d'une substance de faible poids moléculaire.

12. Utilisation d'un film selon l'une quelconque des revendications 5 à 7, comme pansement d'une plaie.

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Description

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a controlled-releasing medicament-containing preparation for intra-oral use. In particular it is more especially concerned with such a preparation (and the process of using it) in the form of a very thin extruded thermoplastic film (which can be in single layer or laminated multi-layer form) having at least one bioadhesive layer containing 22.4-68.3% by weight of a specified thermoplastic cellulose ether and 23.75-60% by weight of a specified homopolymer of ethylene oxide which can adhere to the mucosa of the oral cavity. The extruded film drug delivery system of the present invention, which has incorporated therein the medicament to be dispensed, is so thin and flexible when wet as to be unobtrusive to the patient after it has been properly positioned and placed in the mouth.

Description of the Prior Art

Several systems have previously been described which pertain to the delivery of drugs into the oral cavity. These include:

1. Treatment of periodontal disease with tetracycline. chlorhexidine or metronidazole loaded into hollow cellulose acetate fibers. These fibers are packed in the periodontal pockets and provide controlled release of the drug to the infected area.
2. Cast films containing ethyl cellulose/propylene glycol with chlorhexidine or metronidazole for treatment of periodontal disease.
3. An orthodontic appliance with a hydroxyethyl methacrylate/methyl methacrylate copolymer (HEMA/MMA) matrix. Sodium fluoride is incorporated into the HEMA/MMA matrix to provide sustained fluoride release and enhanced anticaries activity. HEMA/MMA with fluoride may also be attached to the tooth in the form of a wafer-like tablet.
4. Silicone/ethyl cellulose/polyethylene glycol films containing sodium fluoride are applied as coatings on orthodontic bands or in chewing gum. Controlled release of fluoride and anticaries activity is claimed.

The above systems are discussed in the "The Compendium of Continuing Education" Vol VI, No. 1, Jan.1985 p. 27-36 review article "Controlled Drug Delivery: A New Means of Treatment of Dental Disease", by J. Max Goodson, D.D.S., Ph.D. of the Forsyth Dental Center. Other systems, described in GB patent application 2,042,888 and U.S. Patents 4,292,299/4,226,848 (Teijin Ltd., Japan), use combinations of cellulosic and polyacrylate polymers. The preferred materials are hydroxypropyl cellulose ("Klucel") and a copolymer of acrylic acid ("Carbopol") that is administered in the form of thin tablets (discs), granules or powder. Other polymers that might be added are vinyl copolymers, polysaccharides, gelatin and collagen. U.S. patent 4,517,173 (Nippon Soda Co. Ltd, Japan) uses various celluloses in a multi-layered non-extruded cast film preparation.

Examples of prior art products currently on the market include ointments such as ORABASE* with Benzocaine (Squibb), Kenalog* (Triamcinolone Acetonide) in ORABASE* (Squibb) and Mycostatin* (Nystatin) ointment (Squibb).

The prior art products and delivery systems described above are useful but have the following disadvantages:

Tablets, appliances, hollow fibers are "bulky" in the mouth, are difficult to keep in place and inconvenient to apply.

Ethyl cellulose and/or silicone films do not adhere to mucosal tissue.

Ointments (i.e., ORABASE*) have an unpleasant feel and do not last very long.

Except for ORABASE*, all the foregoing systems require professional application to the tooth or periodontal pockets.

The bioadhesive film of the present invention alleviates many of the above problems. It may be applied easily by the consumer. It has very little or no mouthfeel, it has good adhesion to the mucosal tissues, and provides controlled release of the medicament.

Also EP-A-0 063 604 discloses a mucous membrane-adhering film preparation in which the one surface of water-soluble high polymer film containing pharmaceutical agents is treated to be made difficultly water-soluble. JP-A-5 890 507 discloses a film formed by an injection moulding machine or an extrusion moulding machine, the film comprising a mixture of a water-soluble polymer (water-soluble cellulose derivative), an active component (drug absorbable through the mucous membrane) arbitrary additives (diluent, taste or

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scent improvers, colorants etc) and a plasticizer (polyethylene glycol).

Object of the Invention

It is an object of this invention to provide an extruded film that is an effective and convenient intra-oral drug delivery system and method for applying and delivering controlled dosages of therapeutic agents into the oral cavity. This technology may also be extended for controlled drug delivery in skin care, gynecological applications, wound care and like uses.

Summary of the Invention

The invention involves a pharmaceutically acceptable controlled-releasing medicament-containing extruded single or multi-layered thin film, capable of adhering to a wet mucous surface, comprising a water soluble or swellable polymer matrix bioadhesive layer which can adhere to a wet mucous surface and which bioadhesive layer consists essentially of 22.4-68.3% by weight of hydroxypropyl cellulose of molecular weight above 100,000 23.75-60% of a homopolymer of ethylene oxide of molecular weight above 100,000, 0-12.5%, of a water-insoluble polymer selected from ethyl cellulose, propyl cellulose, Carboxy methyl cellulose free acid, polyethylene and polypropylene, and 2.85-5% of a plasticizer, said film having incorporated therein a pharmaceutically effective amount of said medicament, the presence of medicament and optional components making the total 100%.

The present invention is directed to an extruded single or multi-layered laminated thin (1-10 mils or 0.025-0.25 mm) film, composed of selected water soluble and/or insoluble polymers. Various therapeutic agents are incorporated into the film during manufacture which are useful for treatment of oral disorders (i.e., denture discomfort, caries, periodontal disease, aphthous ulcers, etc.).

The extruded film of the present invention must have at least one bioadhesive layer, but may also have a reservoir layer and/or an outer protective barrier membrane layer. The therapeutic agent may be incorporated into any or all of the layers. When properly formulated and fabricated, these films will adhere to wet mucosal surfaces, provide a protective barrier for injured tissue and deliver controlled/sustained dosages of medication to the infected areas. The film may be designed for localized drug delivery (i.e., the periodontal pocket, an aphthous lesion), or may allow diffusion of the drug into the oral cavity.

An example of a non-localized system would be the delivery of sodium fluoride for caries prevention. A single or laminated film with good adhesion to the tooth or mucosal tissue may be employed in which the fluoride release rates may be controlled by varying film solubilities and/or concentration of fluoride in a multi-layered film.

An example of a localized application of medication would be in the treatment of aphthous lesions. A laminated two layer film with benzocaine incorporated into the adhesive layer would directly contact the injured mucosa. The outer layer would consist of non-soluble/non-adhesive polymers that provide durability, protection and directs the delivery of benzocaine toward the lesion.

The film forming polymers that are useful in this invention are selected from pharmaceutical grade materials, or those that are considered generally regarded as safe (GRAS) as food additives. They include, hydroxypropyl cellulose, and polyethylene oxide homopolymers. Small amounts of other polymers. e.g., polyvinyl ether-maleic acid copolymers and the like may be used in small amounts as well, replacing a small portion of the other polymers. The above materials are either water soluble or swellable and are most useful in the bioadhesive layer of the film. Various non-soluble polymers may also be incorporated for modification of the film's permeability properties, such as ethyl cellulose, propyl cellulose, polyethylene, polypropylene and carboxymethylcellulose (free acid) in an amount of up to 12.5% by weight. By varying the ratios of the above polymers both the solubility and the adhesive properties of each layer of film may be controlled. Therefore, depending on the desired delivery rate, the type of disorder to be treated, the area to be treated and the medication being administered it is possible to custom design the film by selecting and blending various polymers. The final film product may also be fabricated into flexible tapes of varied thickness and width, "spots" of different sizes and shapes or other pre-shaped forms.

The medicaments and pharmaceutical agents set forth in the prior art discussed above may generally be delivered by the drug delivery system of the present invention. Usable medicaments are those which are capable of withstanding the heats and pressures generated in the extrusion process involved in making the film of the present invention. Preferred medicaments include:

Anesthetics/Analgesics - benzocaine, dyclonine HCl, phenol, aspirin, phenacetin, acetaminophen, potassium nitrate, etc.

Anticaries Agents - sodium fluoride, sodium monofluorophosphate, stannous fluoride, etc.

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Anti-inflammatories - hydrocortisone acetate, triamcinolone acetonide, dipotassium, glycyrrhizinate, etc.
Antihistamines - chlorpheniramine maleate, ephedrine HCL, diphenhydramine HCL, etc.
Antibiotics - i.e., tetracycline, doxycycline hyclate, meclocycline, minocycline, etc.
Antibacterials - chlorhexidine, cetyl pyridinium chloride, benzethonium chloride, dequalinium chloride, silver sulfadiazene, phenol, thymol, hexedine, hexetidine, alexidine, etc.
Fungistats - nystatin, miconazole, ketoconazole, etc.

The above are illustrative examples of therapeutic agents that are used to treat oral disorders. The present invention is not to be limited to these specific materials especially where it is intended to deliver drug outside of the oral cavity e.g. to skin where other drugs may be desirable.

The film of the present invention has the advantage of being an extruded film, rather than a cast film. When a multi-layered film is involved, the different layers can be coextruded and then laminated together, or else each layer can be separately extruded one on the other, and then laminated together, so that the final multi-layered film is still very thin. The films of the present invention can be made in thicknesses of only 1-10 mils or 0.025-0.25 mm. The films are so thin that when placed in the mouth after they become wet they soon become unobtrusive, and hardly noticeable by most patients.

The film must always have a bioadhesive layer, which enables it to adhere to wet mucosal surfaces. The bioadhesive layer has 22.4-68.3 wt % of hydroxpropyl cellulose, 23.75-60 wt % of a homopolymer of ethylene oxide and 2.85-5 wt % of a glycol plasticizer (all percents are % by weight).

The Hydroxypropyl cellulose (HPC), useful for purposes of the present invention is commercially available from Hercules, Inc. (Wilmington, DE) under the tradename KLUCEL*. Preferred grades include Klucel MF, with a molecular weight around 600,000 and having a viscosity of 4,000-6,000 cps (Brookfield) in 2 percent water solutions, or Klucel HP, having a molecular weight around 1,000,000 and viscosity of 1500-2500 cps in 1 percent water solution. Any HPC having a Molecular Weight above about 100,000 is useful for purposes of this invention.

The homopolymer of ethylene oxide useful for purposes of the present invention has a relatively high molecular weight, i.e., above 100,000 and preferably above 3,000,000. Such polymers are commercially available from various sources. The Union Carbide Corporation material, "Polyox WSR-301", which has a molecular weight of approximately 4,000,000 - 5,000,000 is most preferred for purposes of the present invention.

The "plasticizer" useful for purposes of the present invention are selected from glycols such as propylene glycol and polyethylene glycol; polyhydric alcohols such as glycerin and sorbitol; glycerol esters such as glycerol triacetate; fatty acid triglycerides such as NEOBEE* M-5 and MYVEROLS*; mineral oil; vegetable oils such as castor oil, etc.

For the uses for the present invention contemplated here, the plasticizer should be non-toxic. The purpose of the plasticizer is to improve polymer melt processing by reducing the polymer melt viscosity and to impart flexibility to the final product.

The preferred plasticizer for use in the present invention is either propylene glycol or polyethylene glycol (such as is available from Union Carbide Corporation as their series of Carbowaxes which runs from 200 to 600 molecular weight, of which we prefer to use Carbowax 400, which has a molecular weight of 400, average.

In addition to the polymers and plasticizer which are required ingredients of the films of the present invention, minor amounts of other non-essential but customary ingredients will often be used if desired, e.g., antioxidants, preservatives, flavors, colorants.

Detailed Description

The following examples will serve to illustrate the present invention in greater detail. The units shown in the examples are parts by weight. The thickness of the layers is expressed in either mils (.001 inches) or millimeters. For easy conversion, 4 mils is approximately equal to 0.1 mm.

EXAMPLE 1 - TRIPLE LAYERED LAMINATE CONTAINING SODIUM FLUORIDE FOR ANTICARIES PROTECTION:

This three layered film laminate is comprised of a "bioadhesive" layer, a sodium fluoride "reservoir" layer and, an "outer protective barrier membrane" layer, in which the composition and thickness of each layer are as shown below:

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Ingredients	Bioadhesive Layer (4 mils) (0.1 mm)	% w/w Reservoir Layer (1 mil) (0.025 mm)	Outer Protective Barrier Membrane Layer (1 mil) (0.025 mm)
Polyethylene oxide homopolymer (Union Carbide-Polyox* WSR-301)	60.0	-	-
Hydroxypropyl Cellulose (Hercules, Inc.-Klucel* MF)	30.0	20.0	24.0
Polyethylene (Allied Chemical-6A) (Low Density)	5.0	-	-
Propylene Glycol, U.S.P.	3.0	-	-
Polyethylene Glycol 400 (Union Carbide)	2.0	-	-
Ethyl Cellulose (Hercules, Inc.-N100F)	-	59.0	69.6
Caprylic/Capric Triglyceride (PVO Incorporated-Neobee M-5)	-	5.0	6.0
Sodium Fluoride, U.S.P.	-	16.0	0.4
	100.0	100.0	100.0

The process used to make the above laminate was :

a) Powder Blending - Each layer is made separately and all ingredients used therein except propylene glycol and Neobee M-5 (liquid plasticizers) are placed in a Patterson Kelley (PK) V-blender equipped with liquid addition capabilities. The ingredients which are all powders are blended for approximately 10-15 minutes while the liquid plasticizer is slowly added to the mix. Three separate powder blends are made, one for each layer.

b) Extrusion Process - A standard Johnson 2-1/2 inch (0,0635 m) vinyl/polyolefin extruder equipped with a single three stage screw was used to extrude the "powder blend". The temperature conditions for the water soluble powders are however quite different from those used for vinyls and polyolefins. The

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temperature (°C) profile for the "reservoir" and "membrane layers" of the triple laminate was as follows:

Barrel Zone 1	100
Barrel Zone 2	125
Barrel Zone 3	135
Barrel Zone 4	145
Barrel Zone 5	160
Barrel Zone 6	170
Adapter -	180
Die Zone 1	180
Die Zone 2	180
Die Zone 3	180

The films which had a width of 18 inches (0,45 m), were extruded at approximately 20 feet/minute (6 m/min) through a flat lipped die. The temperature profile for the "bioadhesive layer" was:

Barrel Zone 1	125
Barrel Zone 2	140
Barrel Zone 3	165
Barrel Zone 4	170
Barrel Zone 5	185
Barrel Zone 6	185
Adapter -	185
Die Zone 1	185
Die Zone 2	185
Die Zone 3	185

Each layer is extruded separately with the first layer extruded as a "free film". Successive layers are extruded onto each other and laminated by passing them through heated stainless steel rollers.

Test Results:

In vitro fluoride ion release studies were conducted on samples of the above described triple laminate film measuring 0.5 cm x 1.25cm (0.625 cm^2) according to the following procedures:
The test sample is adhered to a glass slide by prewetting the film and placing the bioadhesive layer on the glass surface. The slide is then immersed in a beaker containing 100 ml of distilled water with continuous stirring. Five milliliter aliquots are withdrawn from the solution, at prescribed time intervals, and analyzed for fluoride content with an Orion Ionanlyzer equipped with a fluoride specific electrode. Release rates are then calculated from the data.

The results obtained indicated fluoride release rates in the order of 0.05-0.2 mgs/cm^2/hr for 24 hours. This falls within the desirable range for maintaining constant low levels of fluoride in the mouth and enhanced anticaries activity. Release rates may be tailored to desired use levels by modification of the film composition and construction.

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EXAMPLE 2 - SINGLE LAYER ADHESIVE FILM CONTAINING HYDROCORTISON ACETATE (0.5%) AS AN ANTI-INFLAMMATORY AGENT:

The composition of the film, which was 0.1 mm. thick, was as follows:

Ingredients	% w/w
Ethylene Oxide Homopolymer (Polyox* WSR-301)	59.4
Hydroxypropyl Cellulose (Klucel* MF)	30.0
Polyethylene (AC-6A)	5.0
Propylene Glycol	3.0
Polyethylene Glycol 400	2.0
Butylated Hydroxy Toluene (BHT) FCC (preservative)	0.1
Hydrocortisone Acetate	0.5
	100.0

The powder blending process and extruder conditions used were the same as those described in Example I for the "bioadhesive layer" of the sodium fluoride trilaminate. In vitro tests were performed on the above film and demonstrated a prolonged drug release pattern.

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EXAMPLE 3 - SINGLE LAYER ADHESIVE FILM CONTAINING TRIAMCINOLONE ACETONIDE (0.1%) AS AN ANTI-INFLAMMATORY:

The composition of the film, which was 0.1 mm. thick, was as follows:

Ingredients	% w/w
Ethylene Oxide Homopolymer (Polyox WSR-301)	59.9
Hydroxypropyl Cellulose (Klucel MF)	29.9
Polyethylene (AC-6A)	5.0
Propylene Glycol	3.0
Polyethylene Glycol 400	2.0
BHT	0.1
Triamcinolone Acetonide	0.1
	100.0

The powder blending process and extruder conditions used to make the film of this Example 3 were the same as those of the "bioadhesive layer" of Example I.

Other desired active medicament ingredients may be incorporated into the adhesive films of any of Examples 1-3 in place of the particular medicament used in said examples. These include Benzocaine (analgesic), Potassium nitrate (analgesic), Silver sulfadiazene (antimicrobial).

Chlorhexidine (antimicrobial), miconazole nitrate (antifungal), Benzethonium chloride (antimicrobial), Tetracycline (antibiotic) and other similar therapeutic compounds.

EXAMPLE 4 - ANALGESIC FILMS WITH POTASSIUM NITRATE

This example shows 5 variations of the film having different solubilities, resulting in different release rates.

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Ingredients	% w/w 1	2	3	4	5
Polyethylene oxide homopolymer (Polyox* WSR-301)	23.75	57.00	55.00	55.00	57.00
Hydroxypropyl Cellulose, N.F. (Klucel* HF)	68.30	-	-	-	-
Hydroxypropyl Cellulose, N.F. (Klucel* MF)	-	28.40	29.90	22.40	22.40
Ethyl Cellulose	-	4.75	5.00	12.50	12.50
Polyethylene Glycol 400	1.90	1.90	2.00	2.00	2.00
Polyethylene Glycol 8000	0.95	-	-	-	-
Propylene Glycol, U.S.P.	-	2.85	3.00	3.00	3.00
BHT, F.C.C.	0.10	0.10	0.10	0.10	0.10
Potassium Nitrate, F.C.C.	5.00	5.00	5.00	5.00	3.00

The above ingredients are blended in a Patterson-Kelly powder blender equipped with liquid addition capabilities. The resulting powder blend is then extruded into film on a Killion or Johnson vinyl extruder using processing procedures similar to those of the bioadhesive layer of Example I.

EXAMPLE 5 - ANESTHETIC FILMS WITH BENZOCAINE (LAMINATE)

This is an example of a two-layer laminate. The processing conditions used were similar to those of the bioadhesive layer and outer protective barrier membrane layer of Example I.

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A.	Inner medicated bioadhesive layer	
	Polyoxyethylene Homopolymer (Polyox* WSR-301)	57.00
	Hydroxypropyl Cellulose, N.F. (Klucel* MF)	28.40
	Polyethylene (AC-6A)	4.75
	Propylene Glycol, U.S.P.	2.85
	Polyethylene Glycol 400	1.90
	BHT, F.C.C.	0.10
	Benzocaine, U.S.P.	5.00
		100.00
B.	Outer protective/barrier layer	
	Hydroxypropyl Cellulose (Klucel* MF)	78.00
	Ethyl Cellulose	20.00
	Polyethylene Glycol 400	2.00
		100.00

Part A was extruded on a Johnson extruder followed by subsequent extrusion and lamination of Part B to A.

Samples were applied to oral lesions, and provided profound anesthetic effects (lasting several hours) within minutes of application.

The identical two-layer laminate may also be made by coextruding the inner medicated bioadhesive layer (Part A) and the outer protective barrier layer (Part B) through separate die slots within a coextruder and laminating the two layers together.

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EXAMPLE 6 - ANESTHETIC FILMS WITH PHENOL AND DYCLONINE HCl

Four variations of a single layer bioadhesive film were made as shown below:

Ingredients	1	2	3	4
Polyethylene oxide homopolymer (Polyox* WSR-301)	59.10	54.00	59.70	58.20
Hydroxypropyl Cellulose (Klucel HF)	29.45	26.91	29.75	29.00
Ethyl Cellulose	4.93	4.50	4.98	4.85
Propylene Glycol, U.S.P.	2.96	2.70	2.99	2.91
Polyethylene Glycol 400	1.97	1.80	1.99	1.94
BHT, F.C.C.	0.09	0.09	0.09	0.10
Phenol, U.S.P.	1.50	-	-	-
Dyclonine HCl	-	10.00	0.50	3.00

Following the procedures for the bioadhesive layer of Example I, the powders were blended in P-K blender equipped with liquid addition capabilities. Resulting powders were extruded on a Killion laboratory-sized extruder.

EXAMPLE 7 - SILVER SULFADIAZENE FILMS - ANTIMICROBIAL

Three different single-layered bioadhesive films containing 1.0% 0.5% and 0.5% respectively of silver sulfadiazene (SSD) were prepared on a heated Carver laboratory press (designed to simulate extruded conditions) as shown below.

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Ingredients	% w/w A	% w/w B
Polyethylene oxide homopolymer (Polyox* WSR-301)	60.00	60.00
Hydroxypropyl Cellulose (Klucel* HF)	28.9	29.4
Polyethylene (AC-6A)	5.0	5.0
Propylene Glycol, U.S.P.	3.0	3.0
Polyethylene Glycol 400	2.0	2.0
BHT, F.C.C.	0.1	0.1
Silver Sulfadiazine	1.0	0.5
	100.0	100.0

Effects on wound repair and activity against Staphylococcus aureus were evaluated in the guinea pig model. Full-thickness excisions were inoculated with 3.8 x 10^5 organisms, (Staph. aureus) and wound surface microbiology samples taken 10 minutes and 24 hours after treatment. Test films were placed on the wound and covered with BIOCLUSIVE* Transparent Dressings secured with elastic tape. Wound contraction was measured over an eight-day period using OPTOMAX* Computer-Assisted Image Analysis. The three films tested were the following:

A. 1.0% Silver Sulfadiazene, 125 ° C/2 minutes/4 tons
B. 0.5% Silver Sulfadiazene, 125 ° C/2 minutes/4 tons
C. 0.5% Silver Sulfadiazene, 150 ° C/3 minutes/4 tons

SILVADENE Cream and un untreated occluded control. The results indicated that:

1. SILVADENE* treated wounds significantly inhibited full-thickness wound contraction.
2. Film A, B and C inhibited wound contraction relative to that of BIOCLUSIVE* dressed wounds.
3. The three SSD films each permitted substantially faster wound contraction than that of wounds treated daily with SILVADENE* cream.
4. All films were very active against S. aureus 24 hours after inoculation.

The films may be scaled up by using an extruder. This example demonstrates the feasibility of such a film to perform its intended purpose. Use of a press for larger samples would result in a non-uniform and lower-quality film than an extruded film.

Based on the above findings, the films were very effective antibacterial agents, while mildly inhibiting wound contraction. They offer clinicians a convenient and more effective delivery system for antimicrobials which can be place in wounds beneath any dressing or can be laminated to any acceptable dressing face.

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Claims

1. A pharmaceutically acceptable controlled-releasing medicament-containing extruded single or multilayered thin film, capable of adhering to a wet mucous surface, comprising a water soluble or swellable polymer matrix bioadhesive layer which can adhere to a wet mucous surface and which bioadhesive layer consists essentially of 22.4-68.3% by weight of a hydroxypropyl cellulose having a molecular weight above 100,000, 23.75-60% by weight of a homopolymer of ethylene oxide having a molecular weight above 100,000, 0-12.5% by weight of a water-insoluble polymer selected from ethyl cellulose, propyl cellulose, carboxymethyl cellulose free acid, polyethylene and polypropylene, and 2.85-5% of a plasticizer, said film having incorporated therein a pharmaceutically effective amount of said medicament, the presence of medicament and optional components making the total 100%.

2. The extruded film of claim 1, made in a form which is so thin and flexible when wet as to be unobtrusive to the patient when properly positioned and placed in the patient's mouth.

3. The extruded film of claim 2 having a thickness no greater than 0.25 millimeters.

4. The extruded film of claim 3 wherein, in the bioadhesive layer the homopolymer of ethylene oxide has a molecular weight from 3,000,000 to 5,000,000.

5. The extruded film of Claim 3, in multi-layer laminated form, which in addition to the bioadhesive layer also contains a reservoir layer in which at least a major portion of the medicament is contained.

6. The extruded multi-layer film of Claim 5 in which the reservoir layer consists essentially of a polymer matrix comprised of both a water soluble or swellable polymer and a non-water soluble polymer selected from ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and also hydroxypropyl cellulose.

7. The extruded film of Claim 4 in multi-layer laminated form, which in addition to the bioadhesive layer also contains an outer protective-barrier membrane layer.

8. The extruded multi-layer film of Claim 7 in which the outer protective-barrier membrane layer is thinner than the bioadhesive layer, and said outer protective barrier layer consists essentially of a polymer matrix of a major proportion of a non-water-soluble polymer selected from ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and a minor proportion of hydroxypropyl cellulose.

9. The extruded multi-layer film of Claim 1 in the form of a triple layered laminate containing sodium fluoride for anticaries protection having the following composition:

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Ingredients	Bioadhesive Layer (0.1 mm)	% w/w Reservoir Layer (0.025 mm)	Outer Protective Barrier Membrane Layer (0.025 mm)
Polyethylene oxide homopolymer (MW 3,000,000 minimum)	60.0	-	-
Hydroxypropyl Cellulose (MW 1,000,000)	30.0	20.0	24.0
Polyethylene (Low Density)	5.0	-	-
Propylene Glycol, U.S.P.	3.0	-	-
Polyethylene Glycol (MW 400)	2.0	-	-
Ethyl Cellulose	-	59.0	69.6
Caprylic/Capric Triglyceride	-	5.0	6.0
Sodium Fluoride	-	16.0	0.4
	100.0	100.0	100.0

Patentansprüche

1. Ein pharmazeutisch verträglicher, dünner extrudierter Film, der ein Medikament enthält und kontrolliert freisetzt, mit einer einzigen oder mit mehreren Schichten, der die Fähigkeit aufweist, daß er auf der nassen Schleimhautoberfläche festkleben kann, umfassend eine wasserlösliche oder quellbare Polymermatrix einer bioadhäsiven Schicht, die auf der nassen Oberfläche der Schleimhaut kleben kann, wobei die bioadhäsive Schicht im wesentlichen aus 22,4 - 68,3 Gew.-% Hydroxypropyl-Cellulose mit einem Molekulargewicht von oberhalb 100 000, 23,75 - 60 Gew.-% eines Homopolymers von Ethylenoxid mit einem Molekulargewicht von oberhalb 100 000, 0 - 12,5 Gew.-% eines wasserunlöslichen Polymers, ausgewählt aus Ethyl-Cellulose, Propyl-Cellulose, Carboxymethyl-Cellulose in Form der freien Säure, Polyethylen und Polypropylen und 2,85 - 5 % eines Weichmachers besteht, wobei der Film eine pharmazeutisch wirksame Menge des Medikamentes inkorporiert enthält und das Medikament und die wahlweise enthaltenen Komponenten insgesamt 100 % ergeben.

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2. Extrudierter Film nach Anspruch 1, der in einer Form hergestellt ist, die so dünn und flexibel ist, daß er, wenn er naß ist, den Patienten nicht stört, wenn er im Mund des Patienten an die richtige Stelle gelegt und eingebracht worden ist.

3. Extrudierter Film nach Anspruch 2 mit einer Dicke, die nicht größer als 0,25 mm ist.

4. Extrudierter Film nach Anspruch 3, bei dem die bioadhäsive Schicht des Homopolymers von Ethylenoxid ein Molekulargewicht von 3 000 000 bis 5 000 000 aufweist.

5. Extrudierter Film nach Anspruch 3 in einer mehrschichtigen laminierten Form, die zusätzlich zur bioadhäsiven Schicht noch eine Reservoir-Schicht enthält, in der zumindest ein Hauptanteil des Medikamentes enthalten ist.

6. Extrudierter mehrschichtiger Film nach Anspruch 5, in dem die Reservoir-Schicht im wesentlichen aus einer polymeren Matrix besteht, die sowohl aus einem wasserlöslichen und quellbaren Polymer und einem nichtwasserlöslichen Polymer besteht, das ausgewählt ist aus Ethyl-Cellulose, Propyl-Cellulose, Polyethylen und Polypropylen und auch Hydroxypropyl-Cellulose.

7. Extrudierter Film nach Anspruch 4 in Form eines mehrschichtigen Laminates, das zusätzlich zur bioadhäsiven Schicht auch eine äußere Schicht aus einer protektiven Membranbarriere enthält.

8. Extrudierter mehrschichtiger Film nach Anspruch 7, bei dem die äußere Schicht mit einer protektiven Membranbarriere dünner ist als die bioadhäsive Schicht und in dem die protektive Barriereschicht im wesentlichen aus einer Polymermatrix aus einem Hauptanteil eines nichtwasserlöslichen Polymers, das ausgewählt ist aus Ethyl-Cellulose, Propyl-Cellulose, Polyethylen und Polypropylen und einem geringeren Anteil von Hydroxypropyl-Cellulose, besteht.

9. Extrudierter mehrschichtiger Film nach Anspruch 1 in Form eines dreischichtigen Laminats, das Natriumfluorid zum Antikariesschutz enthält und das die folgende Zusammensetzung aufweist:

Bestandteile	bioadhäsive Schicht (0,1 mm)	% Gew./Gew. Reservoirschicht (0,025 mm)	äußere protektive Schicht der Membranbarriere (0,025 mm)
Homopolymer des Polyethylenoxids (MG mindestens 3 000 000)	60,0	-	-
Hydroxypropyl-Cellulose (MG 1 000 000)	30,0	20,0	24,0
Polyethylen (geringe Dichte)	5,0	-	-
Propylen-Glycol, U.S.P.	3,0	-	-
Polyethylen-Glycol (MG 400)	2,0	-	-
Ethyl-Cellulose	-	59,0	69,6
Capryl/Caprinsäure-Triglycerid	-	5,0	6,0
Natriumfluorid	-	16,0	0,4
	100,0	100,0	100,0

Revendications

1. Film mince extrudé mono- ou multicouche pharmaceutiquement acceptable contenant un médicament à libération contrôlée pouvant adhérer sur une surface de muqueuse humide, comprenant une couche bioadhésive de matrice de polymère gonflable ou soluble dans l'eau qui peut adhérer sur une surface de muqueuse humide et cette couche bioadhésive est constituée essentiellement de 22,4-68,3 % d'hydroxypropylcellulose ayant un poids moléculaire supérieur à 100 000, de 23,75-60% en poids d'un homopolymère d'oxyde d'éthylène ayant un poids moléculaire supérieur à 100 000, 0-12,5 % en poids d'un polymère insoluble dans l'eau choisi parmi l'éthylcellulose, la propylcellulose, la carboxyméthylcellulose exempte d'acide, le polyéthylène et le polypropylène, et 2,85-5 % d'un plastifiant, ledit film

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contient une quantité pharmaceutiquement efficace du médicament qui y est incorporée, la présence du médicament et de composants éventuels faisant le complément du total de 100 %.

2. Film extrudé de la revendication 1, d'une forme suffisamment fine et souple quand il est humide de façon à ne pas gêner le patient quand il est placé et positionné correctement dans la bouche du patient.

3. Film extrudé de la revendication 2 ayant une épaisseur non supérieure à 0,25 millimètre.

4. Film extrudé de la revendication 3 dans lequel, dans la couche bioadhésive l'homopolymère d'oxyde d'éthylène a un poids moléculaire de 3 000 000 à 5 000 000.

5. Film extrudé de la revendication 3 sous forme feuilletée multicouche, qui contient aussi en plus de la couche bioadhésive une couche réservoir dans laquelle se trouve au moins une portion majeure du médicament.

6. Film multicouche extrudé de la revendication 5 dans lequel la couche réservoir est constituée essentiellement d'une matrice polymère contenant à la fois un polymère gonflable ou soluble dans l'eau et un polymère non soluble dans l'eau choisi parmi l'ethylcellulose, la propylcellulose, le polyéthylène et le polypropylène, et aussi de l'hydroxypropylcellulose.

7. Film extrudé de la revendication 4 sous forme feuilletée multicouche, qui contient en plus de la couche bioadhésive une couche membrane barrière de protection externe.

8. Film extrudé multicouche de la revendication 7 dans lequel la membrane barrière protectrice externe est plus mince que la couche bioadhésive, et ladite couche barrière protectrice externe est constituée essentiellement d'une matrice polymère composée en proportion majoritaire d'un polymère non soluble dans l'eau choisi dans le groupe de l'éthylcellulose, de la propylcellulose, du polyéthylène et du polypropylène, et d'une proportion mineure d'hydroxypropylcellulose.

9. Film multicouche extrudé de la revendication 1 sous forme d'un lamifié à triple couche contenant du fluorure de sodium pour la protection anticaries qui a la composition suivante :

Ingrédients	couche Bioadhésive 0,1 mm	% pds/pds Couche Réservoir (0,025 mm)	couche Membrane Barrière Protectrice Externe (0,025 mm)
Oxyde de Polyéthylène homopolymère (PM 3 000 000 minimum)	60,0	-	-
Hydroxypropylcellulose (PM 1 000 000)	30,0	20,0	24,0
Polyéthylène (basse densité)	5,0	-	-
Propylèneglycol, U.S.P.	3,0	-	-
Polyéthylèneglycol (PM 400)	2,0	-	-
Ethylcellulose	-	59,0	69,6
Triglycéride caprylique/caprique	-	5,0	6,0
Fluorure de sodium	-	16,0	0,4
	100,0	100,0	100,0

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Abstract not available for EP 0452446 (A1)
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An oral and dental hygiene preparation consists of tensides, polishing agents, flavourings and other usual additives, incorporated in a binder or mixture of binders in the form of water-soluble or water-dilatable, physiologically acceptable foil-forming substances. The mixture is processed to a foil, which is predivided into dosage units.

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Beschreibung

Zahnpflegemittel werden seit vielen Jahren als Pasten, sogenannte Zahnpasten hergestellt. Dabei ist der wesentliche Ausgangsstoff eine Schlämmkreide, die mit Wasser, Glycerin, waschaktiven Stoffen und Verdickungsmitteln zu einer Paste verarbeitet und in Tuben oder Spendern abgefüllt wird. Die Zahnpasta hat den Markt erobert, während andere Zahnpflegemittel wie Tropfen, Zahnseifen und - pulver oder Granulate kaum noch eine Rolle spielen. Mit den Mitteln soll der bakterielle Zahnbelag entfernt, Kariesprophylaxe betrieben sowie die Reinigung der Zähne schonend und durch die Bürstenbehandlung wesentlich unterstützt durchgeführt und der Mundraum gründlich gereinigt und angenehm erfrischt werden.

In neuerer Zeit hat sich das Bild der Zahnpasten nicht wesentlich verändert, obwohl die Rezepturen in vielerlei Hinsicht abgewandelt wurden. Die Verwendung einer recht groben Kreideform zum mechanischen Reinigen der Zähne wich mehr und mehr modernen, feineren Poliermitteln auf Basis von Aluminiumoxid oder Siliciumdioxid (Kieselgele). Neben Tensiden finden strukturbildende Komponenten und ausgefeilte Geschmackskorrigentien Verwendung. Oft werden Wirkstoffe wie insbesondere verschiedene Fluorderivate oder Mineralsalze zugefügt. Das Volumen konnte teilweise reduziert werden; sicherlich hat die Einführung und allgemeine Verwendung elektrischer Zahnbürsten hierbei einen starken Einfluß gehabt.

Die Handhabung von Zahnpasten ist jedoch mit einer Reihe von Nachteilen verbunden. Weil die Dosierung aus einfachen Tuben Schwierigkeiten bereitet, hat man in neuerer Zeit Zahnpastaspender entwickelt, welche jeweils eine vorbestimmte Menge Zahnpasta abgeben. Diese Spender sind jedoch verhältnismäßig groß und daher keinesfalls zur Mitnahme auf Reisen geeignet. Tuben sind druckempfindlich und daher auf Reisen ebenfalls nicht ideal. Sowohl in Spendern als auch in Tuben kann Zahnpasta austrocknen, so daß die angebrauchten Behälter dann weggeworfen werden müssen. Ferner lassen sich sowohl Tuben als auch Spender nicht vollständig entleeren. Nach Verbrauch bleiben die aus Metall oder Plastik hergestellten Behälter zurück und verursachen Umweltprobleme.

Aus der GB-A-21 63 348 sind Zahnreinigungstabletten bekannt, welche durch Zerbeißen und längeres Kauen im Munde eine pastenartige Konsistenz annehmen und dann zur Zahnreinigung dienen können. Eine Anwendung in der üblichen Weise durch Aufbringung auf eine Zahnbürste und anschließendes Einführen in den Mund ist nicht möglich. Verbrauchern mit schadhaften Zähnen oder Zahnersatz ist ein Zerbeißen spröder, harter Tabletten nicht möglich. Ferner können Kautabletten dieser Art auch nicht zur Reinigung künstlicher Zähne bzw. Gebisse verwendet werden.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine neue Verabreichungs- und Dosierungsform für Mund- und Zahnpflegemittel zu entwickeln, welche die vorstehend genannten Nachteile nicht aufweist, sich jedoch ähnlich wie Zahnpasta mit Hilfe einer Zahnbürste anwenden läßt.

Insbesondere soll eine genaue Dosierung für eine Zahnreinigung ermöglicht und sichergestellt werden, daß das Mittel vollständig aufgebraucht werden kann, ohne daß Reste in der Packung zurückbleiben.

Das erfindungsgemäße Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusätzen ist dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittelmischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildnern bestehen, wobei die gebildete Folie in Dosiseinheiten vorzerteilt ist.

Als Bestandteile des Mund- und Zahnpflegemittels kommen die Komponenten in Frage, welche üblicherweise zur Herstellung von Zahnpasten Verwendung finden, wobei natürliche Rohstoffe besonders bevorzugt sind. Wichtig ist darüber hinaus, daß alle Bestandteile völlig ungiftig und physiologisch unbedenklich sind, was selbstverständlich auch für die verwendeten Folienbildner gilt. Als wesentliche Bestandteile von Zahnpflegemitteln sind zu nennen:

- Schleifmittel wie Kreide (Calciumcarbonat), Calcium- und Natriumphosphate, Aluminiumoxid oder Siliciumdioxid, insbesondere Kieselgele
- Tenside (Schaummittel) wie Natriumlaurylsulfat, Natriumlaurylsulfoacetat, Sarcoside, Monoglyceridsulfate und andere
- Aromastoffe wie Pfefferminzöl, Krauseminzöl, Anisöl, Zimtöl, Nelkenöl, Menthol und ähnliche
- Süßstoffe wie Saccharin, Cyclamat, Aspartam und ähnliche.

Die in Zahnpasten üblicherweise enthaltenen flüssigen Komponenten wie Glycerin, Propylenglykol oder Sorbitsirup müssen den erfindungsgemäßen Mitteln in Folienform nicht in den üblichen Mengen zugesetzt werden, da hier die für Tuben oder Spender erforderliche Plastizität keine Rolle spielt. Weitere übliche Zusätze wie Fluorverbindungen, Mittel gegen Zahnsteinbildung, antibakterielle Wirkstoffe und ähnliche, wie sie in Mund- und Zahnpflegemitteln üblicherweise Verwendung finden, können auch erfindungsgemäß eingesetzt werden.

Als wasserlösliche bzw. -quellbare Folienbildner eignen sich vor allem Stärken, Gelatinen, Glycerin und-/oder Sorbit sowie ferner natürliche oder synthetische Harze und Gumme. Folgende Rahmenrezeptur hat sich

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bewährt:

Gelatine	8 - 10 g
Stärke	3 - 8 g
Glycerin	1 - 2 g
Wasser	30 - 50 g.

In dieser Grundmasse werden die Bestandteile des Mund- und Zahnpflegemittels gelöst bzw. dispergiert, um eine gleichmäßige Verteilung der Stoffe zu erreichen. Die so erhaltene Mischung kann erfindungsgemäß in verschiedener Weise zu einem folienförmigen Mund- und Zahnpflegemittel verarbeitet werden:

a) Es ist einmal möglich, die Masse direkt zu einer Folie zu verarbeiten, welche im allgemeinen eine Dicke zwischen 0,1 und etwa 3 mm aufweist. Durch Sollbruchstellen mittels Stanzung oder Perforierung kann diese Folie in Dosiseinheiten vorzerteilt werden, wobei die Streifenbreite und -länge vorzugsweise etwa der Zahnbürstengröße, d.h. der von den freien Borstenenden gebildeten Fläche des Borstenblocks oder der Längsquerschnittfläche des Borstenblocks in der Borstenebene entsprechen sollte.

b) Alternativ kann die Masse auf eine Trägerfolie aufgebracht werden, deren Zusammensetzung derjenigen des Bindemittels der Masse entspricht, wie dies in der EP-A-219,762 im einzelnen offenbart ist. Auch die auf diese Weise erhaltenen Folien können wie oben angegeben vorzerteilt werden.

c) Es ist ferner möglich, die Masse auf eine Releasefolie oder ein Releasepapier aufzubringen, wie dies aus der EP-A-259 749 bekannt ist. In diesem Fall wird die Beschichtung in einzelne Abschnitte der oben angegebenen Größe vorzerteilt, welche sich ähnlich wie Haftetiketten von der Trägerfolie vor Gebrauch abziehen lassen.

In allen Fällen erhält man eine Darreichungs- und Dosierungsform, deren Anwendung besonders leicht ist, da die jeweils zu verwendende Menge gleichmäßig vorgegeben ist. Eine Dosis wird in Form eines Folienabschnittes abgetrennt bzw. abgezogen und auf die angefeuchtete Zahnbürste bzw. zwischen die Borsten gelegt, wo sie durch die Feuchtigkeitsberührung haftet und anquillt. Durch das Einführen in die Mundhöhle und in Verbindung mit dem Speichel und der intensiven Zahnbürstenbewegung wird der Streifen an- und aufgelöst, so daß die Inhaltsstoffe zur vollen Wirkung gelangen. Nach der Anwendung und der anschließenden Mundspülung mit Wasser verbleiben keinerlei Rückstände im Mund.

Gewünschtenfalls können die Folien in unterschiedlicher Weise bedruckt, geprägt oder gestanzt werden, wobei beispielsweise für Kinder auch bildliche Darstellungen möglich sind. Es entfällt das Öffnen und Schließen von Tubenverschlüssen, es wird keine Zahnpasta vergeudet und die erfindungsgemäße Darreichungsform läßt sich auch besondes gut auf Reisen einsetzen, da sie leicht ist, ein Auslaufen nicht befürchtet werden muß und sie äußerst wenig Platz beansprucht. Die Verpackung ist umweltfreundlich in Pappschachteln ohne Verwendung von Metallen oder Kunststoff möglich.

Die Mittel der Erfindung eignen sich nicht nur zur Zahnpflege im Mund, sondern bei geeigneter Zusammensetzung auch zur Reinigung und Pflege von künstlichen Zähnen und Gebissen. Für diesen letzteren Einsatzzweck ist eine Mehrfachbeschichtung besonders günstig, bei der sich in einer Schicht die reinigenden, desinfizierenden und sauren Komponenten befinden, während sich, ggf. getrennt durch eine ebenfalls wasserlösliche Sperrschicht, in einer zweiten Schicht die CO_2 bzw. O_2 abgebenden Substanzen enthalten sind.

Beispiel

Ein erfindungsgemäßes Zahnpflegemittel hat folgende Zusammensetzung:

Amylogum	57,0 g
Honig	25,0 g
Zitronensäure	2,0 g
Titandioxid	1,0 g
Aroma	1,0 g
Siliciumdioxid	3,0 g
Ca-Hydrog-phos.	10,0 g
Na-Laurylsulfat	1,0 g

Mit der erforderlichen Menge Wasser wird ein Brei hergestellt, der zu einer Folie verarbeitet wird, die ca. 0,5 mm dick ist. Durch Perforation wird die Folie in Abschnitte von 8 x 35 mm unterteilt.

Gegebenenfalls kann die Masse auch als Beschichtung auf ein Releasepapier als Träger aufgebracht und durch Stanzung in Abschnitte der angegebenen Größe vorzerteilt werden.

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Patentansprüche

1. Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen, dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittel-Mischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildnern bestehen, und daß diese Mischung zu einer Folie verarbeitet ist, wobei die so gebildete Folie in Dosiseinheiten vorzerteilt ist.

2. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Stärken, Gelatinen, Glycerin und/oder Sorbitol oder natürliche und/oder synthetische Harze und Gumme enthält.

3. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Amylogum enthält.

4. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß es als Folienbildner eine Mischung aus 8 bis 10 Gewichtsteilen Gelatine, 4 bis 8 Gewichtsteilen Stärke und 1 bis 2 Gewichtsteilen Glycerin enthält.

5. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß es aus einer Trägerfolie aus dem Bindemittel oder der Bindemittel-Mischung besteht, auf welche eine Schicht aufgebracht ist, welche die Bestandteile des Pflegemittels zusammen mit Bindemittel oder der Bindemittel-Mischung enthält, wobei das Bindemittel oder die Bindemittel-Mischung in der Trägerfolie und in der Beschichtung im wesentlichen die gleiche qualitative Zusammensetzung aufweisen.

6. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß eine Beschichtung aus den Bestandteilen des Pflegemittels und dem Bindemittel oder der Bindemittel-Mischung auf eine Trägerfolie in Form eines Trennpapiers, eines Trennfilms oder einer Trennfolie aufgebracht ist, wobei die Beschichtung nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

Claims

1. Oral and dental hygiene preparation based on surfactants, polishing agents, flavours, and other conventional additives, characterised in that the active ingredients and additives are incorporated in a binder or a binder mixture comprising water-soluble or water-swellable, physiologically harmless film formers, and in that said mixture is processed to a film, the film thus formed being predivided into dose units.

2. Oral and dental hygiene preparation according to claim 1, characterised in that it contains as film formers starches, gelatins, glycerol and/or sorbitol or natural and/or synthetic resins and gums.

3. Oral and dental hygiene preparation according to claim 1, characterised in that it contains starch gum as film former.

4. Oral and dental hygiene preparation according to claims 1 to 3, characterised in that it contains as film former a mixture of 8 to 10 parts by weight of gelatin, 4 to 8 parts by weight of starch and 1 to 2 parts by weight of glycerol.

5. Oral and dental hygiene preparation according to claims 1 to 4, characterised in that it comprises a carrier film made of the binder or the binder mixture, onto which is deposited a layer which contains the constituents of the hygiene preparation together with binder or the binder mixture, whereby the binder or the binder mixture in the carrier film and in the coating have essentially the same qualitative composition.

6. Oral and dental hygiene preparation according to claims 1 to 4, characterised in that a coating consisting of the constituents of the hygiene preparation and the binder or the binder mixture is deposited on a carrier film in the form of a release paper, a release film or a release sheet, whereby the coating can be removed in doses from the carrier material after predivision into dose units.

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Revendications

1. Préparation d'hygiène bucco-dentaire à base d'agents tensio-actifs, d'agents de polissage, de substances aromatiques ainsi que d'autres ingrédients habituels, caractérisée en ce que les principes actifs et les ingrédients additionnels sont incorporés à un agent liant ou à un mélange d'agents liants, qui sont constitués d'agents filmogènes solubles ou gonflables dans l'eau, physiologiquement sans danger, le film formé étant prédivisé en unités de dosage.

2. Préparation d'hygiène bucco-dentaire selon la revendication 1, caractérisée en ce qu'elle contient à titre d'agents filmogènes des amidons, des gélatines, de la glycérine et/ou du sorbitol ou des résines et des gommes naturelles et/ou synthétiques.

3. Préparation d'hygiène bucco-dentaire selon la revendication 1, caractérisée en ce qu'elle contient à titre d'agent filmogène de l'amylogum.

4. Préparation d'hygiène bucco-dentaire selon les revendications 1 à 3, caractérisée en ce qu'elle contient à titre d'agent filmogène un mélange de 8 à 10 parties en poids de gélatine, de 4 à 8 parties en poids d'amidon et de 1 à 2 parties en poids de glycérine.

5. Préparation d'hygiène bucco-dentaire selon les revendications 1 à 4, caractérisée en ce qu'elle est constituée d'une feuille de support formée de l'agent liant ou du mélange d'agents liants, feuille de support sur laquelle est appliquée une couche qui contient les composants de la préparation d'hygiène conjointement avec l'agent liant ou le mélange d'agents liants, l'agent liant ou le mélange d'agents liants de la feuille de support et du revêtement ayant essentiellement la même composition qualitative.

6. Préparation d'hygiène bucco-dentaire selon les revendications 1 à 4, caractérisée en ce que l'on applique un revêtement formé des composants de la préparation d'hygiène et de l'agent liant ou du mélange d'agents liants sur une feuille de support sous la forme d'un papier de séparation, d'un film de séparation ou d'une feuille de séparation, le revêtement pouvant être séparé de la matière de support par doses individuelles après prédivision en unités de dosage.

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Description

This invention relates to a drug preparation applicable to the oral mucosa to maintain a long-term administration of a systemic drug.

Known dosage forms for intraoral administration of drugs include solutions, ointments, troches, buccal tablets, and sublingual tablets. Recently, slow-releasing intraoral tablets of the track-field type which are less causative of a feeling of foreign matter (as described in JP-A-55-59109, JP-A-58-154547, and JP-A-58-154548, the term "JP-A" as used herein means an "unexamined published Japanese patent application") and slow-releasing Nifedipine tablets of the track-field type applied to the oral mucosa (as described in JP-A-61-15829 and JP-A-61-17510) have been proposed. For the purpose of further reducing an adverse feeling in the oral cavity, a medical bandage using, as a base, a water-soluble high polymer which exhibits adhesion when dissolved or gelled with water (as described in JP-A-60-142927), preparations applicable to the oral mucosa comprising a water-soluble film having incorporated thereinto a steroid or non-steroid agent (as described in JP-A-61-280423), and sheet preparations comprising a support sheet having thereon a drug, gelatin, agar, gluten, a carboxyvinyl polymer, a polyhydric alcohol, a gum, and a wax as essential components (as described in JP-A-61-85315) have also been proposed.

More recently, there have been proposed bases for application to the oral mucosa which comprise a mixture of a water-soluble substance and a water-insoluble substance; for example, an intraoral bandage composed by a soft film in which at least one of a polycarboxylic acid and a polycarboxylic acid anhydride, and a vinyl acetate polymer are mixed in a compatible state as disclosed in JP-A-61-249472 and JP-A-61-249473; a base comprising a water-insoluble or sparingly water-soluble support having thereon an adhesive layer containing an acrylic acid polymer which exhibits adhesion when dissolved in or swollen with water and a water-insoluble cellulose derivative as disclosed in JP-A-63-160649; a composite for application to the oral mucosa comprising a surface layer containing ethyl cellulose and a vinylpyrrolidone polymer or copolymer having thereon an adhesive layer as disclosed in JP-A-63-171564 and JP-A-63-171565; and an adhesive composition containing a vinylpyrrolidone polymer or copolymer, at least one of hydroxyethyl cellulose and hydroxypropyl cellulose, and a water-retaining softener as disclosed in JP-A-63-174660.

However, none of these known intraoral preparations or bases satisfies both duration of adhesion and freedom from an adverse feeling in the oral cavity on use. For example, since solutions, ointments or the like preparations easily run away with saliva or water , it is difficult to maintain efficacy for a long time with these preparations. Troches, which are large tablets prepared by punching a mixture of a drug and a base, e.g., sacchardides, cause a considerable adverse feeling. Buccal tablets and sublingual tablets are generally designed for rapid mucosal absorption of drugs and are, therefore, of short duration. The track-field type tablets, though slowly releasing a drug, have a thickness as large as 1.3 to 3 mm and lack softness, still involving the problem of an adverse feeling on use. The preparations for application to the oral mucosa comprise a water-soluble film containing a drug have softness and thereby cause a reduced adverse feeling in the oral cavity. However, since the film base is water-soluble, it is easily dissolved in saliva or water in the oral cavity and is, therefore, poor in duration of efficacy. The bases comprising a mixture of a water-soluble substance and a water-insoluble substance are soft and less causative of an adverse feeling upon use. Also, they take time to disappear in the oral cavity and are thus expected to have a longer duration of pharmaceutical effects as compared with bases comprising a water-soluble substance alone. These bases nevertheless exhibit adhesion only for 2 to 10 hours at the longest.

Hence, an intraoral preparation satisfying all three requirements, i.e., freedom from a feeling of foreign matter on use, excellent shape retention on water absorption, and long-term adhesion to the wet oral mucosa, has not yet been developed.

EP-A-0106107 discloses a drug preparation applicable to the oral mucosa comprising an adhesive sheet containing prostaglandin, said sheet comprising a homogeneous mixture comprising one or more high molecular weight compounds. The high molecular Weight compounds may be, for example, a vinyl acetate resin, polyacrylic acid salts and cellulose derivatives.

EP-A-0241179 discloses a pharmaceutical composition comprising a mixture of an active ingredient and a polymer capable of dissolving in an aqueous medium of pH 4.0 or higher.

SUMMARY OF THE INVENTION

It is the object of this invention to provide a drug preparation applicable to the oral mucosa for administering a systemic drug, which is less causative of an adverse feeling in the oral cavity on use, excellent in shape retention on water absorption, and adhesive to the oral mucosa for an extended time.

Said object is achieved by a drug preparation applicable to the oral mucosa comprising a soft

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adhesive film containing a systemic drug, the adhesive film comprising a homogeneous mixture comprising a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative capable of being dissolved in or swollen with water and a lower alcohol, wherein said mixture contains maximum 0.2 equivalent based on said acrylic acid polymer, of a salt or base.

Figure 1 illustrates the relationship of the rate of Propranolol Hydrochloride release to the time.

Figure 2 illustrates the relationship of the rate of Sodium Indometacin release to the time.

When the drug preparation applicable to the oral mucosa according to the present invention is applied to, for example, the fore gingiva of the upper jaw, the adhesive film base absorbs saliva and water in the oral cavity to exhibit adhesion to the oral mucosa. The adhesiveness in retained for a long period of time because of the excellent shape retention. Since the film base is homogeneous and soft, it is tightly adhered to the oral mucosa without causing an adverse feeling during application. The terminology "homogeneous" as used herein means that the vinyl acetate homopolymer, acrylic acid polymer and cellulose derivative in the mixture are homogeneously mixed under optical microscopic observation and that each of these components does not exist solely in parts.

The adhesive film of the drug preparation according to the present invention is obtained using a homogeneous mixture of a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative. A two-component mixture comprising only the vinyl acetate homopolymer and the acrylic acid polymer forms a homogenous and soft film but is swollen with saliva or water in the oral cavity and is inferior in shape retention on application to the oral mucosa. Further, a two-component mixture comprising only the acrylic acid polymer and the cellulose derivative forms a homogeneous and soft film but does not withstand long-term use in the oral cavity because of water-solubility of these components. Furthermore, a two-component mixture comprising only the vinyl acetate homopolymer and the cellulose derivative hardly forms a homogeneous and soft film.

The vinyl acetate homopolymer which can be used in the present invention is not particularly limited, and any known vinyl acetate homopolymer (as disclosed, e.g., in S.Imoto, Plastic Zairyo Koza - (Lectures on Plastic Materials) vol.14 Vinyl Acetate Resins, published by Nikkan Kogyo Press, Japan, on May 15, 1970) can be used as such either alone or in combination thereof. The weight average molecular weight of the vinyl acetate homopolymer is preferably from 40,000 to 200,000.

Examples of the acrylic acid polymer which can be used in the present invention includes an acrylic acid homopolymer; copolymers of acrylic acid and vinyl monomers, such as acrylic esters (e.g., butyl acrylate and 2-ethylhexyl acrylate), methacrylic esters (e.g., methyl methacrylate), and vinyl acetate; and other polymers, e.g., a carboxyvinyl polymer. Among these, an acrylic acid polymer having a carboxyl group content of 20% by weight or more is preferred. These polymers may be used either alone or in combinations thereof.

The cellulose derivative which can be used in the present invention must be capable of being dissolved in or swollen with water and a lower alcohol. Examples of the cellulose derivatives include methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose. The degree of substitution of the cellulose derivative is preferably from 0.1 to 4.5, and more preferably from 1.0 to 2.5. Hydroxypropyl cellulose having a degree of substitution of from 1.3 to 2.0 is most preferred. These cellulose derivatives may be used either alone or as a mixture of two or more thereof.

The weight ratio of acrylic acid polymer (B) to cellulose derivative (C) (B/C) preferably ranges from 1/9 to 9/1. To ensure long-term adhesion to the oral mucosa, the weight ratio B/C suitably ranges from 3/7 to 6/4. The weight ratio of vinyl acetate homopolymer (A) to the sum of acrylic acid polymer (B) and cellulose derivative (C) (A/(B + C)) preferably ranges from 2/8 to 8/2. To further ensure long-term adhesion to the oral mucosa, the weight ratio B/C more preferably ranges from 4/6 to 6/4.

Thus, the working time of the preparation in the oral cavity, which partly depends on the duration of adhesion, can be appropriately controlled by varying the ratio of vinyl acetate homopolymer (A), acrylic acid polymer (B), and cellulose derivative (C).

If desired, the drug preparation of the present invention may further contain a salt or a base. Since the drug preparation comprising only the above-described components assumes acidicity attributed to the acrylic acid polymer, it sometimes give a slight irritation to excitable parts, such as an injured part. Where such an irritation due to acidicity gives rise to troubles, incorporation of a salt or base having a neutralizing effect substantially removes the irritation to the injured part.

Examples of suitable salts and bases are salts of metals and weak acids, e.g., a salt of an alkali metal (e.g., sodium and potassium) and a carboxylic acid (e.g., acetic acid, lactic acid, and citric acid); metal hydroxides, e.g., sodium hydroxide and potassium hydroxide; amines, e.g., triethanolamine and diisopropanol amine; and mixtures thereof. A salt of an alkali metal (e.g., sodium and potassium) and a carboxylic acid (e.g., acetic acid, lactic' acid, and citric acid) is preferably used.

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The amount of the salt or base to be incorporated is maximum 0.2 equivalent based on the acrylic acid polymer. For example, a monovalent metal salt is preferably used in an amount of from 0.03 to 0.2 equivalent based on the acrylic acid polymer. Amounts less than 0.03 equivalent produce insufficient effects to reduce the irritation of an injured part. If the amount exceeds 0.2 equivalent, water resistance of the adhesive film is reduced, failing to attain sufficient adhesion to the oral mucosa.

The drug preparation applicable to the oral mucosa according to the present invention can be obtained as follows. A vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative are dissolved in a solvent commonly compatible to them, and a systemic drug is added to the solution to form a film-forming composition. The systemic drug in the composition may be either in a dissolved state or in a dispersed state so that the mode of addition is arbitrarily chosen. The film-forming composition is cast on a releasable liner and dried to form a film.

Examples of the solvent commonly compatible to the film-forming components include an alcohol and a water-alcohol mixed solvent. Taking the solubility of the cellulose derivative into consideration, lower alcohols, e.g., methanol and ethanol are exemplified as the alcohol. The water content in the mixed solvent is preferably not more than 30% by weight. If it exceeds 30% by weight, the vinyl acetate homopolymer tends to be hardly dissolved.

Examples of the releasable liner on which the film-forming composition is cast include a release-treated polyethylene laminated paper, a polyethylene film, and a silicon-treated polyethylene terephthalate film.

Drying of the cast film is carried out in a high-temperature air bath using a drying oven or a drying tower, and a vacuum drier.

The thickness of the drug preparation of the present invention can be adjusted by controlling the amount of the composition cast and is preferably in the range of from 5 to 500 μm. From the standpoint of film strength and feeling on use, a thickness of from 10 to 100 μm is more preferred.

The drug preparation applicable to the oral mucosa according to the present invention basically comprises a homogeneous and soft adhesive film which is obtained from a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative as described above. If desired, a water-insoluble support may be provided on the adhesive film to endew the preparation with improved shape retention on water absorption.

Examples of the water-insoluble support includes a film of a synthetic resin, e.g., polyethylene, a vinyl acetate homopolymer, an ethylene-vinyl acetate copolymer, polyvinyl chloride, and polyurethane; a metal foil, e.g., an aluminum foil and a tin foil; and a laminate film comprising cloth or paper and a synthetic resin film. From the viewpoint of safety and feeling on use, it is preferable to use a film of a synthetic resin, e.g., polyethylene, a vinyl acetate homopolymer, and an ethylene-vinyl acetate copolymer as a support. In order to assure ease in handling and to avoid to give an adverse feeling on use, the water-insoluble support preferably has a thickness of from 10 to 100 μm.

The above-described drug preparation of a laminate type can be prepared by, for example, hot pressing the adhesive film and the water-insoluble support film. Alternatively, the laminate type drug preparation can be obtained by casting the film-forming composition on the water-insoluble support followed by drying.

The thus obtained drug preparation according to the present invention, when applied to the wet oral mucosa, absorbs water and is swollen with the water to exhibit excellent adhesion and shape retention for an extended time without causing an adverse feeling, thereby liberating a systemic drug present in the preparation for a prolonged time while protecting the site. During the application, the drug can be prevented from running off due to saliva, etc., and the administration of the drug can be maintained in a stable manner.

The drug preparation of the present invention contains a systemic drug and administers it through the oral mucosa. Some drugs, when orally administered, are difficult in manifestation of efficacy commensurate with dosages because they undergo primary metabolism in the liver. Moreover, some drugs produce undesired side effects to organs, such as stomach. In order to eliminate these disadvantages associated with oral administration of drugs, preparations applicable to the skin which deliver the active ingredient by cutaneous absorption have recently called attention. However, the skin essentially functions to prevent entrance of a foreign substance into the body and does not easily absorb drugs. This is the reason why studies have been directed to the administration route through the oral mucosa which is considered to have a higher absorption of a drug than the skin. By the route through the oral mucosa, the drug preparation according to the present invention makes it possible to effectively deliver a systemic drug present in the preparation into the body.

The systemic drug which can be incorporated into the drug preparation of the invention may be either solid or liquid at room temperature, and any systemic drug which can be dissolved or dispersed in the soft adhesive film can be employed. The method for dissolving or dispersing the systemic drug in the soft adhesive film is not particularly

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limited. For example, the vinyl acetate homopolymer, the acrylic acid polyer and the cellulose derivative are dissolved in a solvent which is compatible With these components, and the systemic drug is separately dissolved or dispersed in the same solvent. The resulting solutions (or solution and dispersion) are mixed with each other to form a film-forming composition, and the film-forming composition is then cast on a releasable liner followed by drying so as to form the preparation.

Examples of the systemic drugs include general anesthetic agents, hypnotics, sedatives, antiepileptics, analeptics, awakening agents, anti-dizziness agents, psychoneurotropic agents, neuromuscular blocking agents, autonomic neutrotropic agents, antispasmodics, anti-Perkinson's disease, antihistaminics, stimulation therapeutics, antiallergic agents, cardiotonics, antiarrhythmics, diuretics, hypotensives, vasopressors, coronary vasopressors, peripheral vasopressors, anti-arteriosclerotic agents, agents for other circulatory organs, respiration accelerating agents, antitussive expectorants, treating agents of peptic ulcers, pituitary hormone, thyroid hormone, parathormone, androkinin, female sex hormone (i.e., vesicular ovarian follicle hormone and corpus luteum hormone), other hormones, oxytocics, agents for the urogenital system, oxygen preparations, anti-diabetic agents, other metabolic drugs, anti-tumor agents, antibiotics, chemotherapeutics, and narcotics.

The amount of the systemic drug to be incorporated into the drug preparation depends on the kind of the drug and is usually selected from 0.001 to 40% by weight, preferably from 0.002 to 20% by weight, based on the adhesive film in view of the pharmacological effects and adhesion to the oral mucosa.

The drug preparation applicable to the oral mucosa according to the present invention is less causative of an adverse feeling on use, excellent in shape retention on water absorption, and adhesive to the oral mucosa for an extended period of time. Accordingly, the present invention makes it possible to maintain a stable administration of a systemic drug.

As described above, the drug preparation applicable to the oral mucosa of the present invention which comprises a soft adhesive film prepared from a homogeneous mixture of a vinyl acetate homopolymer, an acrylic acid polymer, and a specific cellulose derivative is soft, less causative of an adverse feeling in the oral cavity on use and excellent in shape retention on water absorption. Further, since the drug preparation can be adhered to the oral mucosa for a long period of time, a systemic drug present in the preparation can be stably administered for a long time. Furthermore, because of the homogeneity and softness of the film base, the drug preparation can be deformed in perfect accordance with the shape of the oral mucosa simply by lightly pressing and adhered close to the mucosa.

The present invention is now illustrated in greater detail by way of the following examples. In these examples, all parts, percents and ratios are by weight unless otherwise specified.

Prior to conducting the examples, an agar gel as a substitution for the oral mucosa was prepared as follows.

Preparation of Agar Gel:

Distilled water was added to 2 g of an agar powder (Japanese Pharmacopeia) to make 100 g, and the mixture was boiled to completely dissolve the agar. The solution was poured into a dish and allowed to cool to prepare an agar gel.

EXAMPLE 1

Five parts of a vinyl acetate homopolymer (weight average molecular weight: 129,000), 2 parts of a carboxyvinyl polymer (carboxyl group content: 58-63% by weight) (as the acrylic acid polymer), 3 parts of hydroxypropylmethyl cellulose (degree of substitution: 1.86-1.90) (as the cellulose derivative), 0.2 part of diisopropanolamine (as the base for neutralizing the acrylic acid polymer), and 2 parts of Propranolol Hydrochloride (as the systemic drug) were added to 90 parts of a 2/8 water-methanol mixture as a common solvent to prepare a film-forming composition containing the systemic drug. The composition was cast on a silicon-release paper, dried, and stripped off to obtain a 30 μm thick adhesive film. A 20 μm thick soft alumina foil as a water-insoluble support was hot-pressed on the resulting adhesive film to obtain a drug preparation applicable to the oral mucosa.

EXAMPLE 2

Five parts of a vinyl acetate homopolymer (weight average molecular weight: 129,000), 2 parts of a carboxyvinyl polymer (carboxyl group content: 58-63% by weight) (as the acrylic acid polymer), 3 parts of hydroxypropylmethyl cellulose (degree of substitution: 1.86-1.90) (as the cellulose derivative), and 0.5 parts of Sodium Indometacin (as the systemic drug) were added to 90 parts of a 1/9 water-methanol mixture as a common solvent to prepare a film-forming composition. The composition was cast on a silicon-release paper, dried, and stripped off to obtain a 60 μm thick adhesive film. A 20 μm thick soft vinyl acetate film as a water-insoluble support was hot-pressed on the resulting adhesive film to obtain a preparation applicable to the oral

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mucosa.

Evaluation:

Specimens having a size of 1 cm x 2 cm were cut out of each of the drug preparations obtained in Examples 1 and 2 and adhered to the surface of the above-prepared agar gel. After a prescribed period of time, the specimen was peeled off the agar gel and extracted from 50 mℓ of methanol. The drug in the extract was determined by high performance liquid chromatography. The resulting data of Examples 1 and 2 were plotted in Figs. 1 and 2, respectively, with rate of drug release as ordinate and time as abscissa.

It can be seen from Figs. 1 and 2 that the drug preparation according to the present invention keeps adhered to the agar gel, a substitution for the oral mucosa, for a long time so that the active ingredient in the preparation is stably and steadily released with time.

Further, the specimens were adhered to the oral mucosa of panel members to conduct organoleptic tests of the feeling. As a result, the specimens were judged to have little adverse feeling.

Claims

1. A drug preparation applicable to the oral mucosa comprising a soft adhesive film containing a systemic drug, said adhesive film comprising a homogeneous mixture comprising a vinyl acetate homopolymer, an acrylic acid polymer, and a cellulose derivative capable of being dissolved in or swollen with water and a lower alcohol, wherein said mixture contains maximum 0,2 equivalent based on said acrylic acid polymer of a salt or base.

2. The drug preparation of claim 1, wherein said cellulose derivative is selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose.

3. The drug preparation of claim 1, wherein said acrylic acid polymer and cellulose derivative are present in a weight ratio of from 1/9 to 9/1.

4. The drug preparation of claim 3, wherein said acrylic acid polymer and cellulose derivative are present in a weight ratio of from 3/7 to 6/4.

5. The drug preparation of claim 1, wherein the weight ratio of said vinyl acetate homopolymer to the sum of said acrylic acid polymer and cellulose derivative is from 2/8 to 8/2.

6. The drug preparation of claim 5, wherein said acrylic acid polymer and cellulose derivative are present in a weight ratio of from 4/6 to 6/4.

7. The drug preparation of claim 1, wherein said adhesive film has a thickness of from 5 to 500 μm.

8. The drug preparation of claim 1, wherein said preparation further comprises a water-insoluble soft film support laminated on said adhesive film.

9. The drug preparation of claim 8, wherein said support has a thickness of from 10 to 100 μm.

10. The drug preparation of claim 8, wherein said support is a polyethylene film, a vinyl acetate homopolymer film or an ethylene-vinyl acetate copolymer film.

Patentansprüche

1. Auf die Mundschleimhaut aufbringbare Arzneimittelzubereitung umfassend einen weichen Klebefilm, der ein systemisches Arzneimittel enthält, wobei der Klebefilm ein homogenes Gemisch, umfassend ein Vinylacetathomopolymer, ein Acrylsäurepolymer und ein Cellulosederivat, das in Wasser und einem niederen Alkohol aufgelöst oder damit gequollen werden kann, umfaßt, worin das Gemisch maximal 0,2 Äquivalente, bezogen auf das Acrylsäurepolymer, eines Salzes oder einer Base enthält.

2. Arzneimittelzubereitung nach Anspruch 1, worin das Cellulosederivat ausgewählt ist aus der Gruppe bestehend aus Methylcellulose, Ethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose und Hydroxypropylmethylcellulose.

3. Arzneimittelzubereitung nach Anspruch 1, worin das Acrylsäurepolymer und das Cellulosederivat in einem Gewichtsverhältnis von 1/9 bis 9/1 vorhanden sind.

4. Arzneimittelzubereitung nach Anspruch 3, worin das Acrylsäurepolymer und das Cellulosederivat in einem Gewichtsverhältnis von 3/7 bis 6/4 vorhanden sind.

5. Arzneimittelzubereitung nach Anspruch 1, worin das Gewichtsverhältnis des Vinylacetathomopolymers zu der Summe des Acrylsäurepolymers und des Cellulosederivats 2/8 bis 8/2 beträgt.

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6. Arzneimittelzubereitung nach Anspruch 5, worin das Acrylsäurepolymer und das Cellulosederivat in einem Gewichtsverhältnis von 4/6 bis 6/4 vorhanden sind.

7. Arzneimittelzubereitung nach Anspruch 1, worin der Klebefilm eine Dicke von 5 bis 500 µm hat.

8. Arzneimittelzubereitung nach Anspruch 1, worin die Zubereitung ferner einen wasserunlöslichen weichen Filmträger auf dem Klebefilm laminiert umfaßt.

9. Arzneimittelzubereitung nach Anspruch 8, worin der Träger eine Dicke von 10 bis 100 µm hat.

10. Arzneimittelzubereitung nach Anspruch 8, worin der Träger ein Polyethylenfilm, ein Vinylacetathomopolymerfilm oder ein Ethylen-Vinylacetat-Copolymerfilm ist.

Revendications

1. Préparation pharmaceutique applicable sur la muqueuse buccale, comprenant un film adhésif souple contenant un médicament systémique, ledit film adhésif comprenant un mélange homogène qui comprend un homopolymère d'acétate de vinyle, un polymère d'acide acrylique et un dérivé de cellulose capable de se dissoudre ou de gonfler dans l'eau et un alcool inférieur, ledit mélange contenant au maximum 0,2 équivalent, par rapport audit polymère d'acide acrylique, d'un sel ou d'une base.

2. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit dérivé de cellulose est choisi dans le groupe constitué par la méthylcellulose, l'éthylcellulose, l'hydroxyéthylcellulose, l'hydroxypropylcellulose et l'hydroxypropylméthylcellulose.

3. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit polymère d'acide acrylique et ledit dérivé de cellulose sont présents en un rapport en masse compris entre 1/9 et 9/1.

4. Préparation pharmaceutique selon la revendication 3, dans laquelle ledit polymère d'acide acrylique et ledit dérivé de cellulose sont présents en un rapport en masse compris entre 3/7 et 6/4.

5. Préparation pharmaceutique selon la revendication 1, dans laquelle le rapport en masse dudit homopolymère d'acétate de vinyle à la somme dudit polymère d'acide acrylique et dudit dérivé de cellulose est compris entre 2/8 et 8/2.

6. Préparation pharmaceutique selon la revendication 5, dans laquelle ledit polymère d'acide acrylique et ledit dérivé de cellulose sont présents en un rapport en masse compris entre 4/6 et 6/4.

7. Préparation pharmaceutique selon la revendication 1, dans laquelle ledit film adhésif a une épaisseur de 5 à 500 µm.

8. Préparation pharmaceutique selon la revendication 1, dans laquelle ladite préparation comprend en outre un support formé d'un film souple insoluble dans l'eau laminé sur ledit film adhésif.

9. Préparation pharmaceutique selon la revendication 8, dans laquelle ledit support a une épaisseur de 10 à 100 µm.

10. Préparation pharmaceutique selon la revendication 8, dans laquelle ledit support est un film de polyéthylène, un film d'un homopolymère d'acétate de vinyle ou un film de copolymère éthylène-acétate de vinyle.

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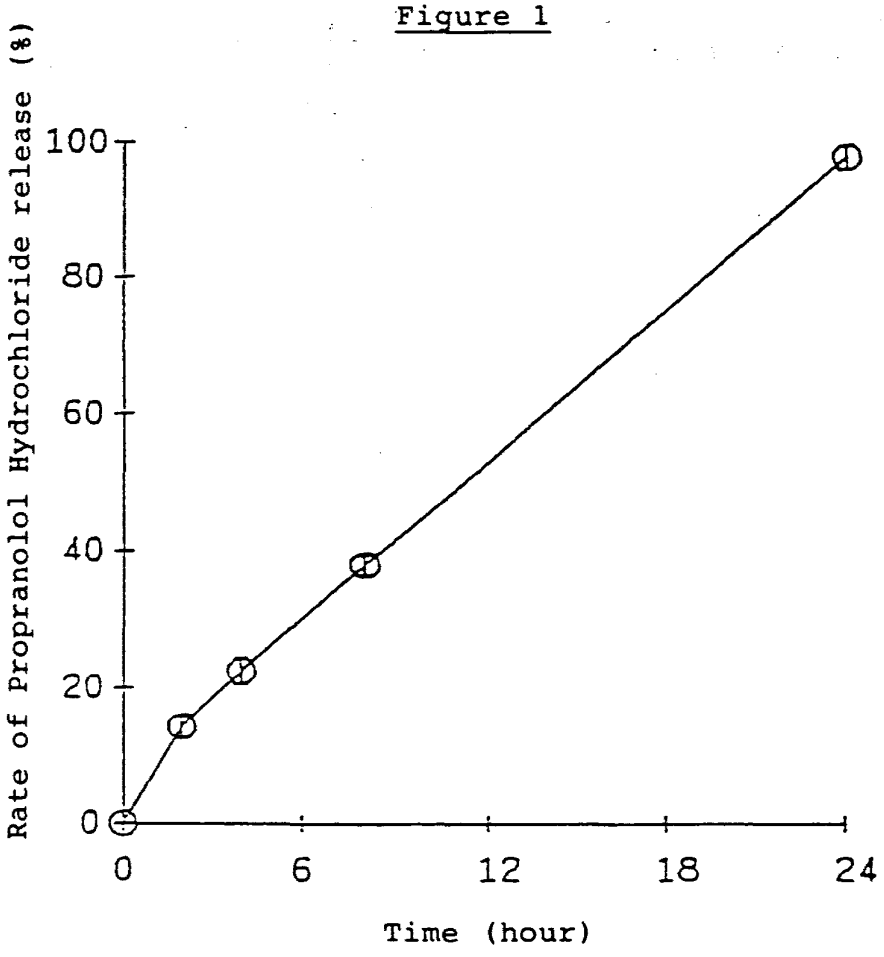
Figure 1


Rate of Propranolol Hydrochloride release (%)
100
80
60
40
20
0
0
6
12
18
24
Time (hour)