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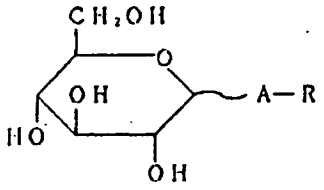
CLAIMS

1. An agent for accelerating transmucosal absorption of a poorly absorbable drug, wherein the agent comprises one or more ether or thioether compounds of C_6-C_{18} aliphatic hydrocarbon and monosaccharide or disaccharide.

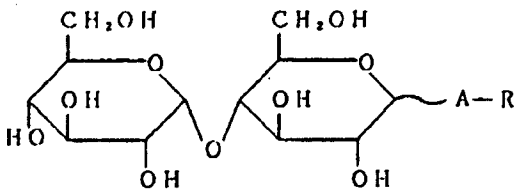
2. The agent of claim 1, wherein the ether or thioether compound of aliphatic hydrocarbon and monosaccharide is represented by Formula (1):



(1)

wherein A represents an oxygen atom or sulfur atom; and R represents a C_6-C_{18} aliphatic hydrocarbon group.

3. The agent of claim 1, wherein the ether or thioether compound of aliphatic hydrocarbon and disaccharide is represented by Formula (2):



(2)

wherein A represents an oxygen atom or sulfur atom; and R represents a C_6-C_{18} aliphatic hydrocarbon group.

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審査請求　未請求　発明の数 1　(全6頁)

⑤4発明の名称　経粘膜吸収促進剤

⑳特　願　昭62-311680

㉒出　願　昭62(1987)12月8日

特許法第30条第1項適用　昭和62年9月18日　日本薬剤学会発行の「日本薬剤学会第3年会講演要旨集」において発表

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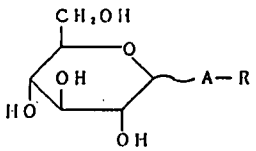
明　細　書

1．発明の名称　経粘膜吸収促進剤

2．特許請求の範囲

(1) 単糖類もしくは二糖類と炭素数6～18の脂肪族炭化水素のエーテル化合物もしくはチオエーテル化合物の1種以上を有効成分として含有する難吸収性薬物の経粘膜吸収促進剤。

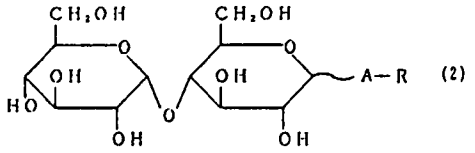
(2) 単糖類と脂肪族炭化水素のエーテル化合物もしくはチオエーテル化合物が下記一般式(1)で表わされる化合物である特許請求の範囲第1項記載の経粘膜吸収促進剤。



(1)

(式中、Aは酸素原子又は硫黄原子を、Rは炭素数6～18の脂肪族炭化水素基を示す)

(3) 二糖類と脂肪族炭化水素のエーテル化合物もしくはチオエーテル化合物が下記一般式(2)で表わされる化合物である特許請求の範囲第1項記載の経粘膜吸収促進剤。



(2)

(式中、Aは酸素原子又は硫黄原子を、Rは炭素数6～18の脂肪族炭化水素基を示す)

3．発明の詳細な説明

(産業上の利用分野)

本発明は新規な経粘膜吸収促進剤に関する。

(従来の技術)

吸収促進剤を含有する粘膜投与製剤の開発は、水溶性薬物や生理活性ペプチド等の難吸収性薬物を注射によらず有効に全身に適用するためのアプローチの1つとして注目されているが、実用に供した例は依然として少ない。理想的な吸収促進剤が具備すべき条件としては、強力かつ安全でまた安定であること、さらに製剤化した時にもその効力が損なわれず、主薬並びに製剤の安定性にも影響を与えないことなどが挙げられる。

粘膜からの吸収性を向上させるための研究は、従来より盛んに行われており、親水性界面活性剤の使用、脂肪酸類及びミセルの使用、エナミン誘導体、サリチル酸誘導体の添加等がある。(J. Pharm. Sci. 66 (7) 955 (1955); 薬剤学 38 (2) 67 (1978); Clin. Res. 25 (3) 386A; J. Pharm. Dyn. 3 24 (1980); Int. J. Pharm. 2 101 (1979); 特公昭55-8486; 特公昭55-8456; 特開昭57-158719; 特開昭58-177995; 特開昭59-176209等)。

しかしこれらの中には、組織粘膜を損傷したり、効果が不十分であったり、製剤化が困難である等の欠点を有するものが多く、より有効且つ安全で使用し易い吸収促進剤の開発が期待されている。

(発明が解決しようとする問題点)

本発明の目的は、より効果が強力で、安全且つ安定した経粘膜吸収促進剤を提供することにある。

(問題点を解決するための手段)

本発明は単糖類もしくは二糖類と炭素数6~18の脂肪族炭化水素のエーテル化合物もしくはチオエーテル化合物の1種以上を有効成分として含有する難吸収性薬物の経粘膜吸収促進剤に係る。

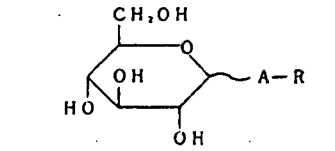
本発明者は有用な経粘膜吸収促進剤の開発を目的として鋭意研究を重ねた結果、実用上更に有用な上記本発明を完成するに至った。

本発明における単糖類としては例えばL-アラビノース、D-キシロース、D-リボース、D-グルコース、D-マンノース、D-ガラクトース、D-フルクトース、また二糖類としてはマルトース、セロビオース、トレハロース、ゲンチオビオース、イソマルトース、乳糖、シヨ糖等が挙げられる。

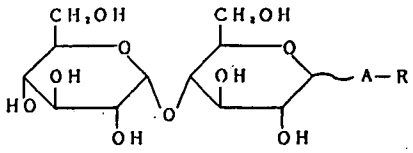
本発明における炭素数6~18の脂肪族炭化水素は直鎖状でも分枝状でもよく、又飽和或いは不飽和のどちらでもよい。

上記飽和炭化水素から水素原子が1つ除かれて生成する飽和炭化水素基としては、例えばヘキシル、ヘプチル、オクチル、ノニル、デシル、ウンデシル、ドデシル、トリデシル、テトラデシル、ヘキサデシル、オクタデシル、2-メチルヘキシル、2-エチルペンチル、2-エチルヘキシル、2-エチルヘプチル、2-エチルオクチル、2-エチルノニル、2-エチルデシル、2-エチルウンデシル、3,7-ジメチルオクチル、2-ヘキシルデシル、2-オクチルデシル、2,4,4-トリメチルペンチル等の直鎖及び分枝鎖のものが挙げられる。又、不飽和炭化水素基としては、例えばCis-3-ヘキセニル、1-エテニルヘキシル、オレイル、リノレイル等が挙げられる。

上記糖類と脂肪族炭化水素とのエーテルもしくはチオエーテル化合物の中でも下記式(1)及び(2)



(1)



(2)

(式中、Aは酸素原子又は硫黄原子を、Rは炭素数6~18の脂肪族炭化水素基を示す)で表わされる化合物が好ましい。

これらの好ましい化合物の具体例としては以下のものが挙げられる。

n-オクチル-β-D-グルコピラノシド、

2-エチルヘキシル-α,β-D-グルコピラノシド、

n-オクチル-β-D-チオグルコピラノシド、

n-ヘプチル-β-D-チオグルコピラノシド、

n-ラウリル-β-D-マルトピラノシド

これらの糖類の脂肪族炭化水素との(チオ)エーテル類は生体粘膜、例えば直腸粘膜、その他の胃腸管粘膜、眼粘膜、口腔粘膜、膣粘膜、鼻粘膜を通しての薬物の吸収性を著しく高め、バイオアベイラビリティーを良好に改善せしめることができる。他方これらの糖類の脂肪族炭化水素との(チオ)エーテル類は生体粘膜刺激性が少なく安全な化合物であり、容易に入手できるものである。

本発明で吸収促進効果を期待される薬物として

は、生体膜透過性が、増強剤を必要とする程度に低い薬物であり、例えば抗炎症剤、循環器官用剤、抗微生物剤、ホルモン剤、制癌剤、抗アレルギー用剤、呼吸器官用剤、中枢神経系用剤、末梢神経系用剤、生物学的製剤等にその例を見い出すことができる。

抗炎症剤としては、例えばアロプリノールが挙げられ、循環器官用剤としては、例えばメチルドパ、グアネチジンの如き抗高血圧剤、トラピジル、クエン酸ニカメタートの如き血管拡張剤、プロプラノロール、コンドロイチン硫酸の如き抗血液凝固剤等を挙げることができる。

抗微生物剤としては、例えばペニシリンG、ペニシリンV、メチシリン、クロキサシリン、アンピシリン、ヘタシリン、シクラシリン、アモキシシリン、カルベニシリン、スルベニシリン等のペニシリン型抗生物質、セファピリン、セファロリジン、セフォキシチン、セファロチン、セファゾリン、セファログリシン、セファレキシン等のセファロスポリン型抗生物質、ストレプトマイシン、カナマイシン、ゲンタマイシン、フラジオマイシン等のアミノグリコシド型抗生物質などが挙げられる。

ホルモン剤としては、例えばインシュリン、アンジオテンシン、バソプレシン、プロチレリン、ゴナドトロピン放出ホルモン、コルチコトロピン、黄体刺激ホルモン、黄体形成ホルモン、カルシトニン、ガストリン等が挙げられる。

制癌剤としては、例えば5－フルオロウラシル、ウラシル、6－メルカプトプリン、メトトレキサート、ブレオマイシン、ダウノルビシン、ドキソルビシン、L－アスパラギナーゼなどが挙げられる。

抗アレルギー用剤、呼吸器官用剤としては、例えばクロモグリケートの如き抗喘息剤などが挙げられる。中枢神経系用剤としては、例えば、臭化水素酸スコポラミン等が挙げられる。末梢神経系用剤としては、例えばプロカイン、メピバカイン、テトラカインなどが挙げられる。生物学的製剤としては、例えばトリプシン、キモトリプシン、ウロキナーゼ、インターフエロン、インターロイキンなどが挙げられる。

上記薬物は本発明に適用できるものの1例であつて全てではないと理解されるべきである。

又、本発明の粘膜吸収促進剤は上記薬剤と同時に又はその前後に投与することができるが、好ましくは予め配合剤としておくのが良い。

本発明の経粘膜吸収促進剤を用いた粘膜投与製剤にあつては、有効成分の配合量は薬物の種類、量、製剤の形態などによつて異なり一概には言えないが、製剤全重量に対して0.1～20重量％が好ましく、より好ましくは0.5～5重量％である。

本発明の経粘膜吸収促進剤を用いた粘膜投与製剤は例えば坐剤、溶液剤、懸濁剤、フイルム剤、エアゾール剤、錠剤、顆粒剤、細粒剤等が挙げられるが、目的とする剤形に応じて、薬物と経粘膜吸収促進剤以外の成分を含有せしめることができる。例えば坐剤とする場合の基剤としては炭素数6～30の脂肪酸とグリセリンのエステル類、例えばダイナミツト・ノーベル社製、ウイテツプゾール、ミグリオール(いずれも商標)、ヤシ油、大豆油等の植物油、又はこれらを水素添加、アセチル化、分画抽出等により改質したもの等が挙げられ、またソフトカプセル坐剤とする場合には剤皮としてゼラチン等が挙げられる。溶液剤とする場合にはエタノール、精製水、グリコール等が通常用いられ、懸濁剤の場合にはアラビアゴム、トラガント、ゼラチン、メチルセルロース、カルボキシメチルセルロース(CMC)等が通常用いられる。フイルム剤の場合にはヒドロキシプロピルセルロース、メチルセルロース、ポリビニルピロリドン、ポリビニルアルコール等の基剤が用いられ、錠剤、顆粒剤、細粒剤の場合には乳糖、結晶セルロース、とうもろこしでんぷん等の賦形剤やヒドロキシプロピルセルロース、メチルセルロース等の結合剤等が通常用いられる。又エアゾール剤の場合には噴射剤としてジクロロジフルオロメタン等が通常用いられる。

これらの添加物を含有する粘膜投与製剤は、通常行われている公知の方法によつて製造すること

ができ、その投与量も公知の量で良く、通常成人体重当り1日の有効成分が約0.01～20mg／kgの範囲とするのが好ましい。

(実　施　例)

次に本発明の吸収促進剤を配合した製剤の具体的な処方例を掲げる。

処方例1

セファロリジン	500mg
n－ラウリル－β－D－マルトピラノシド	30mg
ウイテップゾール W－35	1470mg
1坐剤当り	2000mg

上記配合割合で坐剤を調製した。

処方例2

アンピシリンナトリウム	250mg
2－エチルヘキシル－α,β－D－チオグルコピラノシド	40mg
ウイテップゾール W－35	1710mg
1坐剤当り	2000mg

上記配合割合で坐剤を調製した。

処方例3

インシュリン	50 U
n－オクチル－β－D－グルコピラノシド	2mg
精製水	適量
1回噴霧量当り	0.1mℓ

上記配合割合で経鼻投与(ネブライザー)用の溶液剤を調製した。

処方例4

セファロチンナトリウム	250mg
n－オクチル－β－D－チオグルコピラノシド	100mg
結晶セルロース	150mg
デンプングリコール酸ナトリウム	150mg
ヒドロキシプロピルセルロース	20mg
ヒドロキシプロピルセルロースフタレート	300mg
マクロゴール 6000	30mg
1包当り	1000mg

上記配合割合で腸溶性顆粒剤を調製した。

処方例5

セフピラミド	18重量部
n－ラウリル－β－D－マルトピラノシド	2重量部
ウイテップゾール W－35	80重量部

上記配合割合で坐剤を調製した。

処方例6

セフピラミド	18重量部
n－ラウリル－β－D－マルトピラノシド	1重量部
ウイテップゾール W－35	81重量部

上記配合割合で坐剤を調製した。

処方例7～9

pH7.4のリン酸緩衝食塩水100mℓに対し、n－オクチル－β－D－グルコピラノシド(n－OG)をそれぞれ100mM(約2.9W/V%)、50mM(約1.5W/V%)、20mM(約0.6W/V%)の濃度に調製して溶液剤とした。

処方例10～12

処方例7と同様にしてn－オクチル－β－D－チオグルコピラノシド(OTG)をそれぞれ100mM(約3.1W/V%)、50mM(約1.5W/V%)、10mM(約0.3W/V%)の濃度に調製して溶液剤とした。

処方例13～14

処方例7と同様にしてn－ヘプチル－β－D－チオグルコピラノシド(HTG)をそれぞれ100mM(約2.9W/V%)、50mM(約1.5W/V%)の濃度に調製して溶液剤とした。

処方例15～17

処方例7と同様にして2－エチルヘキシル－α,β－D－グルコピラノシド(b－OG)をそれぞれ100mM(約2.9W/V%)、50mM(約1.5W/V%)、35mM(約1.0W/V%)の濃度に調製して溶液剤とした。

処方例18～21

処方例7と同様にしてn－ラウリル－β－D－マルトピラノシド(LM)をそれぞれ50mM(約2.8W/V%)、10mM(約0.5W/V%)、5mM(約0.26W/V%)、2.5mM(約0.13W/V%)の濃度に調製して溶液剤とした。

処方例22

セフピラミド　18重量部
n－ヘキシル－β－D－グルコピラノシド　2重量部
ウイテップゾール W－35　80重量部
上記配合割合で坐剤を調製した。

処方例23
セフピラミド　18重量部
n－ヘキシル－β－D－チオグルコピラノシド　2重量部
ウイテップゾール W－35　80重量部
上記配合割合で坐剤を調製した。

処方例24
セフピラミド　18重量部
n－オクタデシル－β－D－グルコピラノシド　2重量部
ウイテップゾール W－35　80重量部
上記配合割合で坐剤を調製した。

処方例25
セフピラミド　18重量部
1－エテニルヘキシル－α－D－グルコピラノシド　2重量部
ウイテップゾール W－35　80重量部
上記配合割合で坐剤を調製した。

処方例26
セフピラミド　18重量部
9－オクタデセニル－β－D－グルコピラノシド　2重量部
ウイテップゾール W－35　80重量部
上記配合割合で坐剤を調製した。

次に吸収試験を示し、経粘膜吸収促進作用を説明する。

＜吸収試験＞

当試験においては、Wistar系雄性ラット(240～300g)の結腸下部より肛門部までの6cmを吸収部位として行った。

(1) 処方例7～21の溶液剤及び対照例としてpH 7.4のリン酸塩緩衝食塩水100mlに難吸収性の薬物モデルとして水溶性の蛍光色素である6－カルボキシフルオレセイン(CF)0.1gを溶解し、16時間絶食したペントバルビタール麻酔下のラットの大腸ループ内に体重250g当り125μl投与後、頸動脈より経時的に採血を行い、血中6－カルボキシフルオレセイン濃度を蛍光光度法(EX：490nm、EM：520nm)により定量した。結果を第1～5図に示す。

(2) 処方例7(n－OG、約2.9W/V%)、処方例10(OTG、約3.1W/V%)の溶液剤及び対照例としてpH 7.4のリン酸塩緩衝食塩水100mlにセフピラミド12g又はペプレオマイシン1.6gを各々溶解し、16時間絶食したペントバルビタール麻酔下のラットの大腸ループ内に上記の各溶液を体重250g当り125μl投与後、頸動脈より経時的に採血を行い、血中セフピラミド又はペプレオマイシン濃度をペーパーディスク法(bacillus sub. ATCC6623)により定量し、それぞれの血中濃度下面積(AUC)を求めた。結果を第1表に示す。

第1表

薬物	粘膜吸収促進剤	最高血中濃度 (μg/ml)	$AUC^{0-2.5h}$ (μg・min/ml)
セフピラミド (60mg/kg)	－	－	223.6± 35.7
	n－OG 100mM	51.6±12.0	2594.9±225.9
	OTG 100mM	45.3± 5.7	2692.0±189.3
ペプレオマイシン (8mg/kg)	－	－	50.8± 11.3
	n－OG 100mM	3.6± 0.4	233.3± 16.3
	OTG 100mM	4.9± 0.8	361.2± 25.1

(3) 処方例5、6及び対照例としてセフピラミド18重量部、ウイテップゾール W－35(82重量部)の配合割合より成る処方を固化、成形した坐剤83mgを16時間絶食したラットの直腸に投与し、以下吸収実験(2)と同様に採血及び血中濃度の定量を行った。結果を第6図に示す。

以上の吸収試験から本発明の経粘膜吸収促進剤は難吸収性薬物の粘膜吸収に優れた効果を有することが明らかである。

4．図面の簡単な説明

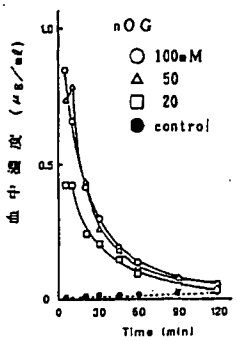
第１～６図は吸収試験における薬物の血中濃度の経時変化を示すグラフである。

（以　上）

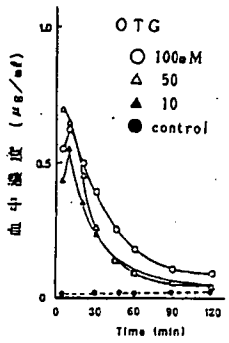
出　願　人　　大鵬薬品工業株式会社

代　理　人　　弁理士　田　村　　巌

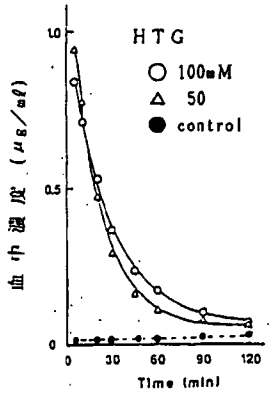
第 1 図



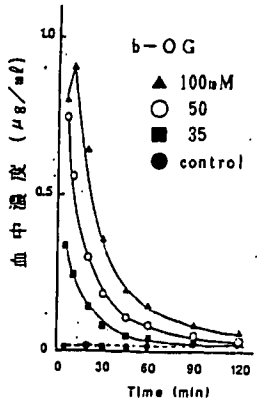
第 2 図



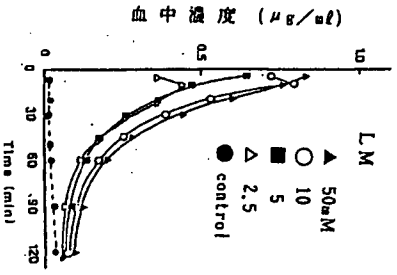
第 3 図



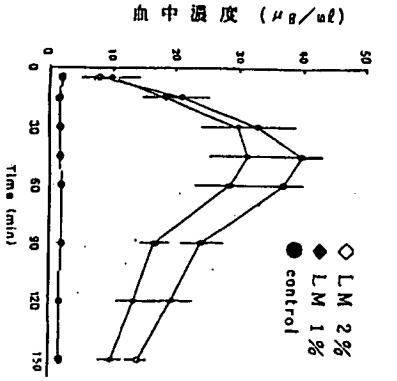
第 4 図



第 5 図



第 6 図



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(54) Title: REVERSIBLE GELATION COMPOSITIONS AND METHODS OF USE

(57) Abstract

Reversibly gelling aqueous compositions are disclosed which undergo significant changes in viscosity in response to substantially simultaneous changes in both temperature and pH. The compositions are formed of relatively low concentrations of a stable combination of at least one pH-sensitive reversibly gelling polymer and at least one temperature-sensitive reversibly gelling polymer. The compositions can be formulated to exhibit a sol-gel transition over a wide range of conditions and viscosities and may be modified to incorporate a pharmaceutical compound for utilization as droppable or injectable drug delivery systems which will gel following administration to a physiological system for the sustained delivery of such pharmaceutical compounds.

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REVERSIBLE GELATION COMPOSITIONS AND METHODS OF USE

FIELD OF THE INVENTION

The present invention relates in general to macromolecular polymer mixtures exhibiting reversible gelation properties. More particularly, the present invention is directed to aqueous compositions that reversibly gel in response to simultaneous variations in at least two physical parameters such as temperature and pH or ionic strength. These compositions can be designed to reversibly gel at varying viscosities over a relatively wide range of conditions, making them particularly suitable for use as droppable, oral, or injectable drug delivery systems for the sustained and controlled delivery of pharmaceutical medicaments and diagnostic agents.

BACKGROUND OF THE INVENTION

Various approaches to the production of reversibly gelling solutions have been developed over the years. Principal efforts have been devoted to the development of gelatinous drug delivery systems for topical and subcutaneous applications and, more recently, for the administration of ophthalmic drugs to the eye. In general, sustained release drug delivery systems incorporate pharmaceutical agents in solid or semi-solid vehicles which are applied to or implanted under the skin of a patient by medical personnel. Additionally, unlike conventional drug delivery systems, ocular drug delivery systems also must address the additional problem of drug loss through the lacrimal drainage system as well as the needs of patient comfort and ease of administration.

Early approaches to the solution of the problems associated with ocular drug delivery systems utilized semi-solid ointments or gels applied directly to the conjunctiva or cul-de-sac of the eye to retain the pharmaceutical agents contained therein on the ocular surface against such physiological factors as tear turnover, tear drainage, blinking, and other mechanical losses. For example, U.S. Patents Nos. 3,944,427 and 3,700,451 disclose gelatinous drug delivery compositions containing agar, xanthine gum, and carob gum in liquid mediums in order to enhance their residence time upon the skin or mucosae and the resultant bioavailability of the medicinal products contained therein. Similarly, European Patent Application No. 0 300 888 A1, filed July 18, 1988, recently disclosed the use of rhamsan gum to thicken ophthalmic compositions for droppable and topical application.

Though effective at increasing drug retention times, lack of patient acceptability remains as a significant drawback to the use of such known viscous drug delivery compositions in the eye. Many patients experience difficulty in applying the appropriate amount of such compounds to the eye and resist the unpleasant side effects of eyelid crusting and vision blurring. As a result, these compounds may only be suitable for use in the evening or during non-active hours.

A known alternative approach to these problems was the use of a formulation which is liquid at room temperature but which forms a semi-solid when warmed to body temperature. Such a thermally triggered system is disclosed in U.S. Patent No. 4,474,751, where an aqueous drug delivery system that forms a semi-solid "gel" at body temperature is formed from proprietary polymers known as "Tetronic®" polyols. Generally speaking, these compositions are formed from approximately 10% to 50% of the specific polymers in an aqueous base. By adjusting the pH of these drug delivery systems through the addition of buffering agents, the gelling transition temperature can be raised to physiological temperatures on the order of 35°C.

Similar drug delivery systems which can be injected subcutaneously or intramuscularly are disclosed in United States Patent No. 4,474,752. These compounds also contain from 10% to 50% by weight Tetronic® polymers and gel at temperatures from about 30° to 10°C.

A thermal setting gel drug delivery system is also described in U.S. Patent No. 4,188,373, utilizing "Pluronic® polyols" as the thermally gelling polymer. Adjusting the concentration of the polymer gives the desired "sol-gel" transition temperature. However, producing a compound which sets at physiologically useful temperature ranges limits the available viscosity of the gelled product.

Alternatively, it has been proposed to utilize formulations which gel in response to changes in pH as drug delivery vehicles. By carefully controlling the pH of such mixtures, a solution which forms a gel upon mixing with aqueous tear fluid could theoretically be produced. However, it is believed that the relatively high buffering capacity of such pH responsive compositions can lead to slow gelling, irritation and discomfort in patient eyes.

Though successful at achieving increased drug retention times, the relatively high polymer concentrations required by such formulations undesirably increase both the buffering capacity and the amount of thermal energy necessary to induce gelation of the compounds which may

lead to irritation and discomfort when used in the eye. What is more, the high polymer concentrations also contribute to unacceptably high product costs and generally slow the gelling process as well, leading to migration of the compounds from the site of application or injection.

Accordingly, it is a principal object of the present invention to provide a reversibly gelling polymer solution having significantly lower polymer concentrations than has previously been attainable by the prior art in order to reduce both the buffering and thermal capacities of the solution to ensure its rapid and complete transition from liquid to gel upon application to a physiological system such as an oral dosage, the surface of the eye, or an injectable drug depot.

It is a further object of the present invention to provide a reversibly gelling solution which can be utilized as a drug delivery vehicle or wetting solution that can easily be administered by a patient in the form of a freely flowing liquid or drops which gel immediately following administration with minimal side effects, thereby providing ready patient control of drug dosage and improved patient acceptability.

It is a further object of the present invention to provide an oral dosage, drop-instillable, injectable or other depot form drug delivery vehicle which will prolong drug contact time for improved bioavailability and for sustained drug release.

SUMMARY OF THE INVENTION

Generally stated, the present invention accomplishes the above-described objectives by providing aqueous compositions that reversibly gel in response to substantially simultaneous variations in at least two physical parameters such as temperature, pH, or ionic strength. What is more, the compositions of the present invention can be tailored to exhibit a specific sol-gel transition over predetermined temperature and pH ranges to make the compositions particularly well suited for use as drop-instillable aqueous wetting agents and drug delivery systems, as well as for use as injectable sustained release drug delivery systems.

More particularly, it has been surprisingly discovered that superior reversibly gelling compositions can be produced from unusually low concentrations of uniquely synergistic polymer systems which stably exist in aqueous solutions. In contrast to prior art gelation systems that rely on only a single triggering mechanism which may be either changes in pH, ionic strength, or changes in temperature, the compositions of the present invention reversibly gel in response to sub-

stantially simultaneous changes in both temperature and pH over predetermined ranges. What is more, the synergistic gelation action of the compositions of the present invention produces rapid and complete viscosity changes of an order of magnitude without the undesirable side effects associated with the high polymer concentration, single gelation mechanism compositions of the prior art.

These properties make the compositions of the present invention particularly well suited for uses as topically applied lubricants and wetting agents as well as for drug delivery vehicles where sustained and controlled delivery of bioactive agents is desired. For example, wetting agents, ocular drug delivery vehicles, oral and injectable drug delivery compositions can be produced in accordance with the teachings of the present invention which exhibit steady state flow characteristics at or near room temperature and a pH range of 2.5 to 6.5, yet almost instantaneously transform to highly visco-elastic gels when exposed to physiological conditions of pH and temperature on the order of pH 7.4 and 37°C.

Exemplary compositions are formed in accordance with the teachings of the present invention from aqueous solutions containing effective concentrations of a stable physical admixture or combination of at least one thermally-sensitive gelling polymer and at least one pH-sensitive gelling polymer. Thermally-sensitive gelling polymers for practicing the present invention can be selected from the group including alkyl cellulose, hydroxyalkyl cellulose, cellulosic ethers, Pluronic® polymers and Tetronic® polymers, with methylcellulose being particularly preferred. Exemplary pH-triggered gelling polymers that produce thickening at increased pH are preferably acidic polymers such as those containing carboxyl groups. Those skilled in the art will appreciate that small amounts of crosslinking agents such as divinyl benzene, divinyl glycol and polyalkenyl polyethers will facilitate the formation of three dimensional polymer network structures in the resultant cross-linked polyacrylates. Carboxy vinyl linear or branched or crosslinked polymers of the monomers, such as methacrylic acid, ethacrylic acid, β-methylacrylic acid, cis-α-methylcrotonic acid, trans-α-methylcrotonic acid, α-butylcrotonic acid, α-phenylacrylic acid, α-benzylacrylic acid, α-cyclohexylacrylic acid, and the like are examples of such acidic pH-sensitive gelling polymers. Conversely, where thickening is desired at decreased pH, polymers containing weakly basic pendant groups such as poly-N-N-dimethylaminoethylmethacrylate may be employed.

In contrast to the relatively high polymer concentrations required by the individually triggered prior art compositions (on the order of 10% or more by weight), the reversibly gelling compositions of the present invention preferably contain only approximately 0.25% to 5% by weight thermally-sensitive gelling polymer and only 0.1% to 0.5% by weight pH-sensitive gelling polymer. This substantially lower polymer concentration significantly reduces the amount of thermal energy required to induce gelation as well as reducing the buffering capacity of the compositions of the present invention, making them markedly superior topical wetting agents and drug delivery compounds. When utilized in the ocular milieu, the compositions of the present invention eliminate the discomfort, vision blurring and crusting produced by the known prior art compositions yet produce rapid conformational changes to high viscosity.

However, it is contemplated as being within the scope of the present invention to utilize thermally-sensitive gelling polymer concentrations ranging from approximately 0.1% to 30% by weight and pH-sensitive gelling polymer concentrations ranging from approximately 0.01% to 10% by weight. As discussed in detail below, these relatively broader polymer concentration ranges increase the scope of the available viscosities and sol-gel transition temperatures that may be produced in accordance with the teachings of the present invention. Thus, viscosities ranging from 200 to approximately 1 million cP at sol-gel transition temperatures ranging from 0°C to 60°C can be attained with the present invention. Nonetheless, for ophthalmic uses, the previously described polymer concentration ranges are preferred.

For use as drug delivery vehicles, the aqueous compositions of the present invention can be modified through the incorporation of a suitable pharmaceutical medicament or diagnostic compound in a concentration ranging from approximately 0.0001% to 50% by weight. As those skilled in the art will appreciate, when compatible medicaments and/or diagnostic compounds are incorporated into the aqueous compositions of the present invention, the drugs will also be incorporated into the gelling matrix following delivery to the target site. As a result, the drug containing visco-elastic gel will reside at the applied location, thereby prolonging the retention and delivery of the incorporated drug. Similarly, fine suspensions of solid drug compositions or particulate drug containing delivery systems may also be incorporated into the reversibly gelling compositions of the present invention. Injection

into subcutaneous drug delivery depots or topical delivery by drop installation of the solutions will then position such delivery systems at the site of choice for sustained bioavailability. This enhanced bioavailability and improved duration of action may lead to overall lower drug dosages being required with resultant improved side effect profiles.

Modifications to the viscosity ranges, pH ranges and temperatures at which the sol-gel transition takes place can be produced in the compositions of the present invention by varying the polymer concentrations as well as through the incorporation of small amounts of univalent or divalent salt. Typically, the addition of small quantities of salt giving a salt-to-combined polymer ratio up to 0.5 and preferably on the order of 0.045 to 0.075 will decrease the viscosity of the composition in the ungelled state if desired. Alternatively, it is contemplated as being within the scope of the present invention to incorporate up to approximately 0.2% to 0.9% by weight salt.

Further objects and advantages of the reversibly gelling compositions of the present invention, as well as a better understanding thereof, will be afforded to those skilled in the art from a consideration of the following detailed explanation of preferred exemplary embodiments thereof. Reference will be made to the appended sheets of drawings which will now be first described briefly.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graphical illustration showing the viscosity of a Methocel/Carbopol (Carbopol concentration fixed at 0.3% by weight) mixture as a function of the concentration of a Methocel at room temperature and pH 4.0 Carbopol;

FIG. 2 is a graphical illustration showing the viscosity of a Methocel/Carbopol (Carbopol concentration fixed at 0.3% by weight) mixture as a function of the concentration of a Methocel at 37°C and pH 7.4 Carbopol;

FIG. 3 is a graphical illustration showing the viscosity of a Methocel (1%)/Carbopol (0.3%) mixture as a function of salt concentration at room temperature and pH 4.0;

FIG. 4 is a graphical illustration showing the viscosity of a Methocel (1%)/Carbopol (0.3%) mixture as a function of salt concentration at 37°C and pH 7.4;

FIG. 5 is a graphical illustration showing the viscosity of a Pluronic®/Carbopol (Carbopol concentration fixed at 0.3% by weight) mixture as a function of the concentration of Pluronic® at room temperature and pH 5.0 Carbopol;

FIG. 6 is a graphical illustration showing the viscosity of a Pluronic®/Carbopol (Carbopol concentration fixed at 0.3% by weight) mixture as a function of the concentration of Pluronic® at 37°C and pH 7.4 Carbopol;

FIG. 7 is a graphical illustration showing the viscosity of a Tetronic®/Carbopol (Carbopol concentration fixed at 0.3% by weight) mixture as a function of the Tetronic® concentration at room temperature and pH 5.0 Carbopol; and

FIG. 8 is a graphical illustration showing the viscosity of a Tetronic®/Carbopol (Carbopol concentration fixed at 0.3% by weight) mixture as a function of the Tetronic® concentration at 37°C and pH 7.4 Carbopol.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The reversibly gelling aqueous compositions of the present invention are primarily intended for use as drop instillable, oral and injectable drug delivery vehicles as well as for topically applied lubricants, wetting agents and cleaning agents. Accordingly, the preferred exemplary embodiments of the present invention exhibit good, usable flow characteristics at room temperature, yet rapidly gel to highly visco-elastic compounds exhibiting viscosities several orders of magnitude greater at physiological temperatures and pH. Thus, the preferred exemplary embodiments exhibit significant increases in viscosity in response to substantially simultaneous upshifts in both temperature and pH to those conditions encountered in the ocular milieu or at typical injectable drug delivery sites. However, those skilled in the art will appreciate that alternative compositions which gel in response to simultaneous increases in temperature and decreases in pH or the converse may also be produced in accordance with the teachings of the present invention where desired. Similarly, alternative compositions which gel at temperatures significantly above or below those encountered in physiological systems or which exhibit markedly different viscosities relative to those of the preferred embodiments may also be produced. Thus, for purposes of explanation and without limiting the scope of the present invention, the following exemplary

embodiments will be discussed in the context of drop instillable or injectable reversibly gelling compounds intended for use in physiological systems.

As those skilled in the art will also appreciate, in addition to responding to changes in both temperature and pH, the ability to produce dramatic changes in viscosity with very small polymer concentrations is a significant feature of the present invention which overcomes many of the disadvantages associated with prior art compositions. For example, the polymer concentrations utilized in accordance with the teachings of the present invention significantly reduce the buffering capacity of the aqueous compositions so produced, thereby effectively eliminating the irritation associated with high buffering capacity compounds such as the pH triggered gelling compositions of the prior art. Similarly, reducing the polymer concentration also reduces the thermal energy requirement of the reversibly gelling compositions and, as a result, the compositions of the present invention gel almost instantaneously pon application. This instantaneous gelation further reduces migration and loss of the compositions of the present invention over the prior art compounds. As an additional benefit, the low polymer concentration compositions of the present invention produce transparent, colorless gels, making them particularly well suited for use as ocular drug delivery vehicles.

In its broadest capacity, an exemplary embodiment of the aqueous compositions of the present invention which exhibits reversible gelation in response to simultaneous variations in both temperature and pH over predetermined ranges comprises an aqueous solution incorporating a stable combination or admixture of at least one thermally-sensitive gelling polymer and at least one pH-sensitive gelling polymer in sufficient amounts to effectively produce reversible gelation over the desired temperature and pH ranges. Preferred thermally-sensitive gelling polymers include alkyl cellulose, hydroxyalkyl cellulose, cellulosic ethers, Pluronic® polymers and Tetronic® polymers, with methylcellulose being particularly preferred. Preferred pH-sensitive gelling polymers which increase viscosity with increasing pH are selected from the family of linear, branched or crosslinked acidic polymers such as those containing carboxyl groups, particularly carboxy vinyl polymers of monomers such as acrylates, methacrylic acid, ethacrylic acid, β-methylacrylic acid, cis-α-methylcrotonic acid, trans-α-methylcrotonic acid, α-butylcrotonic acid, α-phenylacrylic acid, α-

benzylacrylic acid, α-cyclohexylacrylic acid, and the like. Exemplary concentrations giving the widest range of viscosities and sol-gel transition temperatures range from approximately 0.1% to 40% by weight thermally-sensitive gelling polymer and from approximately 0.01% to 10% by weight pH-sensitive gelling polymer. For physiological systems, the preferred exemplary concentrations giving the preferred sol-gel transition temperatures and associated viscosities range from approximately 0.1% to 5% by weight thermally-sensitive gelling polymer, and from approximately 0.01% to 0.5% by weight pH-sensitive gelling polymer.

Thus, an exemplary composition of the present invention comprises a homogeneous association complex of a macromolecular mixture of methylcellulose, a polysaccharide available from Dow Chemical under the trade name Methocel, and a cross-linked polyacrylic acid such as Carbopol 940, a hydrophilic acrylic polymer available from the B. F. Goodrich Company. Methocel consists of cellulose chains with a moderate to high degree of hydrophobic methyl group substitution, while Carbopol is a hydrophilic acrylic polymer. When these polymers are mixed in the preferred exemplary aqueous concentrations ranging from 0.1% to 10% by weight Carbopol and from 0.01% to 30% by weight Methocel, a stable combination of the aqueous polymer mixture is formed. This is in direct contrast to the teachings of the prior art wherein aqueous polymer mixtures are extremely difficult, if not impossible, to form due to molecular interaction and precipitation. More importantly, by varying the concentration ranges of this aqueous composition, a wide variety of viscosities and sol-gel transition temperatures and pHs can be produced.

For example, at formation conditions, the pH of the composition will generally range from approximately 2.5 to 6.5, with a preferable range of 4.0 to 5.5. The osmolality will generally range from 20 to 500, with a preferable range between approximately 50 to 400. The osmolality can be adjusted through the addition of physiologically acceptable salts and non-ionic additives such as sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium lactate, magnesium phosphate, mannitol, sucrose and glycerine. However, sodium chloride is the preferred tonicity adjuster. More significantly, at temperatures ranging from 0°C to 45°C, and preferably between 15°C to 30°C, the viscosity of the composition can be adjusted to range from 20 to 40,000 cP (measured at a shear rate of 2.6 sec^{-1}), with a preferred range between 100 to 30,000 cP to produce a drop instillable or injectable viscous fluid. Taking these same formulations and exposing

them to physiological conditions of pH approximately 7.4 and temperature approximately 37°C results in viscosities ranging from 200 to 1 million cP with preferable ranges between approximately 50,000 to 400,000 cP. As a result, the compositions of the present invention can be tailored to produce drop instillable ocular wetting agents, cleaning agents or drug delivery systems which will remain in the eye from fractions of an hour up to ten hours or more, and preferably from two to six hours.

More specifically, when mixed in the exemplary aqueous concentrations of approximately 1% to 3% by weight methylcellulose and 0.2% to 0.4% by weight Carbopol, a stable combination of the aqueous polymer mixture is formed which exhibits a viscosity on the order of 10,000 cP at room temperature (25°C) and at a pH of between 3.0 and 5.0. When this composition is subjected to physiological temperatures and pH on the order of 37°C and pH 7.4 two simultaneous intermolecular conformational changes are believed to occur. First, increased ionization produces unwinding of the coils of the acrylic chain. This is accompanied by the expulsion of the hydrophobic functional components of the methylcellulose chain. As a result, within approximately 60 to 120 seconds a three-dimensional network is formed with a concomitant increase in visco-elasticity of several orders of magnitude to approximately 140,000 cP. As those skilled in the art will appreciate, compatible medicaments, diagnostic compounds and microfine particulate drug delivery vehicles incorporated into the composition will be entrapped in the visco-elastic polymer matrix so produced for sustained release applications where desired.

That such significant increases in viscosity should occur with such low polymer concentrations in response to simultaneous changes in both temperature and pH comes in complete contrast to the teachings of the prior art. As noted above, prior art systems for which high viscosity change is induced by temperature change alone require preparations with high polymer concentrations typically much greater than 10% by weight. What is more, with such high concentrations, the heat transfer limitations of the preparations themselves may result in relatively slow or incomplete viscosity increases. Moreover, the high polymer concentrations of the prior art may cause discomfort, polymer crusting on the eyelids, vision blurring, and altered anatomical conditions such as blockage of the lacrimal duct. Similarly, systems for which viscosity change is induced by pH changes alone typically require high polymer concentrations. These pH-triggered systems exhibit

a significantly greater buffering capacity than the thermally-triggered systems. In the ocular milieu this high buffering capacity may lead to incomplete gelation and local irritation. Accordingly, the compositions of the present invention are significantly advantageous over these known systems in two major ways. First, for use in physiological conditions, the compositions of the present invention can have significantly less total polymer content; and, second, these compositions effectively utilize both the buffering and heat capacity of the ocular milieu to rapidly and completely induce conformational changes leading to substantially higher viscosity.

As with the compositions of the present invention in general, the rheological properties of the exemplary aqueous solutions of thermally-sensitive methylcellulose and pH-sensitive polyacrylate are effected by the molecular weights of the respective polymers, their concentration, temperature, pH and the presence of other solutes. However, it should be emphasized that the properties of the aqueous compositions of the present invention are uniquely and unexpectedly synergistic. For example, because methylcellulose is non-ionic, in solution alone it is visco-elastically stable over a wide range of pH from approximately 3 to 11. The viscosity of polyacrylate solutions alone is proportional to the polymer concentration, both at lower and higher pH. For example, at polymer concentrations between 0.1% and 0.4% by weight, aqueous polyacrylate solutions are very inviscid over a pH range of 3 to 7. Additionally, aqueous solutions containing more than 0.5% by weight polyacrylate have a much higher buffer capacity and need additional neutralizing base to increase their viscosity. However, mixtures of such pH-sensitive and thermally-sensitive polymers in accordance with the teachings of the present invention exhibit viscosities which are substantially in excess of the sum of the individual viscosities of the individual aqueous polymer solutions at both lower and higher pH. For example, at pH 4.0, the viscosity of a 3% by weight methylcellulose solution measured with a Carri-Med rheometer at a shear rate of approximately 2.6 sec^{-1} is approximately 18,000 cP. Similarly, the viscosity of a 0.2% Carbopol solution at pH 4.0 is approximately 50 cP. The viscosity of the mixture of these two polymers produced in accordance with the teachings of the present invention at pH 4.0 is approximately 30,000 cP. As those skilled in the art will appreciate, 30,000 cP is substantially greater than the anticipated combined viscosity of 18,050 cP.

The following table is an illustrative listing of the rheological properties that can be expected with the aqueous compositions of the present invention utilizing an exemplary formulation of Methocel A4M methylcellulose and Carbopol (940), a crosslinked polyacrylate.

TABLE 1

Viscosity for Typical Methocel (1% by Weight)/Carbopol (0.3% by Weight) Preparation

Temperature	25°C		37°C	
pH	4.0	7.4	4.0	7.4
Viscosity, cP (shear rate approximately 2.6 sec^{-1})	11,500	90,800	20,000	140,000

FIGS. 1 and 2 more clearly show the rheologic properties of exemplary Methocel/Carbopol mixtures in accordance with the teachings of the present invention. As shown in FIGS. 1 and 2, the viscosity of an exemplary aqueous Methocel/Carbopol composition is plotted as a function of the concentration of Methocel (the Carbopol concentration being fixed at 0.3% by weight) at room temperature and pH 4 in FIG. 1 and at 37°C and pH 7.4 in FIG. 2. As shown in FIG. 1, aqueous compositions exhibiting a viscosity ranging from approximately 20 to in excess of 40,000 cP can be produced at room temperature and pH 4 which, as shown in FIG. 2, gel to viscosities ranging from approximately 200 to well in excess of 200,000 at physiological conditions. As those skilled in the art will also appreciate, the foregoing temperature and pH conditions discussed in Table 1 are exemplary of those present at room temperature (25°C) and in the ocular milieu where the cul-de-sac of the eye is bathed with isotonic lacrimal fluid at pH 7.4 and approximately 37°C. Thus, it is readily apparent that the exemplary composition disclosed in Table 1 is a freely-flowing viscous liquid at its formulation temperature and pH which, upon contract with tear fluid and physiologic conditions, forms a highly visco-elastic gel.

Additionally, the highly visco-elastic gels formed at the physiologic temperature and pH are transparent with a specific gravity of approximately 1.01 and a refractive index of approximately 1.33. Thus, the aqueous compositions of the present invention can easily be administered to the eye in drop form and will rapidly gel under the combined effect of both temperature and pH when placed in the eye thereby preventing their rapid elimination from the eye through the

lacrimal drainage system. Moreover, the favorable optical properties and low polymer concentration of the compositions should cause minimal or no visual perturbation once gelled *in situ*. It should also be appreciated that these exemplary gelled compositions exhibit a muco-adhesive property which further aids their retention in the cul-de-sac of the eye. Also, the gelled polymers are self-lubricating and relatively soft and deformable which increases patient comfort and acceptability.

As shown in FIGS. 3 and 4, it should also be noted that the viscosity of the aqueous compositions of the present invention can be modified by adding a pharmaceutically acceptable salt such as mono- or di-valent salts including sodium chloride, potassium chloride, calcium chloride or mixtures thereof, as well as suitable alkali metal salts such as sodium sulfate and the like. Preferred salt to total polymer ratios will range from 0 to approximately 0.5 and preferably from approximately 0.045 to 0.075. As shown in FIGS. 3 and 4, the addition of salt exhibits its most significant relative effect on the lower viscosity of the aqueous system. For example, slight increases in the salt concentration apparently preferentially decrease the lower viscosity ranges while exhibiting a comparatively minor decrease on the upper viscosity ranges.

The rheological properties of alternative exemplary compositions produced in accordance with the teachings of the present invention are illustrated in FIGS. 5 through 8. FIGS. 5 and 6 illustrate the viscosity of a Pluronic®/Carbopol mixture prepared in accordance with the teachings of the present invention. Pluronic® polymers are block copolymers of propylene oxide and ethylene oxide and are thermally-sensitive gelling polymers. It is contemplated as being within the scope of the present invention to form reversibly gelling aqueous compositions comprising stable mixtures of from 0.01% to 10% by weight pH-sensitive gelling polymers such as Carbopol, and from approximately 1% to 30% by weight Pluronic® polymer. As shown in FIGS. 5 and 6, such mixtures form viscous liquids at room temperature and pH 5 and rapidly gel to highly visco-elastic gels at physiologic conditions.

Similarly, alternative compositions can be formulated within the scope of the present invention utilizing Tetronic® polymers. Tetronic® polymers are tetrafunctional block copolymers derived from the sequential addition of propylene oxide and ethylene oxide to ethylenediamine. As shown in FIGS. 7 and 8, reversibly gelling aqueous compositions

produced in accordance with the teachings of the present invention utilizing Tetronic® polymers can also be formulated to remain liquid at room temperature and lower pHs on the order of 4.0 to 5.5 while gelling to highly visco-elastic gels at physiological conditions. It should be noted that these alternative polymer compositions extend the temperature ranges available for gelling and formulation without significantly modifying the pH and osmolality conditions associated with these compositions.

Though the foregoing exemplary compositions all reversibly gel in response to simultaneous upshifts in both temperature and pH, it is also possible to utilize the teachings of the present invention to produce aqueous compositions which are liquid at higher pH and lower temperatures and gel at lower pH (neutral or lower) and higher temperatures. For example, polymers containing weakly basic pendant groups such as amine containing polymers of poly-N,N dimethylaminoethyl methacrylate can be combined with methylcellulose, Pluronic® or Tetronic® polymers or combinations thereof. Such combinations will be liquid at higher pH and lower temperature while gelling at lower pH and higher temperature.

As those skilled in the art will appreciate, the aqueous compositions of the present invention may be utilized as wetting agents or lubricants for contact lenses or the treatment of conditions such as dry eye. However, it is preferred that the compositions be utilized as drug delivery vehicles for administering a variety of pharmaceutical medicaments and diagnostic compounds.

The most promising drugs for incorporating into the aqueous drug delivery compositions of the present invention are levobunolol, pilocarpine, dipivefrin and others which exhibit poor bioavailability. Other exemplary drugs or diagnostic agents which can be administered by the aqueous compositions of the present invention include, but are not limited to:

(1) antibacterial substances such as beta-lactam antibiotics, such as cefoxitin, n-formamidoyl-thienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, carbenicillin, colistin, penicillin G, polymyxin B, vancomycin, cefazolin, cephaloridine, chibrorifamycin, gramicidin, bacitracin, sulfonamides; aminoglycoside antibiotics such as gentamycin, kanamycin, amikacin, sisomicin and tobramycin; nalidixic acid and analogs such as norfloxacin and the antimicrobial combination of flucalanine/pentizidone; nitrofurazones, and the like;

(2) antihistaminics and decongestants such as pyrilamine, chlorpheniramine, tetrahydrazoline, antazonline, and the like;

(3) anti-inflammatorics such as cortisone, hydrocortisone, hydrocortisone acetate, betamethasone, dexamethasone, dexamethasone sodium phosphate, prednisone, methylprednisolone, medrysone, fluorometholone, fluocortolone, prednisolone, prednisolone sodium phosphate, triamcinolone, indomethacin, sulindac, its salts and its corresponding sulfide, and the like;

(4) miotics and anticholinergics such as echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, epinephrine, dipivolyl epinephraine, neostigmine, echothiophate iodide, demecarium bromide, carbachol, methacholine, bethanechol, and the like;

(5) mydriatics such as atropine, homatropine, scopolamine, hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium, eucatropine, and the like; and other medicaments used in the treatment of eye conditions or diseases such as

(6) antiglaucoma drugs, for example, betaxalol, pilocarpine, timolol, especially as the maleate salt and R-timolol and a combination of timolol or R-timolol with pilocarpine. Also included are epinephrine and epinephrine complex or prodrugs such as the bitartrate, borate, hydrochloride and dipivefrin derivatives and hyperosmotic agents such as glycerol, mannitol and urea;

(7) antiparasitic compounds and/or anti-protozoal compounds such as ivermectin; pyrimethamine, trisulfapyrimidine, clindamycin and corticosteroid preparations;

(8) antiviral effective compounds such as acyclovir, 5-iodo-2'-deoxyuridine (IDU), adenosine arabinoside (Ara-A), trifluorothymidine, and interferon and interferon inducing agents such as Poly I:C;

(9) carbonic anhydrase inhibitors such as acetazolamide, dichlorphenamide, 2-(p-hydroxyphenyl)thio-5-thiophenesulfonamide, 6-hydroxy-2-benzothiazolesulfonamide and 6-pivaloyloxy-2-benzothiazole-sulfonamide;

(10) anti-fungal agents such as amphotericin B, nystatin, flucytosine, natamycin, and miconazole;

(11) anesthetic agents such as etidocaine cocaine, henoxinate, dibucaine hydrochloride, dyclonine hydrochloride, naepaine, phenacaine hydrochloride, piperocaine, proparacaine hydrochloride, tetracaine hydrochloride, hexylcaine, bupivacaine, lidocaine, mepivacaine and prilocaine;

(12) ophthalmic diagnostic agents such as

(a) those used to examine the retina and chloride-sodium fluorescein;

(b) those used to examine the conjunctiva, cornea and lacrimal apparatus such as fluorescein and rose bengal; and

(c) those used to examine abnormal pupillary responses such as methacholine, cocaine, adrenaline, atropine, hydroxyamphetamine and pilocarpine;

(13) ophthalmic agents used as adjuncts in surgery such as alpha-chymotrypsin and hyaluronidase;

(14) chelating agents such as ethylenediamine tetraacetate (EDTA) and deferoxamine;

(15) immunosuppressive agents and anti-metabolites such as methotrexate, cyclophosphamide, 6-mercaptopurine, and azathioprine;

(16) peptides and proteins such as atrial natriuretic factor, calcitonin-gene related factor, lutinizing hormone, releasing hormone, neuroterisin, vasoactive intestinal peptide, vasopressin, cyclosporine, interferon, substance P enkephalins, epidermal growth factor, eye-derived growth factor, fibronectin, insulin-like growth factor and mesodermal growth factor;

(17) lubricating agents such as sodium hyaluronate or polyvinyl alcohol; and

(18) combinations of the above such as antibiotic/anti-inflammatory as in neomycin sulfate-dexamethasone sodium phosphate, concomittant anti-glaucoma therapy such as timolol maleate-aceclidine.

As those skilled in the art will appreciate, the foregoing listing of pharmaceutical compounds is exemplary only. Because the drug delivery compositions of the present invention are uniquely suited for utilization in a wide variety of physiological applications such as the ocular, oral, nasal, rectal or subcutaneous administration of pharmaceutical compounds, a wide variety of pharmaceutical agents may be incorporated therein. Accordingly, the foregoing listing of pharmaceutical agents is not intended to limit the scope of the present invention and is exemplary only.

Preferably, when utilized as an aqueous drug delivery vehicle for drop instillation, oral administration or injection, the compositions of the present invention can be modified to include from approximately 0.0001% to 50% by weight pharmaceutical medicament or diagnostic agent.

To prepare an aqueous drug delivery vehicle in accordance with the teachings of the present invention, an appropriately effective amount of the pharmaceutical compound of choice is simply incorporated into the aqueous composition at the composition formulation temperatures and pHs. Preferably, the compound of choice will be soluble in the solution or will be homogeneously dispersed and will not react with the polymer system. Soluble pharmaceutical compounds will readily dissolve in the aqueous composition, whereas insoluble compounds will preferably be particularized for even dispersion throughout the compositions. Along these lines, it is also contemplated as being within the scope of the present invention to incorporate insoluble or erodible microparticulate drug delivery systems such as those known in the art into the aqueous compositions. In this manner, controlled release drug delivery systems can be incorporated into the aqueous compositions of the present invention and retained in position when administered by drop or injection.

Following gelation, the medicament or diagnostic agent will be incorporated into the gelled polymer matrix and will remain on site for sustained drug delivery as the solidified gel slowly erodes and the incorporated pharmaceutical agent diffuses out into the surrounding lacrimal or physiological fluid. Additionally, it should be noted that by varying the concentration of pharmaceutical compound within the aqueous composition, it is possible to modify and control the quantity of pharmaceutical compound delivered by drop or injection. For example, a liquid drug delivery vehicle can be prepared in accordance with the teachings of the present invention containing from about 0.01 to about 5% of the medicament or pharmaceutical agent of choice on a weight to weight basis. For drop instillation methodologies the drop size will preferably range from approximately 20 μl to 50 μl, with 25 μl drops being particularly preferred. Thus, from one drop of the liquid composition which contains about 25 μl of solution, one would obtain about 0.0025 mg to about 1.25 mg of drug.

The following non-limiting examples are offered as being illustrative of the properties of exemplary compositions of the present invention. In the following example, concentrations are expressed in weight percent (% w/w), deionized water is utilized to make the formulations, and the formulation temperatures are 25° C.

EXAMPLE I

Thirty gm of water was heated to about 90°C. To this heated water, 3 gm of Methocel A4M (available from Dow Chemicals, Midland, MI) was added and the mixture was stirred until the polymer particles were thoroughly wetted and evenly dispersed. Sixty-seven gm cold water was added to lower the temperature of the dispersion to about 10°C for complete solubilization. The final mixture was brought to 100 gm of total weight by adding deionized water to give 3% w/w of Methocel mixture. The resultant mixture was stirred for two hours at 2.5 rpm.

In a separate container, 0.9 gm of Carboxypolymethylene (available from B. F. Goodrich, Cleveland, OH, as Carbopol 940) was completely dispersed and stirred in 90 gm of deionized water. The mixture was agitated at 100 rpm for two hours following which water was added to bring the final mixture weight to 100 gm and 0.9% w/w of Carbopol content.

A physical admixture of 20 gm of the 3% w/w of Methocel solution (prepared as mentioned above) and 20 gm of the 0.9% w/w Carbopol solution was prepared. 0.06 gm of Levobunolol was dissolved in 18 gm of deionized water and added to the physical admixture of the polymers. The resultant drug containing aqueous solution was then titrated with 5N NaOH to pH 4.5 following which the final formulation was brought to 60 gm by adding deionized water. The resultant formulation was as follows: 1% Methocel, 0.3% Carbopol and 0.1% Levobunolol. The viscosity was measured using a Carri-Med Rheometer and a rheogram depicting shear stress v/s shear rate was obtained. The formulation had a viscosity of 12,000 cP at a shear rate of 2.64/sec. The mixture was a smooth flowing liquid having droppable characteristics.

EXAMPLE II

Methocel A4M mixture, 3% w/w, was prepared as set forth under Example I. Forty grams of this solution was blended with 0.12 gm of Carbopol 940, 0.6 gm of Levobunolol and 18 gm of deionized water. The mixture was then stirred at 50 rpm at room temperature for 15 hours. The resultant drug containing mixture was titrated with 5N NaOH to pH 4.2 following which deionized water was added to bring the final formulation weight to 100% (60 gm) followed by stirring at 50 rpm for another two hours. The final formulation obtained was as follows: 2% Methocel, 0.2% Carbopol and 0.1% Levobunolol. The viscosity was measured using a Carri-Med Rheometer and a rheogram depicting shear stress v/s shear rate was obtained. The formulation had a viscosity of

7806 cP at a shear rate of 2.64/sec. The mixture was a smooth flowing liquid having droppable characteristics.

EXAMPLE III

Methocel A4M mixture, 3% w/w, was prepared as set forth under Example I. A preblend of 0.06 gm of salt (Sodium Chloride) and 0.06 gm of Levobunolol was prepared. Forty gm of Methocel solution was blended with 0.18 gm of Carbopol 940, the preblend of salt and Levobunolol and 16 gm of water. The mixture was then stirred at 50 rpm for 15 hours and then titrated with 5N NaOH to pH 4.00. The final formulation was brought to 100% weight (60 gm) by adding deionized water and stirred at 50 rpm for another two hours. The final formulation obtained was as follows: 2% Methocel, 0.3% Carbopol, 0.1% Sodium Chloride and 0.1% Levobunolol. The viscosity was measured using a Carri-Med Rheometer and a rheogram depicting shear stress v/s shear rate was obtained. The formulation had a viscosity of 8317 cP at a shear rate of 2.65/sec. The mixture was a smooth flowing liquid having droppable characteristics.

EXAMPLE IV

Methocel A4M mixture, 3% w/w, was prepared as set forth under Example I. A preblend of 0.06 gm of Levobunolol and 0.18 gm of Carbopol 940 was prepared. A physical admixture of 20 gm of the 3% w/w of Methocel solution and the preblend was prepared, followed by adding 38 gm of deionized water. The mixture was stirred for 15 hours at 50 rpm to assure complete mixing. The resultant drug containing aqueous solution was then titrated with 5N NaOH to pH 4.12 following which the final formulation was brought to 60 gm by adding deionized water followed by mixing for two hours at 50 rpm. The resultant formulation was as follows: 1% Methocel, 0.3% Carbopol and 0.1% Levobunolol. The viscosity of the formulation was measured using a Carri-Med Rheometer and a rheogram depicting shear stress v/s shear rate was obtained. The formulation had a viscosity of 3154 cP at a shear rate of 2.55/sec. The mixture was a smooth flowing liquid having droppable characteristics.

EXAMPLE V

Thirty gm of water was heated to 90°C. To this heated water, 5 gm of Methocel A4M (available from Dow Chemicals, Midland, MI) was added and the mixture was stirred until the polymer particles were thoroughly wetted and evenly dispersed. The remainder of the water, 67 gm, was

added as cold water to lower the temperature of dispersion to about 10°C for complete solubilization. The final mixture was brought to 100 gm of total weight by adding purified water to give 5% w/w of Methocel mixture. The resultant mixture was stirred for two hours at 25 rpm.

Twenty grams of deionized water was measured and to this 0.12 gm of Carbopol 940 (available from B. F. Goodrich) was added. The solution was stirred at 50 rpm for two hours until all the Carbopol was dispersed into the solution. Thirty-six grams of 5% Methocel solution, as prepared above, was added to the Carbopol solution followed by the addition of 0.09 gm of Sodium Chloride. The physical admixture was stirred for 12 hours at 50 rpm to ensure complete mixing and dispersion of the polymers. The mixture was then titrated with 5N NaOH to pH 3.53 following which the final formulation was brought to 100% weight. The final formulation by weight percent was: 3% Methocel, 0.2% Carbopol, 0.15% Sodium Chloride. The viscosity of the formulation was measured using a Carri-Med Rheometer and a rheogram depicting shear stress v/s shear rate was obtained. The formulation had a viscosity of 16,610 cP at a shear rate of 2.64/sc. The mixture was a smooth flowing liquid having droppable characteristics.

EXAMPLE VI

Methocel A4M mixture, 5% w/w, was prepared as set forth under Example V. A preblend of 0.12 gm of Carbopol 940 and 0.14 gm of Sodium Chloride was prepared. This preblend was added to 36 gm of the 5% w/w of Methocel solution followed by the addition of 20 gm of water. The mixture was stirred at 50 rpm for 15 hours and then titrated with 5N NaOH to pH 3.5. The final formulation was then brought to 100% weight by adding deionized water and further stirred for two hours at 50 rpm. The final formulation by weight percent was: 3% Methocel, 0.2% Carbopol, 0.25% Sodium Chloride. The viscosity was measured using a Carri-Med Rheometer and a rheogram depicting shear stress v/s shear rate was obtained. The formulation had a viscosity of 16,600 cP at a shear rate of 2.85/sec. The mixture was a smooth flowing liquid having droppable characteristics.

EXAMPLE VII

Methocel A4M mixture, 3% w/w, was prepared as set forth under Example I. Carbopol 940 (available from B. F. Goodrich), 0.12 gm, was dispersed in 18 gm of deionized water. After complete dispersion, 0.09

gm of Sodium Chloride was added to this Carbopol solution and the resultant mixture was stirred at 50 rpm for 10 hours. Forty grams of 3% Methocel was then added to the Carbopol/Salt solution and the mixture stirred for four hours. The resultant mixture was then titrated with 5N NaOH to pH 4.49 following which deionized water was added to bring the final formulation to 100% weight (60 gm). The final formulation by weight percent was: 2% Methocel, 0.2% Carbopol, 0.15% Sodium Chloride. The viscosity was measured using a Carri-Med Rheometer and a rheogram depicting shear stress v/s shear rate was obtained. The formulation had a viscosity of about 11,500 cP at a shear rate of 2.64/sec. The mixture was a smooth flowing liquid having droppable characteristics.

EXAMPLE VIII

An exemplary aqueous gel mixture was prepared containing 3% Methocel A4M, 0.3% Carbopol 940 and 0.2% salt with a 1% loading of Acid Orange 8 dye for an *in vitro* release kinetic study. A 0.4 gram solidified gel sample of this composition was placed in a USP dissolution kettle (paddle speed 50 rpm) containing 500 ml phosphate buffer at pH 7.4 and 37°C. The dissolution time for the gel was observed to be in excess of nine hours. A T_{50} value of approximately 55 minutes and a T_{90} value of approximately 200 minutes was obtained from the dye release profile of the gel.

EXAMPLE IX

An analysis of *in vivo* gel retention time was undertaken utilizing rabbit eyes. The gel mixture of Example 1 was tagged with high molecular weight FITC dextran (MW approximately 70,000). Gel formation after installation of a 50 microliter drop appeared to be quite rapid and led to the formation of a continuous coating on the pre-corneal surface of the eye by the gel matrix. Photographic and biomicroscopic assessments were obtained over a seven hour observation period. Two significant retention times of the delivery vehicle in the rabbit eye were obtained: (1) a distinct gelatinous formation in the lower cul-de-sac; and (2) a smooth, apparently uniform film over the ocular surface. The distinct gel formation lasted for approximately three hours while the uniform film retention time was 0 to 6.5 hours or more.

EXAMPLE X

Sodium fluorescein was used as a marker with the composition of Example 2 to monitor its penetration into the anterior chamber of the eye. The rabbit eye anterior chamber was monitored using a slit lamp technique and an incremental increase in fluorescence over a period of seven hours after the installation of the gel labelled with fluorescein was observed.

EXAMPLE XI

Probe acute toxicological studies did not reveal any toxicity issues. No irritation, injection, staining or cytotoxicity was observed with the gel mixture in rabbit eyes. Ocular status was noted to be healthy after 24 hours post-installation.

EXAMPLE XII

An exemplary drug delivery vehicle incorporating erodible microparticulate drug delivery vehicles was prepared as follows. Levobunolol was blended into a heated slurry of poly(orthoester) and cooled to solidify the mixture. The drug containing poly(orthoester) was ground to produce microparticulates ranging in size from 1 to 300 μm. These particles were physically dispersed in the exemplary reversible gelling composition of Example I to produce a reversibly gelling drug delivery vehicle incorporating erodible drug containing microparticulates.

EXAMPLE XIII

An exemplary therapeutic agent for the treatment of severe keratoconjunctivitis sicca was produced from an aqueous composition containing 1% by weight Methocel, 0.3% by weight Carbopol 940, and 0.1% by weight sodium hyaluronate and isotonically adjusted with glycerol at pH 4.5 to 5.5. Upon installation of a 50 μl drop in rabbit eyes, almost instantaneous gelation was observed. Examination of the rabbit eyes 24 hours following installation indicated healthy ocular status.

As those skilled in the art will appreciate, though the foregoing examples were primarily directed to ocular drug delivery vehicles, wetting agents and topical compositions, it is contemplated as being within the scope of the present invention to utilize the aqueous compositions of the present invention as drug delivery vehicles which

can be orally administered or injected either subcutaneously or intramuscularly. Following injection of the free-flowing drug delivery vehicle, the aqueous composition will rapidly gel to form a stable drug delivery depot from which the incorporated pharmaceutical compound can diffuse.

However, it is preferred that the aqueous compositions of the present invention be utilized to deliver pharmaceutical compounds to the surface of the eye. In this manner, the pharmaceutical compounds can be retained in contact with the eye surface over an extended period of time to enhance the bioavailability of the incorporated pharmaceutical compound. Such a drug delivery method would comprise the steps of preparing the aqueous composition of the present invention containing the above described effective amount of pharmaceutical compound and introducing the composition into the lacrimal secretions of the eye. Once introduced into the cul-de-sac of the eye, the composition will rapidly gel and resist the dilution and depletion normally associated with tear turnover in the eye. The mucoadhesive gel so formed will remain in the eye for significant periods of time, slowly eroding and releasing the dissolved pharmaceutical agent dispersed within it. This prolonged residence time leads to more effective levels of concentration of the pharmaceutical agent in the tear film and may actually result in a decrease in the overall dosage that need be administered.

Having thus described preferred exemplary embodiments of the present invention, it should be noted by those skilled in the art that the disclosures herein are exemplary only and that alternatives, adaptations and modifications may be made within the scope of the present invention. Thus, by way of example and not limitation, it is contemplated that ionic strength sensitive gelling polymers also may be utilized which thicken when exposed to changes in ionic strength. Accordingly, the present invention is not limited to the specific embodiments illustrated herein.

We claim:

1. An aqueous composition of matter exhibiting the property of reversible gelation in response to substantially simultaneous variations in both temperature and pH over predetermined ranges.

2. The composition of claim 1 comprising an aqueous solution having a reversible viscosity modifying effective concentration of a stable combination of at least one thermally-sensitive gelling polymer and at least one pH-sensitive gelling polymer.

3. The composition of claim 2 wherein said at least one thermally-sensitive gelling polymer is selected from the group consisting of alkylcellulose, hydroxyalkyl cellulose, Pluronic® polymers, and Tetronic® polymers.

4. The composition of claim 2 wherein said at least one thermally-sensitive gelling polymer is methylcellulose.

5. The composition of claim 2 wherein said at least one pH-sensitive gelling polymer is an acidic polymer.

6. The composition of claim 5 wherein said acidic polymer is a carboxyl containing polymer.

7. The composition of claim 6 wherein said carboxyl containing polymer is polyacrylate.

8. The composition of claim 2 wherein said at least one thermally-sensitive gelling polymer is methylcellulose and said at least one pH-sensitive gelling polymer is polyacrylate.

9. The composition of claim 8 wherein said aqueous composition comprises approximately 0.1% to 5% by weight methylcellulose and approximately 0.01% to 10% polyacrylate.

10. The composition of claim 8 wherein said aqueous composition comprises approximately 1% by weight methylcellulose and approximately .3% by weight polyacrylate.

11. The composition of claim 2 further comprising a viscosity modifying amount of salt.

12. The composition of claim 11 wherein said salt is selected from the group consisting of univalent and divalent dissociable ionic compounds.

13. The composition of claim 11 wherein said salt is present in a salt-to-polymer ratio of approximately 0.001 to 0.5.

14. The composition of claim 1 wherein said range of temperature variation is from approximately 0° to 60°C.

15. The composition of claim 1 wherein said range of pH variation is from approximately 2.5 to 7.4.

16. The composition of claim 2 further comprising an effective amount of a pharmaceutical medicament or diagnostic compound.

17. The composition of claim 16 wherein said pharmaceutical medicament or diagnostic compound is incorporated in a microparticulate drug delivery system.

18. The composition of claim 16 wherein said pharmaceutical medicament or diagnostic compound is selected from the group consisting of anti-bacterial substances, anti-histamines and decongestants, anti-inflammatorics, miotics and anti-cholinergics, mydriatics, anti-glaucoma compounds, anti-parasitics, anti-viral compounds, carbonic anhydrase inhibitors, diagnostic agents, ophthalmic agents, chelating agents, immunosuppressive agents, anti-metabolites, anesthetics, anti-fungal compounds, amoebacidal compounds, trichomonacidal agents, analgesics, anti-arthritics, anti-asthmatics, anti-coagulants, anti-convulsants, anti-depressants, anti-diabetics, anti-neoplastics, anti-psychotics, anti-hypertensive agents, muscle relaxants, proteins, peptides and lubricating agents.

19. An aqueous pharmaceutical composition comprising:

approximately 0.1% to 30% by weight thermally-sensitive gelling polymer; and

approximately 0.01% to 10% by weight pH-sensitive gelling polymer.

20. The pharmaceutical composition of claim 19 further comprising a viscosity modifying effective concentration of salt in a salt-to-polymer ratio of 0.045 to 0.075.

21. The pharmaceutical composition of claim 19 wherein said thermally-sensitive gelling polymer is methylcellulose and said pH-sensitive gelling polymer is polyacrylate.

22. An ophthalmic drug delivery system comprising the aqueous composition of claim 19 and an effective concentration of an ophthalmic drug.

23. The ophthalmic drug delivery system of claim 22 wherein said ophthalmic drug is incorporated in a microparticulate drug delivery system.

24. The ophthalmic drug delivery system of claim 22 wherein said ophthalmic drug is selected from the group consisting of anti-bacterial substances, anti-histamines and decongestants, anti-inflammatorics, miotics and anti-cholinergics, mydriatics, anti-glaucoma compounds, anti-parasitics, anti-viral compounds, carbonic anhydrase inhibitors, diagnostic agents, ophthalmic agents, chelating agents, immunosuppressive agents, anti-metabolites, anesthetics, anti-fungal compounds, amoebacidal compounds, trichomonacidal agents, analgesics, anti-arthritics, anti-asthmatics, anti-coagulants, anti-convulsants, anti-depressants, anti-diabetics, anti-neoplastics, anti-psychotics, anti-hypertensive agents, muscle relaxants, proteins, peptides, and lubricating agents.

25. An aqueous injectable drug delivery composition for injection into a body to treat a condition requiring pharmacological treatment or diagnosis comprising the composition of claim 19 and an effective concentration of a drug selected from the group consisting of anti-bacterial substances, anti-histamines and decongestants, anti-inflammatorics, miotics and anti-cholinergics, mydriatics, anti-glaucoma compounds, anti-parasitics, anti-viral compounds, carbonic anhydrase

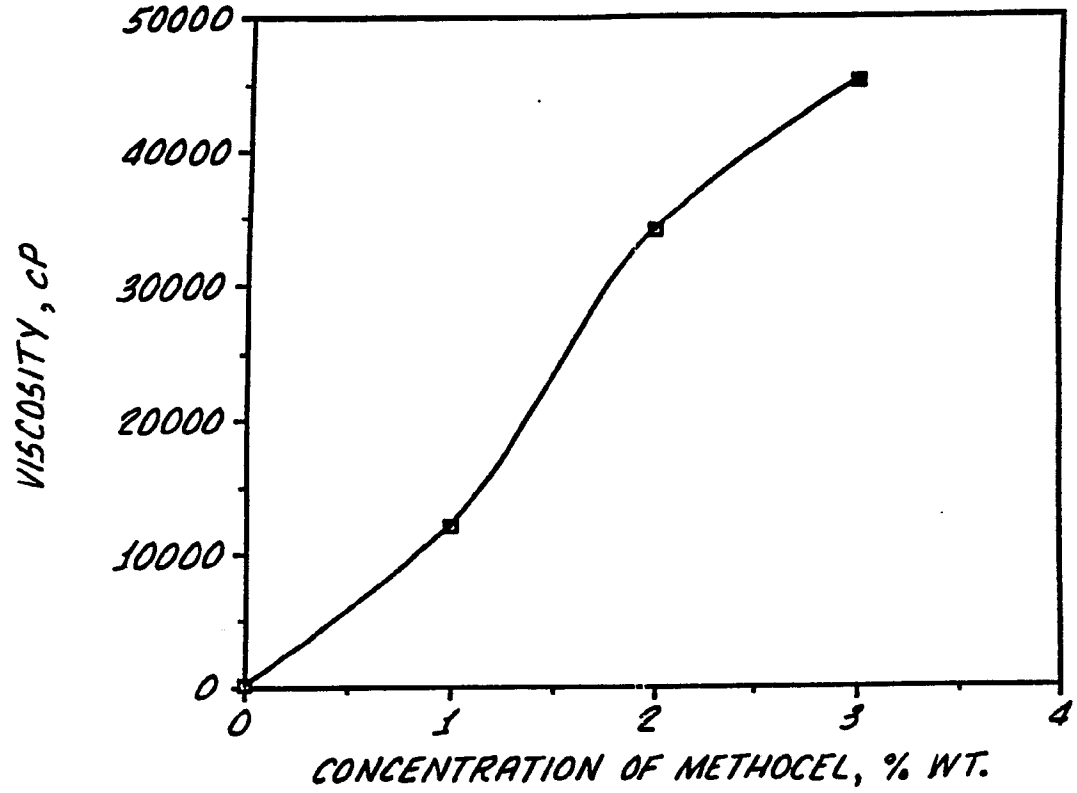
inhibitors, diagnostic agents, ophthalmic agents, chelating agents, immunosuppressive agents, anti-metabolites, anesthetics, anti-fungal compounds, amoebacidal compounds, trichomonacidal agents, analgesics, anti-arthritics, anti-asthmatics, anti-coagulants, anti-convulsants, anti-depressants, anti-diabetics, anti-neoplastics, anti-psychotics, anti-hypertensive agents, muscle relaxants, proteins, peptides and lubricating agents.

26. A method for delivering a pharmaceutical compound over an extended period of time to the surface of an eye needing treatment, said method comprising the steps of:

preparing an aqueous composition of an effective amount of a pharmaceutical compound and a reversible viscosity modifying effective concentration of a stable combination of at least one thermally-sensitive gelling polymer and at least one pH-sensitive gelling polymer; and

introducing said composition into the lacrimal secretions of the eye.

FIG. 1.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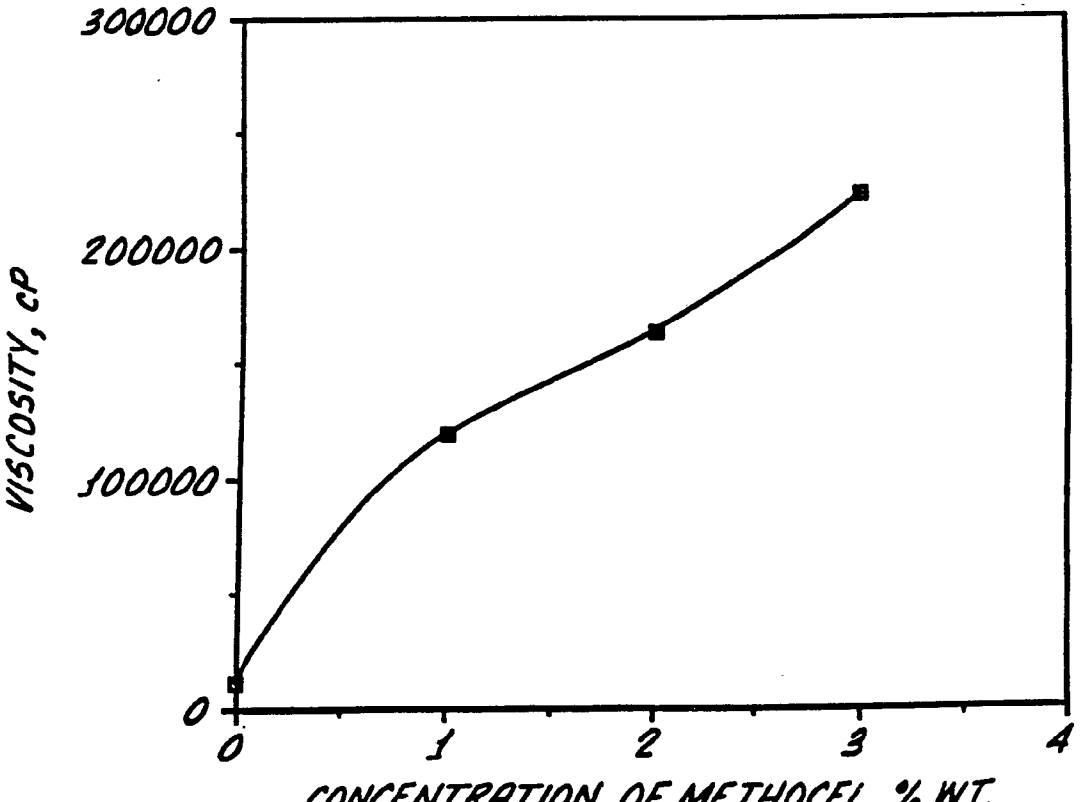
CONCENTRATION OF METHOCEL, % WT.

FIG. 2.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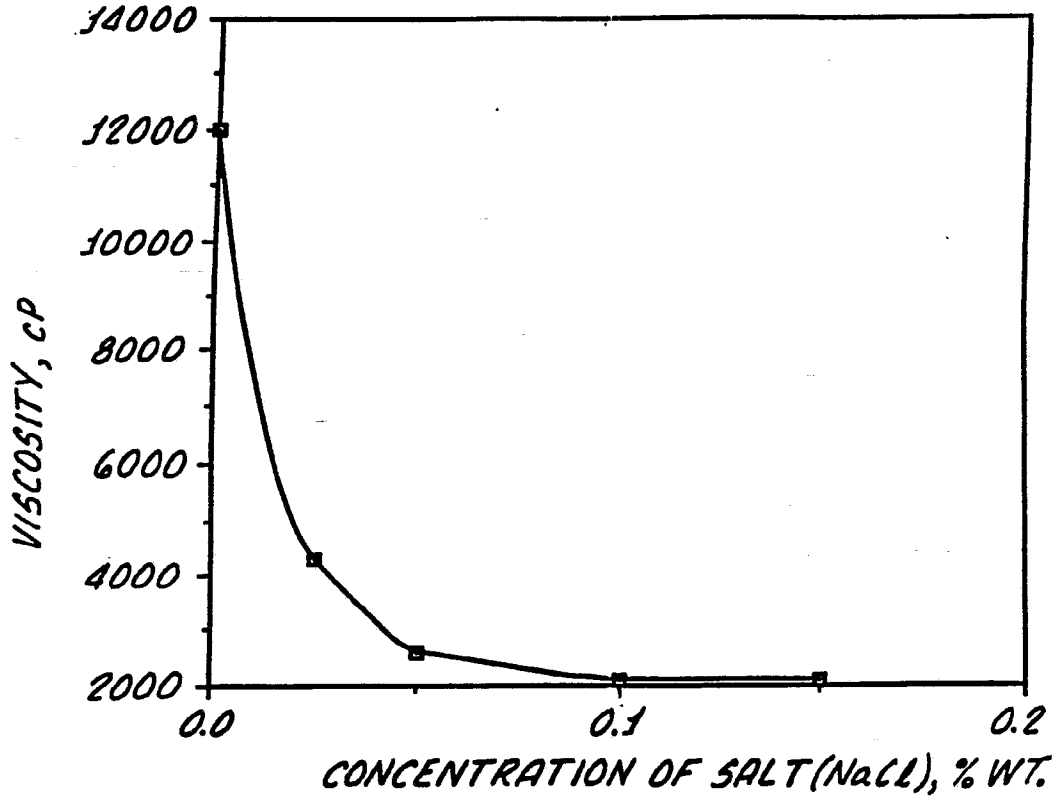
CONCENTRATION OF METHOCEL, % WT.

FIG. 3.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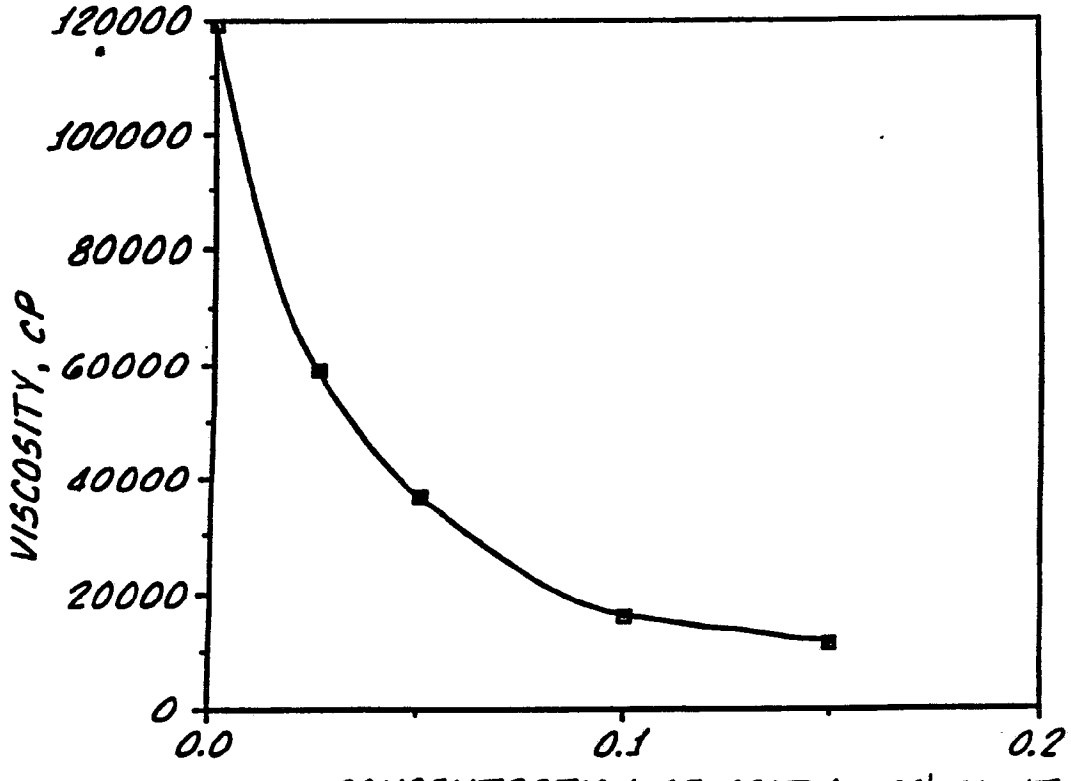
CONCENTRATION OF SALT (NaCl), % WT.

FIG. 4.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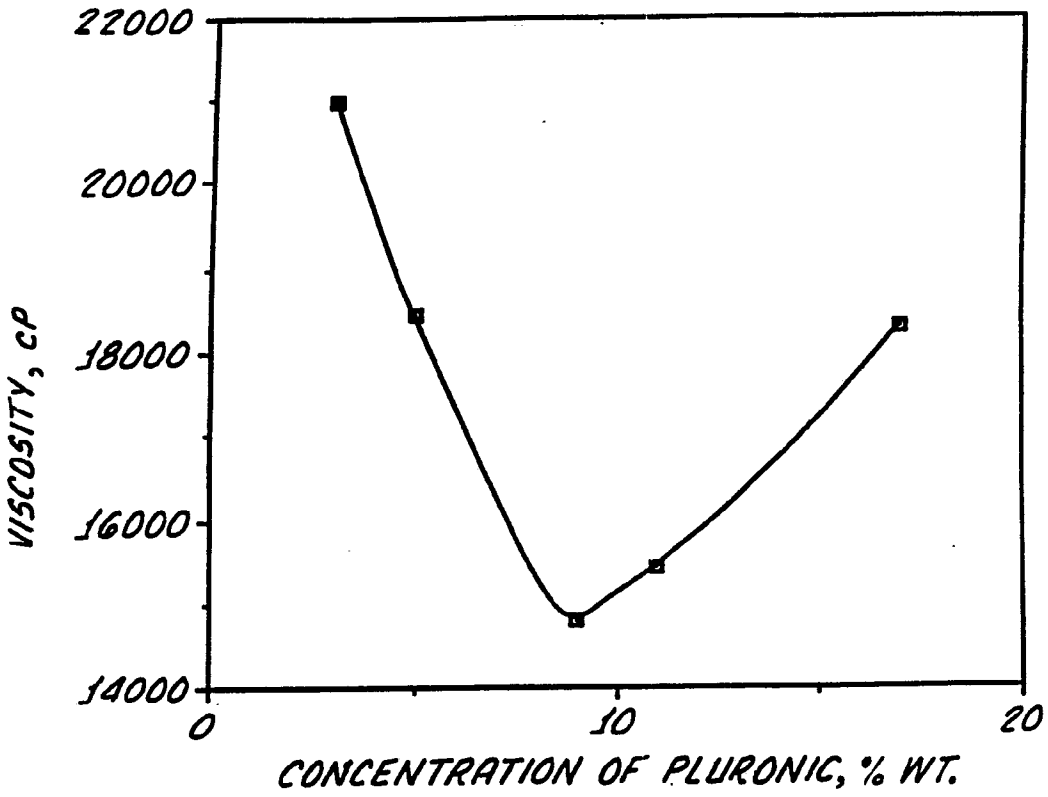
CONCENTRATION OF SALT (NaCl), % WT.

FIG. 5.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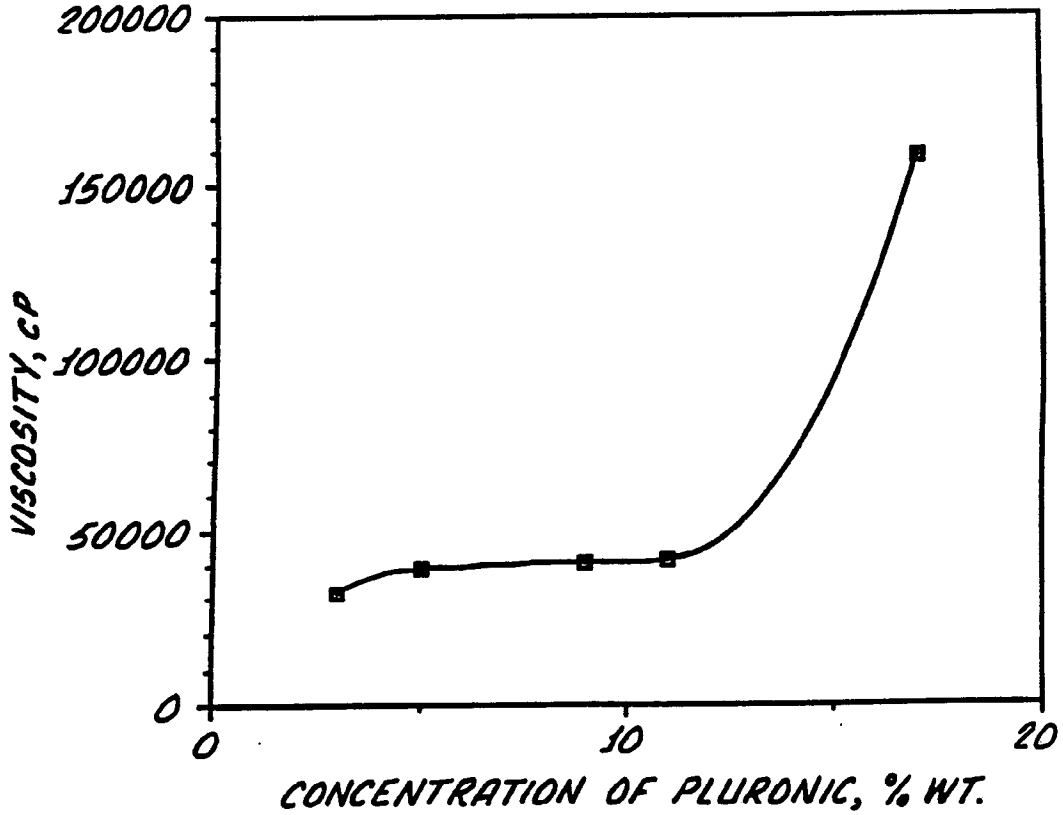
CONCENTRATION OF PLURONIC, % WT.

FIG. 6.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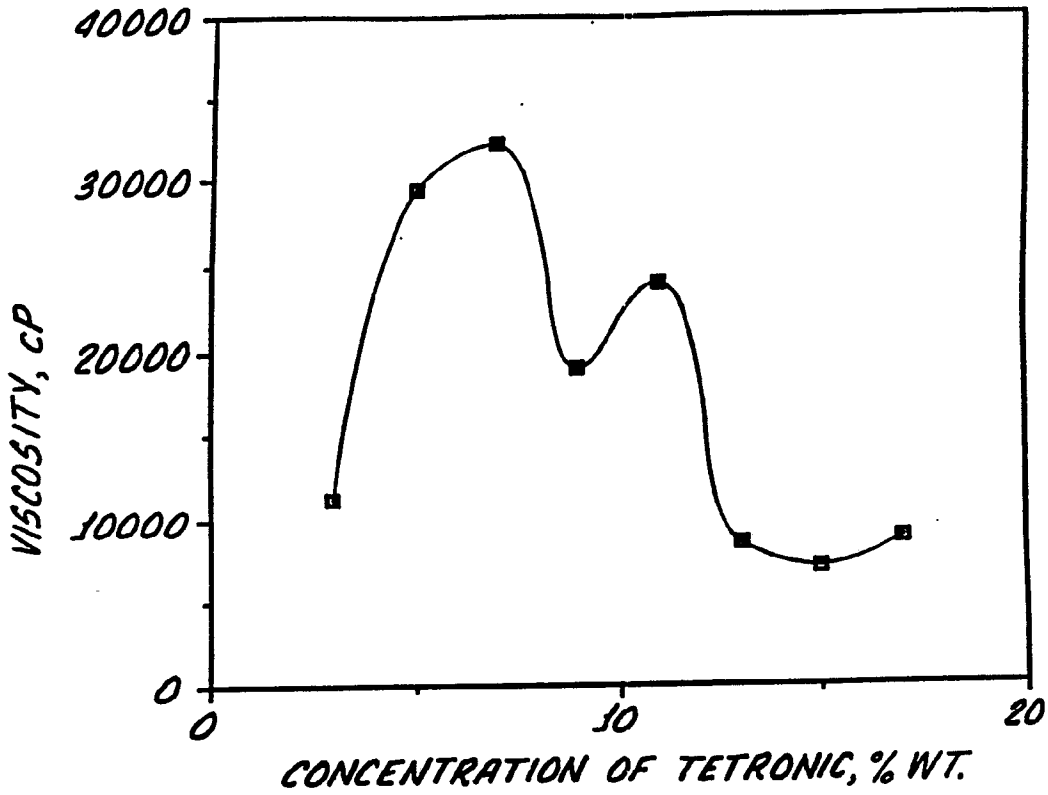
CONCENTRATION OF PLURONIC, % WT.

FIG. 7.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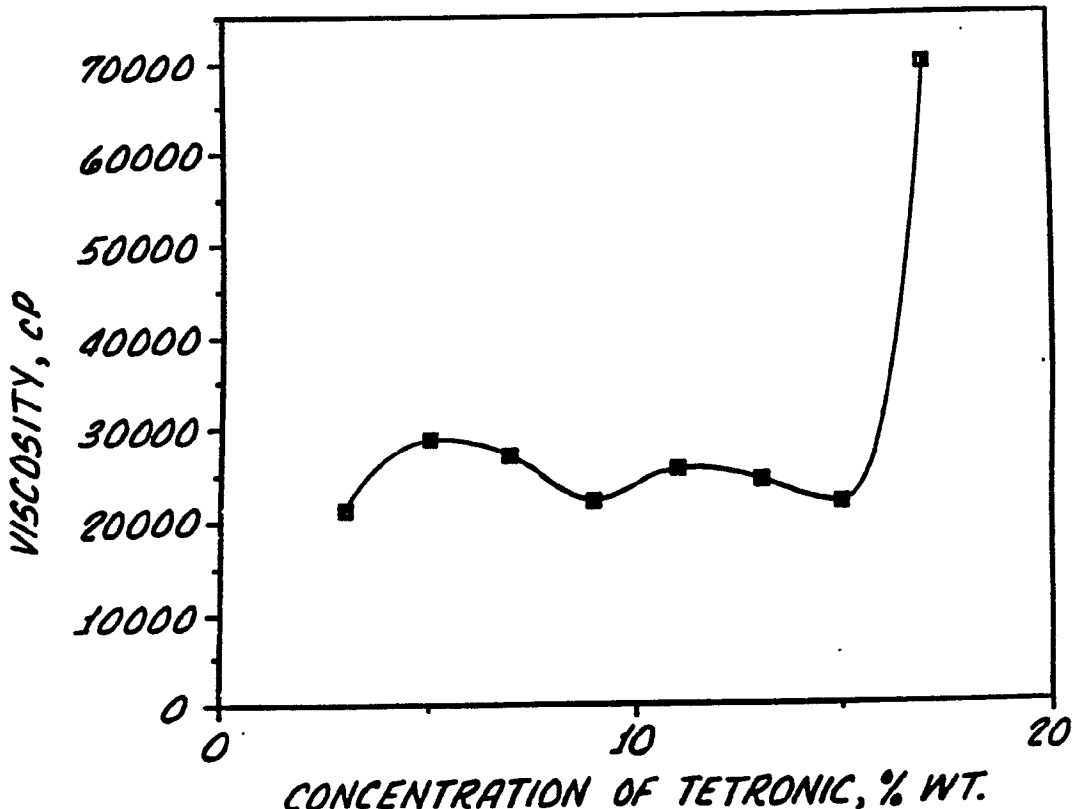
CONCENTRATION OF TETRONIC, % WT.

FIG. 8.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VISCOSITY, cP
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CONCENTRATION OF TETRONIC, % WT.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/04104

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

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II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X Y	US, A, 4,692,454 (MICH ET AL) 08 SEPTEMBER 1987; See entire document.	1-8,16,19,22 1-24

* Special categories of cited documents: [15]

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
13 AUGUST 1991	10 OCT 1991
International Searching Authority [1]	**Signature of Authorized Officer** [20]
ISA/US	Carlos Azpuru

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(54) Title: SUSTAINED RELEASE MATRIX COMPOSITION

(57) Abstract

Sustained release microparticule compositions including a core element comprising an active ingredient of very low solubility and at least two polymers. The core element is optionally coated with an enteric coating and includes dihydropyridines, especially nifedipine as the active ingredient. The compositions are prepared by spraying a core seed with the core element formulation in a fluidised bed coater, centrifugal granulator or spheronizer and drying the composition. The compositions are useful for treating cardiovascular related conditions.

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SUSTAINED RELEASE MATRIX COMPOSITION

The present invention relates to sustained release pharmaceutical microparticle compositions in particular sustained release pharmaceutical microparticle compositions including an active ingredient of very low solubility in water, and to a method of preparing same.

As is known in the prior art it is desirable in the treatment of a number of diseases both therapeutically and prophylactically to provide the active pharmaceutical ingredient in a sustained release form. This is particularly desirable for the treatment of diseases which have to be treated for prolonged periods such as, for example, hypertension. In these instances it is desirable to minimize the frequency of intake of medicaments. This is not only more pleasant for the patient it also increases the reliability of treatment by diminishing the disadvantages of irregular intakes and results in a more nearly constant therapeutic level of active ingredient in the body. Further this minimizes the risks of the active blood levels not being within the required therapeutic indices and avoids blood level peaks usually found after intake of rapid release forms.

Whilst there is known in the prior art numerous sustained release formulations the extension of such sustained release regimen to active pharmaceutical ingredients of very low solubility in water has been extremely limited.

For example, active ingredients of very low solubility include the dihydropyridine compounds which are used as cardiovascular agents. Difficulties often occur in the pharmaceutical formulation of these potent active compounds due to their very low solubility, which can result in erratic and/or poor absorption of the drug from pharmaceutical dosage forms.

One such technique of enhancing drug absorption is to formulate a solid dispersion or co-precipitate system. This technique is well known and is extensively discussed in the article "Pharmaceutical Applications of Solid Dispersion Systems" by Win Loung Chiou and Sidney

Riegelman. J. of Pharm. Sci. Vol. 60, No. 9, September 1971 (1281-1301) which is incorporated herein by reference.

The term Solid Dispersion or Co-Precipitate refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method and is hereinafter simply referred to as a "matrix". Solid dispersions may also be called solid-state dispersions. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this definition.

Whilst numerous attempts have been made to prepare sustained release forms of pharmaceutical formulations including dihydropyridine compounds as the active ingredient, it has not been possible to date to formulate a matrix composition in microparticle form which in use will release such active ingredients at a sufficient rate to provide a therapeutic level of active for extended periods of time, preferably for at least approximately 12 hours or more, preferably 24 hours or more.

Accordingly it is an object of the present invention to overcome, or at least alleviate, one or more of the difficulties related to the prior art.

Accordingly in a first aspect of the present invention there is provided a sustained release matrix pharmaceutical microparticle composition including

a core element including

an active ingredient of very low solubility; and

at least two polymers in a matrix therewith; and optionally

an enteric coating over the core element.

By the term "matrix" as used herein we mean that the active ingredient is in a solid dispersion or co-precipiate with a polymer.

By the term "microparticle composition" as used herein we mean pellets or granules. Preferably the microparticle composition is in the form of pellets.

By "sustained release" as used herein we mean at

least a two fold reduction in dosing frequency as compared to drug presented as a conventional dosage form (e.g. as a solution or a prompt drug-releasing, conventional dosage form). [U.S. Pharmacopeia [USPXXI](1985)(xivi)]. e.g. for at least approximately 12 hours or greater, preferably for at least approximately 24 hours.

By "active ingredient of very low solubility" as used herein we mean pharmaceutically active, orally acceptable ingredients having an aqueous solubility of approximately 1 in 10^3 parts of solvent per part of solute or less, preferably at least approximately 1 in 10^4 parts of solvent per part of solute or less.

By "bioavailability" as used herein we mean the extent to which the active drug ingredient is absorbed from the microparticle composition and which reaches the general circulation intact.

The active ingredient of very low solubility may be selected from the group consisting of dihydropyridines for example Nifedipine, Nitrendipine, Nisoldipine, Nimodipine, Nicardipine, Darodipine, Isradipine, Niludipine, Amlodipine, Felodipine, Lacidipine, BBR-2160, Cronidipine, Diperdine, Mepirodipine, Nilvadipine, Oxodipine, Sangandipine, Clinidipine, Manidipine, Benidipine, pharmaceutically acceptable isomers and salts thereof and mixtures thereof. The active ingredient in the final composition is preferably in crystalline form.

The active ingredient may be present in the core element in any suitable effective amount. The amount of active ingredient is dependent on the potency of the active ingredient and on the desired dosage strength and volume of a unit dose of the drug product. The active ingredient may be present in amounts of approximately 0.1 to 99%, preferably 1 to 95% by weight, based on the total weight of the core element. The active ingredient may preferably be a dihydropyridine compound, more preferably nifedipine. The compound nifedipine may be present in amounts of approximately 5 to 70% by weight, preferably 15 to 50% by weight, based on the total weight of the core element.

In the following description the active ingredient

of very low solubility will be illustrated by reference to the dihydropyridine, nifedipine. However this is illustrative only and the invention is in no way restricted thereto. Nifedipine is a cardiovascular drug and is a potent relaxant of arterial smooth muscle. It dilates both the main coronary arteries and arterials both in normal and in ischaemic myocardioregions. Nifedipine is also a potent inhibitor of coronary artery spasm. Nifedipine is thus indicated in the long-term management of angina pectoris due to coronary heart disease. The usual dose is one 10 mg capsule three times daily but up to two capsules four times daily may be taken. The benefits of a sustained release microparticle composition including nifedipine are thus obvious.

The polymeric component of the sustained release matrix pharmaceutical composition may include, in addition to the active ingredient,

a polymer which is at least partially water-soluble (water-soluble polymer); and

a polymer which is substantially insoluble at acidic pH but at least partially soluble at a less acidic to basic pH (enteric polymer).

The water-soluble polymer may be selected from the group consisting of polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, polyvinyl alcohol and mixtures thereof. Polyethylene glycols or Macrogols of intermediate molecular weights (4000-12000) have been found to be suitable. The polyethylene glycol sold under the trade designation PEG 6000 has been found to be suitable.

The water-soluble polymer may be present in the core element in amounts of from approximately 10 to 80%, preferably 15 to 60% by weight, based on the total weight of the core element.

The enteric polymer, when present, may be selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methyl- cellulose phthalate (HPMCP), polyvinyl acetate phthalate, methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac,

cellulose acetate trimellitate and mixtures thereof. Particularly preferred enteric polymers include synthetic or semi-synthetic resins bearing carboxyl groups. The hydroxypropyl methylcellulose phthalates sold under the trade designations HP50 or HP55 have been found to be suitable.

The enteric polymer may be present in the core element in an amount of from 0 to approximately 50% by weight, preferably 0.1 to 20% by weight, more preferably 0.5 to 10% by weight, based on the total weight of the core element.

Accordingly, in a preferred aspect of the invention there is provided a sustained release pharmaceutical microparticle composition including

a core element including

approximately 1 to approximately 95% by weight based on the total weight of the core element of a pharmaceutically active ingredient of very low solubility; and

approximately 5 to approximately 99% by weight of a polymeric component in a matrix therewith including

a water-soluble polymer; and

an enteric polymer;

and optionally

an enteric coating over the core element.

The core element may further include other compounding ingredients including plasticisers and fillers. Accordingly, in a preferred aspect, the core element may further include

0 to approximately 20% by weight, preferably 5 to 10% by weight, based on the total weight of the core element of a plasticiser selected from the group consisting of diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, glycerol or mixtures thereof; optionally

0 to approximately 50% by weight, preferably 5 to 30% by weight, based on the total weight of the core element of a filler selected from the group consisting of

insoluble materials such as silicon dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrilin potassium, powdered cellulose, and microcrystalline cellulose and mixtures thereof; and optionally

0 to approximately 50% by weight, preferably 5 to 10% by weight, of a water-insoluble polymer selected from any suitable pharmaceutically acceptable polymer substantially insoluble independent of pH. The polymer may be selected from the group consisting of ethylcellulose, acrylic and/or methacrylic ester polymers or mixtures thereof and the like may be used. Polymers or copolymers of acrylates or methacrylates having a low quaternary ammonium content may be used. The acrylic acid ethyl ester: methacrylic acid ester (1:1) copolymer has been found to be suitable.

In a still further preferred aspect the core element may further include 0 to approximately 20% by weight, preferably 1 to 10% by weight of at least one surfactant selected from docusate sodium lecithin, polyoxethylene, sorbitan fatty acids (e.g. tweens) and sorbitan esters (e.g. spans). The surfactant sold under the trade designation Cremaphore RH410 has been found to be suitable.

In a preferred aspect of the present invention the core element of the pharmaceutical microparticle composition according to the present invention may include a core seed.

The size and amount of the core seed may vary substantially from approximately 100μm to 1700μm depending upon the amount of active ingredient to be included. Accordingly, the core seeds may vary from approximately 5 to 99% by weight, preferably 10 to 70% by weight based on the total weight of the core element, depending on the potency of the active ingredient. The core seed may be of such a diameter to provide a final core element having a diameter of approximately 200 to 2000μm.

The core seed may be of any suitable type. A sugar sphere or an active core seed may be used. The core element may further include other carriers or excipients,

stabilizing agents and colorants.

Where the matrix pharmaceutical microparticle composition includes an enteric coating on the core element, the enteric coating may be formed from an enteric polymer as described above. A hydroxypropyl methyl cellulose phthalate coating such as that sold under the trade designation HP50 or HP55 has been found to be suitable.

The enteric coating may further include a plasticiser.

Accordingly in a preferred aspect the enteric coating may include

approximately 40 to 100% by weight, preferably 70 to 95% by weight, based on the total weight of the enteric coating, of at least one enteric polymer,

0 to approximately 30% by weight, preferably 5 to 10% by weight, based on the total weight of the enteric coating of at least one plasticiser selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, dibutyl sebacate and glycerol.

The enteric coating may comprise from approximately 2 to 20% by weight, preferably approximately 4 to 10% by weight, of the pharmaceutical microcapsule composition.

In a preferred form the pharmaceutical microparticle composition may have the following formulation

Percentage ranges for the components of the pharmaceutical microparticle composition (percentages W/W):

	Preferred Range % w/w	More Preferred Range % w/w
Active Ingredient	(5-70)	(10-40)
Water Soluble Polymer	(10-80)	(15-60)
Core Seed	(10-80)	(15-60)
Enteric Polymer	(0.1-50)	(0.5-20)
Plasticiser	(0-10)	(0-1)

The core element may comprise a single or a

plurality of core layers.

In a preferred aspect of the invention, the core element comprises a single layer.

Accordingly in the preferred aspect of the invention there is provided a sustained release matrix pharmaceutical microparticle composition including

a core element comprising a single layer including

approximately 1 to approximately 95% by weight based on the core element of a pharmaceutically active ingredient of very low solubility; and

approximately 5 to approximately 99% by weight of a polymeric component in a matrix therewith including

at least one water-soluble polymer; and

at least one enteric polymer;

and optionally

an enteric coating over the core element.

In a further preferred form the pharmaceutical microparticle composition may have the following formulation:

Percentage ranges for the components of the pharmaceutical microparticle composition (percentages W/W):

	Preferred Range % w/w	More Preferred Range % w/w
Nifedipine	(5-70)	(10-40)
PEG 6000	(10-80)	(15-60)
Sugar spheres	(10-80)	(15-60)
HP 50	(0.1-50)	(0.5-20)
Diethylphthalate	(0-10)	(0-1)

In an alternative preferred aspect of the invention, the core element comprises a plurality of core layers.

Accordingly in an alternative preferred aspect of the invention there is provided a sustained release pharmaceutical microparticle composition including

a core element including a plurality of core layers, wherein the core element includes

approximately 1 to approximately 95% by weight based on the total weight of the core element of a pharmaceutically active ingredient of very low solublity; and

approximately 5 to approximately 99% by weight based on the total weight of the core element of a polymeric component in a matrix therewith,

wherein at least one core layer includes

a water-soluble polymer: and

an enteric polymer in a matrix therewith; and optionally

an enteric coating over the core element.

Preferably where the core element comprises a plurality of core layers, the outer core layer of the core element comprises the two polymers in matrix therewith.

The pharmaceutically active ingredient may be present in the outer core layer in any suitable effective amount. The amount of active ingredient is dependent on the potency of the active ingredient and on the desired dosage strength and volume of a unit dose of the drug product. The active ingredient may be present in amounts of approximately 0.1 to 95% by weight, based on the total weight of the outer core layer. The active ingredient may preferably be a dihydropyridine compound. The compound may be present in amounts of approximately 5 to 70% by weight, preferably 10 to 60% by weight, based on the total weight of the outer core layer.

The water-soluble polymer may be selected from the list of polymers as previously described. The polyethylene glycol sold under the trade designation PEG 6000 has been found to be suitable.

The water-soluble polymer may be present in the outer core layer in amounts of from approximately 10 to 80%, preferably 15 to 60% by weight, more preferably 30 to 50% by weight, based on the total weight of the outer core layer.

The enteric polymer may be selected from the list of polymers previously described. The hydroxypropyl methyl cellulose phthalates sold under the trade designation HP50 or HP55 have been found to be suitable.

The enteric polymer may be present in the outer core layer in an amount of up to approximately 50% by weight, preferably 1 to 20% by weight, more preferably 2 to 15% by weight, based on the total weight of the outer core layer.

Accordingly, in a preferred aspect of the present invention there is provided a sustained release matrix pharmaceutical microparticle composition including a core element including

approximately 1 to 95% by weight based on the total weight of the core element of a dihydropyridine compound;

a core seed;

approximately 20 to 90% by weight based on the total weight of the inner core layer of a water-soluble polymer in a matrix therewith; and

approximately 30 to 80% by weight based on the total weight of the outer core layer, of a water-soluble polymer; and

approximately 2 to 20% by weight based on the total weight of the outer core layer, of an enteric polymer in a matrix therewith,

and optionally an enteric coating over the core element.

As described above the pharmaceutical microparticle composition may include a plurality of core layers. The composition of the core layers may differ in the concentration or nature of the active ingredients therein. For example use of active ingredients of differing crystal size in adjacent layers is preferred. This may extend the period of sustained release even further.

The inner layer and outer core layer of the core element may be present in any suitable amounts in the pharmaceutical microparticle composition. The inner core layer (including sugar seeds where present) may comprise from approximately 40 to 95% by weight, preferably 50 to

85% by weight, of the pharmaceutical microparticle composition. The outer core layer may comprise from approximately 5 to 60% by weight, preferably 15 to 50% by weight, of the pharmaceutical microparticle composition.

Accordingly, the pharmaceutical matrix microcapsule composition may have the following formula:

	CORE ELEMENT			CORE COATING	
	Core Seed	Inner Core Layer	Outer Core Layer	Enteric Layer	Final Comp. %
Nifedipine		50 g	50 g		20.5
PEG 6000		100 g	50 g		30.7
Sugar spheres	200 g				40.6
HP50 (Hydroxypropyl-methylcellulose-phthalate)			10 g	32 g	8.5
Diethyl phthalate				3.5 g	0.6

The components of the core element other than the core seed, when present, may be provided in the form of a solution, dispersion or suspension.

In the form of a solution, the solvent or solvents may be present in amounts of from approximately 25 to 97% by weight, preferably 85 to 97% by weight, based on the total weight of the core formulation. The solvent for the core formulation may be a solvent such as methanol, ethanol, methylene chloride, acetone, isopropanol and mixtures thereof. Methanol, methylene chloride or a mixture thereof is preferred.

In a further aspect of the present invention, there is provided a method for preparing a sustained release pharmaceutical microparticle composition providing

a core seed;

a core formulation including

an active ingredient of very low solubility;

at least two polymers capable of forming a

matrix with the active ingredient; and

a solvent therefor;

introducing the core seed into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying the core formulation onto the core seed to form a matrix core element; and

drying the core element.

The core seed may include a sugar sphere. The active ingredient may be a dihydropyridine compound, preferably nifedipine.

Where a plurality of core layers are to be used the method may further include

providing

a core layer formulation including

at least one active ingredient of very low solubility;

at least two polymers including a water-soluble polymer; and optionally

an enteric polymer; and

a solvent therefor;

introducing the core seed into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying successive layers onto the core seed to form the matrix core element wherein at least one layer includes the core layer formulation.

Where an enteric coating is to be used, the method may further include

providing

a sustained release pharmaceutical microparticle; and

an enteric coating formulation including

an enteric polymer; optionally

a plasticiser; and

a solvent therefor

introducing the microparticle into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying the enteric coating formulation onto the microparticle to form a sustained release microcapsule.

The sustained release core element and sustained

release microcapsules may be subjected to a drying step. The drying step may be conducted in a fluidised bed or drying oven.

Spray coating of core elements may be undertaken utilizing bottom or Wurster, top or tangentially located spray nozzles. A bottom spray nozzle may reside proximate to the base of the fluidised bed facing upwards while a top spraying nozzle is located above the contents of the bed and facing downwards. The spray nozzle may reside in the mid-section of the fluidised bed and be oriented such as to spray tangentially to the rotating core elements.

The sustained release matrix pharmaceutical microparticle composition according to the present invention may include a plurality of microparticles.

The sustained release pharmaceutical composition may be provided in any suitable unit dosage form. An encapsulated form may be used. The pharmaceutical microparticle composition may be provided in a pellet or tabletted pellet form. A tablet may be formed by compression of the pellets optionally with the addition of suitable excipients.

The sustained release pharmaceutical microparticle composition may be in multi-pellet encapsulated, sprinkle, sachet or tabletted forms.

The sustained release pharmaceutical microparticle composition may be administered under a similar dosage regimen to that used in the prior art. However, it is preferred that the pellet composition be administered less frequently. The multi-pellet encapsulated form may for example be administered once every 12 hours, preferably once every 24 hours.

In a preferred aspect of the present invention the sustained release pharmaceutical pellet composition incorporating the dihydropyridine compound may provide effective vasodilation with once daily administration. Versatility of dosing may be achieved with 20 to 90 mg or any other dose strength of capsules required.

In accordance with a further aspect of the present invention, there is provided a method of treating

cardiovascular related conditions in patients requiring such treatment which method includes administering to a patient an effective amount of a sustained release pharmaceutical microparticle composition including

a core element including a dihydropyridine; and

at least two polymers in a matrix therewith; and optionally

an enteric coating over the core element.

The method of treatment according to this aspect of the present invention is particularly applicable to the treatment of Hypertension and/or Angina pectoris due to coronary heart disease, particularly Angina pectoris related to coronary artery spasm, utilising for example nifedipine.

Preferably the sustained release pharmaceutical microparticle composition is provided in a unit dosage form and administration occurs at intervals of approximately 12 to 24 hours.

The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however, that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention specified above.

EXAMPLES

A. SINGLE LAYERED OR "ONE STEP" CORES

EXAMPLE 1 (1/1.5/0.1)*

Formulation		(g)
Sugar spheres	30/35 mesh	200
Nifedipine		100
PEG 6000		150
HP 50		10
Methanol **		540
Methylene Chloride **		540

Finished cores are between 710 - 1000 µm with potency of 22%, yield 460 g.

EXAMPLE 2 (1/1.5/0.3)*

Formulation		(g)
Sugar spheres	30/35 mesh	600
Nifedipine		143
PEG 6000		214.5
HP 50		42.9
Methanol **		1158.3
Methylene Chloride **		1158.3

Finished cores are between 600 - 850 µm with potency of 14%, yield 1000 g.

EXAMPLE 3 (1/1.3/0.2)*

Formulation		(g)
Sugar spheres	30/35 mesh	600
Nifedipine		133.3
PEG 6000		173.3
HP 50		26.7
Methanol **		900
Methylene Chloride **		900

Finished cores are between 600 - 850 µm with potency of 14%, yield 933 g.

Examples 1 to 3 illustrate how the ratio of polymers may be varied to the desired release profile.

EXAMPLE 4 (1/1/0.2)*

Formulation		(g)
Sugar spheres	30/35 mesh	200
Nifedipine		100
PEG 6000		100
PVAP		20
Methanol **		500
Methylene Chloride **		500

Finished cores are between 600 - 850 µm with potency of 24%, yield 420 g.

Example 4 uses a different enteric polymer to Examples 1 to 3.

EXAMPLE 5 (1/1/0.2)*

Formulation		(g)
Sugar spheres	35/45 mesh	600
Nifedipine		208
PEG 6000		208
HP 50		41.6
Methanol **		1123
Methylene Chloride **		1123

Finished cores are between 500 - 710 µm with potency of 19%, yield 1057 g.

Notes: * Defines Nifedipine/Water Soluble Polymer/Enteric Polymer Ratio

** Not present in final formulation.

PROCESS FOR EXAMPLES 1 TO 4 (CORE MANUFACTURE)

To a Fuji Paudal Q400 spheroniser for Examples 1 and 4 or Glatt WSG1 for Examples 2, 3 and 5 the sugar spheres are charged. A dissolved solution containing nifedipine PEG 6000 and HP50 (or PVAP, for Example 4) in a mixture of methanol/methylene chloride (50/50) was applied as atomised droplets onto the sugar spheres. The finished cores are dried for 15 minutes at 40°C.

B. DOUBLE LAYERED or "TWO STEP" SUSTAINED RELEASE CORE

EXAMPLE 6

	CORE ELEMENT		
	Sugar Seed	Inner Core Layer	Outer Core Layer
Nifedipine		50g	50g
PEG 6000		100g	50g
Sugar spheres 30/35	200g		
HP50			10 g
Methylene Chloride**		250	300
Methanol**		250	300

Finished cores are between 710 - 1000 µm with potency of 22% and yield of 460 g.

EXAMPLE 7

	CORE ELEMENT		
	Sugar Seed	Inner Core Layer	Outer Core Layer
Nifedipine		200g	125g
PEG 6000		400g	125g
Sugar Spheres 35/45	300g	-	-
HP 50		-	25g
Methanol **		1000g	675g
Methylene Chloride **		1000g	675g

Finished cores are between 600-850µm with potency of 28% and yield of 1075g.

PROCESS FOR EXAMPLE 6 AND 7 (CORE MANUFACTURE)

To a Fuji Paudal Q400 spheroniser the sugar spheres are charged. A dissolved solution containing the nifedipine, PEG 6000 and mixture of methanol/methylene chloride (50/50) was applied as atomised droplets onto the sugar spheres. The finished inner cores are dried at 40°C for 15 minutes. This batch is returned to commence the second stage or second layer. To this charge a dissolved

solution containing the nifedipine, PEG 6000 and HP50 in the methanol/methylene chloride mixture was supplied as atomised droplets onto the inner cores. The finished cores are dried at 40°C for 15 minutes.

ENTERIC COATING OF CORES

The cores produced from Example 6 was enteric coated using the following process.

To the Glatt WSG/1, 1.6 kg of cores were charged. A dissolved solution containing 117.6 g HP50, 13g of diethyl phthalate in 1.96 kg of ethanol/water mixture was applied as atomised droplets to the fluidising cores. On completion of the spray, the pellets were dried for 50 minutes at an inlet air temperature of 41°C. The weight gain was recorded as 5.8% w/w.

IN-VITRO TESTING

In vitro dissolution profiles were generated at pH 6.8 for Examples 1 to 7 above utilising the following test method dissolution.

Each formulation included 60 mg equivalent to nifedipine and was dissolved in 900 mL at pH of 6.8 with surfactant and an orthophosphate buffer. The apparatus used is baskets. Sampling is carried out using a 0.45 µm filter and samples were determined using a UV spectrophotometer at a wavelength of 340 nm.

The results are provided in Figures 1 to 7.

IN VIVO TESTING

Mean nifedipine concentrations were generated in vivo utilising Example 6 above. These were compared with comparison formulations A and B (see below).

A three way single dose cross over pilot study was performed to assess the bioequivalence of the nifedipine formulations, including batches of Example 6, comparison A and comparison B (reference). Eighteen healthy male subjects received a single 60 mg dose of a formulation after an overnight fast. At the end of the study, each subject had received two formulations (out of a possible 4) and the reference formulation (B). Plasma samples from all subjects were analysed for nifedipine using a validated chromatographic procedure.

Comparison A is not in accordance with the invention and comprises an uncoated core where micronised nifedipine is layered onto sugar spheres.

The formulation comprises

COMPARISON A	W/W%
Nifedipine	31.85
Hydroxypropyl Cellulose	4.14
Polyoxyethylene 20 sorbitan	0.32
Sugar spheres 20/25 mesh	63.69

It does not contain a matrix composition, and as can be evidenced by the high initial plasma peak, does not produce a suitable sustained release profile.

Comparison B is the existing commercially available sustained release product Procardia XL, 60 mg extended release tablets by Pfizer.

The results are provided in Figure 8.

Finally, it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

Claims

1. A sustained release pharmaceutical microparticle composition including

a core element including

an active ingredient of very low solubility; and

at least two polymers in a matrix therewith; and optionally

an enteric coating over the core element.

2. A microparticle composition according to claim 1, wherein the polymer components include

a polymer which is at least partially water-soluble (water-soluble polymer); and

a polymer which is substantially insoluble at acidic pH but at least partially soluble at a less acidic to basic pH (enteric polymer).

3. A microparticle composition according to claim 2, wherein

the water-soluble polymer is selected from the group consisting of polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, polyvinyl alcohol and mixtures thereof; and

the enteric polymer is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate, methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and mixtures thereof.

4. A microparticle composition according to claim 3, wherein

the water-soluble polymer is present in an amount of from approximately 10 to 80% by weight, based on the total weight of the core element; and

the enteric polymer is present in amounts from 0.1% to approximately 50% by weight, based on the total weight of the core element.

5. A microparticle composition according to claim 1 wherein the active ingredient includes a dihydropyridine.

6. A microparticle composition according to claim 5

wherein the dihydropyridine is nifedipine.

7. A microparticle composition according to claim 1, further including

0 to approximately 50% by weight, based on the total weight of the core element of a plasticiser selected from the group consisting of diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, glycerol, dibutyl sebacate or mixtures thereof; optionally

0 to approximately 50% by weight, based on the total weight of the core element of a filler selected from the group consisting of insoluble materials such as silicon dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrilin potassium, powdered cellulose, and microcrystalline cellulose and mixtures thereof; and optionally

0 to approximately 50% by weight, of a water-insoluble polymer selected from the group consisting of ethyl cellulose, acrylic and/or methacrylic ester polymers or mixtures thereof.

8. A microparticle composition according to claim 7 further including approximately 1 to 10% by weight based on the total weight of the core element, of a surfactant.

9. A microparticle composition according to claim 1, wherein the core element includes a core seed.

10. A sustained release pharmaceutical microparticle composition including

a core element including

approximately 1 to approximately 95% by weight based on the total weight of the core element of a pharmaceutically active ingredient of very low solubility; and

approximately 5 to approximately 99% by weight of a polymeric component in a matrix therewith including

a water-soluble polymer; and

an enteric polymer;

and optionally

an enteric coating over the core element.

11. A sustained release pharmaceutical microparticle composition including

a core element including a plurality of core layers, wherein the core element includes

approximately 1 to approximate 95% by weight based on the total weight of the core element of a pharmaceutically active ingredient of very low solubility; and

approximately 5 to approximately 99% by weight based on the total weight of the core element of a polymeric component in a matrix therewith,

wherein at least one core layer includes

a water-soluble polymer: and

an enteric polymer in a matrix therewith;

and optionally

an enteric coating over the core element.

12. A sustained release matrix pharmaceutical microparticle composition including a core element including

approximately 1 to 95% by weight based on the total weight of the core element of a dihydropyridine compound;

a core seed;

approximately 20 to 90% by weight based on the total weight of the inner core layer of a water-soluble polymer in a matrix therewith; and

approximately 30 to 80% by weight based on the total weight of the outer core layer, of a water-soluble polymer; and

approximately 2 to 20% by weight based on the total weight of the outer core layer, of an enteric polymer in a matrix therewith,

and optionally an enteric coating over the core element.

13. A microcapsule composition including a microparticle composition according to claim 1, further including approximately 2 to 20% by weight of an enteric coating over the core element.

14. A microcapsule composition according to claim 13,

wherein the enteric coating includes

approximately 40 to 100% by weight, based on the total weight of the enteric coating, of at least one enteric polymer,

0 to approximately 30% by weight, based on the total weight of the enteric coating of at least one plasticiser selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, dibutyl sebacate and glycerol.

15. A method for preparing a sustained release pharmaceutical microparticle composition providing

a core seed;

a core formulation including

an active ingredient of very low solubility;

at least two polymers capable of forming a matrix with the active ingredient; and

a solvent therefor;

introducing the core seed into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying the core formulation onto the core seed to form a matrix core element; and

drying the core element.

16. A method according to claim 15, further including providing

a core layer formulation including

an active ingredient of very low solubility;

at least two polymers including a water-soluble polymer; and optionally

an enteric polymer; and

a solvent therefor;

introducing the core seed into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying successive layers onto the core seed to form the matrix core element wherein at least one layer includes the core formulation.

17. A method according to claim 16 wherein the core element includes

approximately 1 to approximate 95% by weight

based on the total weight of the core element of a pharmaceutically active ingredient of very low solubility; and

approximately 5 to approximately 99% by weight based on the total weight of the core element of a polymeric component in a matrix therewith,

wherein at least one core layer includes

a water-soluble polymer: and

an enteric polymer in a matrix therewith; and optionally

an enteric coating over the core element.

18. A method according to claim 15, further including providing

a sustained release pharmaceutical microparticle; and

an enteric coating formulation including

an enteric polymer; optionally

a plasticiser; and

a solvent therefor

introducing the microparticle into a fluidised bed coater, a centrifugal granulator or spheronizer; and

spraying the enteric coating formulation onto the microparticle and then spraying an enteric coating formulation onto the core element to form a sustained release coated pellet.

19. A method according to claim 15 wherein

the water-soluble polymer is selected from the group consisting of polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, polyvinyl alcohol and mixtures thereof; and

the enteric polymer is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate, methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and mixtures thereof.

20. A method according to claim 19 wherein

the water-soluble polymer is present in an amount

of from approximately 10 to 80% by weight, based on the total weight of the core element; and

the enteric polymer is present in amounts from 0.1% to approximately 50% by weight, based on the total weight of the core element.

21. A method according to claim 20 wherein the active ingredient includes a dihydropyridine.

22. A method according to claim 21 wherein the dihydropyridine is nifedipine.

23. A method of treating cardiovascular related conditions in patients requiring such treatment which method includes administering to a patient an effective amount of a sustained release pharmaceutical microparticle composition including

a core element including a dihydropyridine; and

at least two polymers in a matrix therewith; and optionally

an enteric coating over the core element.

24. A method according to claim 23 wherein the microparticle composition is administered at intervals of approximately 24 hours or more.

25. A method according to claim 23 wherein the dihydropyridine is nifedipine.

26. A method according to claim 23 wherein

the water-soluble polymer is selected from the group consisting of polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, polyvinyl alcohol and mixtures thereof; and

the enteric polymer is selected from the group consisting of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate, methacrylic acid copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and mixtures thereof.

27. A method according to claim 23 wherein

the water-soluble polymer is present in an amount of from approximately 10 to 80% by weight, based on the total weight of the core element; and

the enteric polymer is present in amounts from

0.1% to approximately 50% by weight, based on the total weight of the core element.

28. A method according to claim 23 wherein the microparticle composition includes

a core element including a plurality of core layers, wherein the core element includes

approximately 1 to approximate 95% by weight based on the total weight of the core element of a dihydropyridine; and

approximately 5 to approximately 99% by weight based on the total weight of the core element of a polymeric component in a matrix therewith,

wherein at least one core layer includes

a water-soluble polymer: and

an enteric polymer in a matrix therewith; and optionally

an enteric coating over the core element.

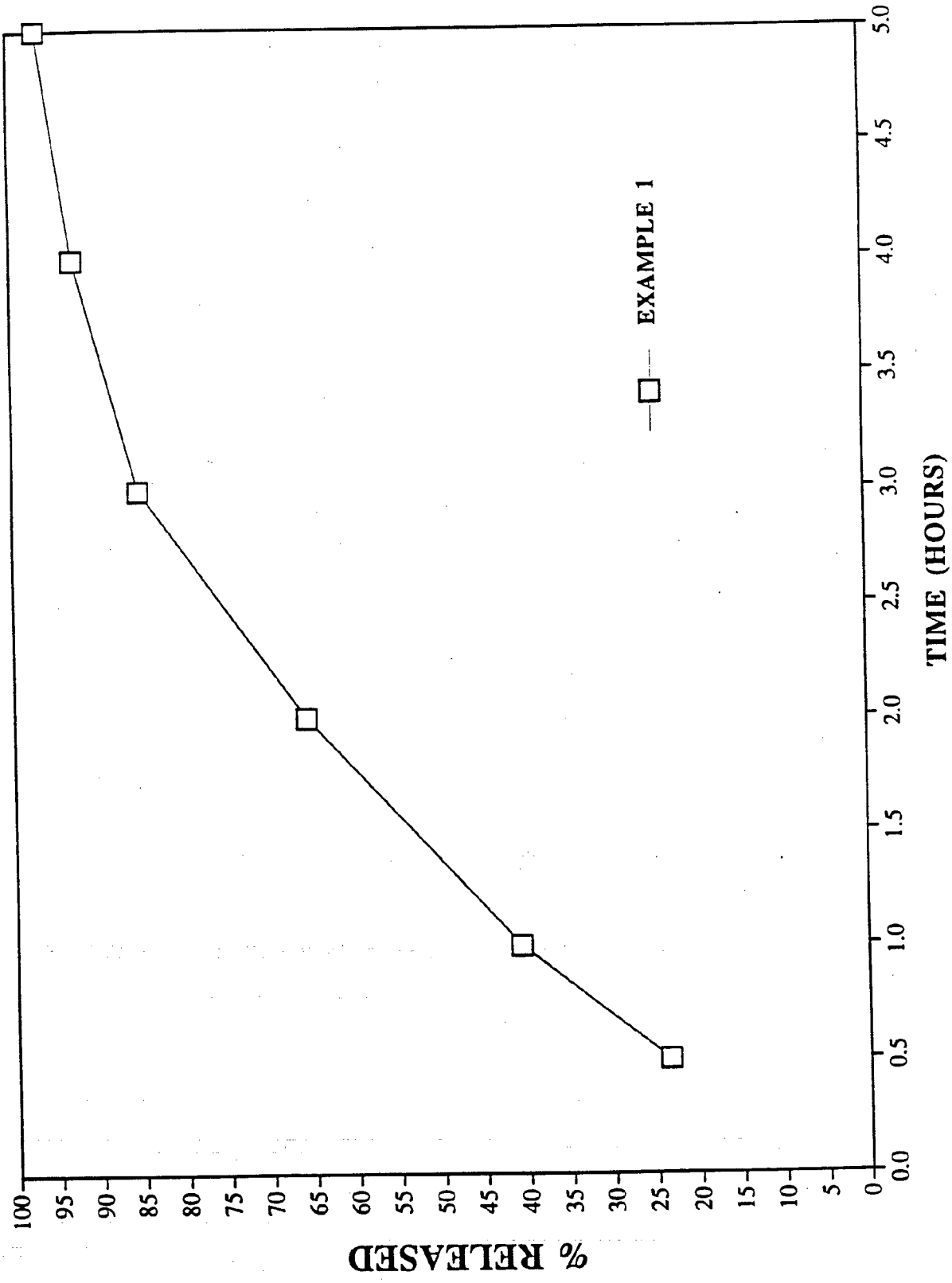
29. A method according to claim 28 wherein the dihydropyridine is nifedipine.

30. A microparticle composition according to claim 1, wherein the composition is in a unit dosage form.

31. A microparticle composition according to claim 30 wherein the composition is in a pellet or tabletted pellet form.

32. A microparticle composition according to claim 1 wherein the active ingredient is in a crystalline form.

Figure 1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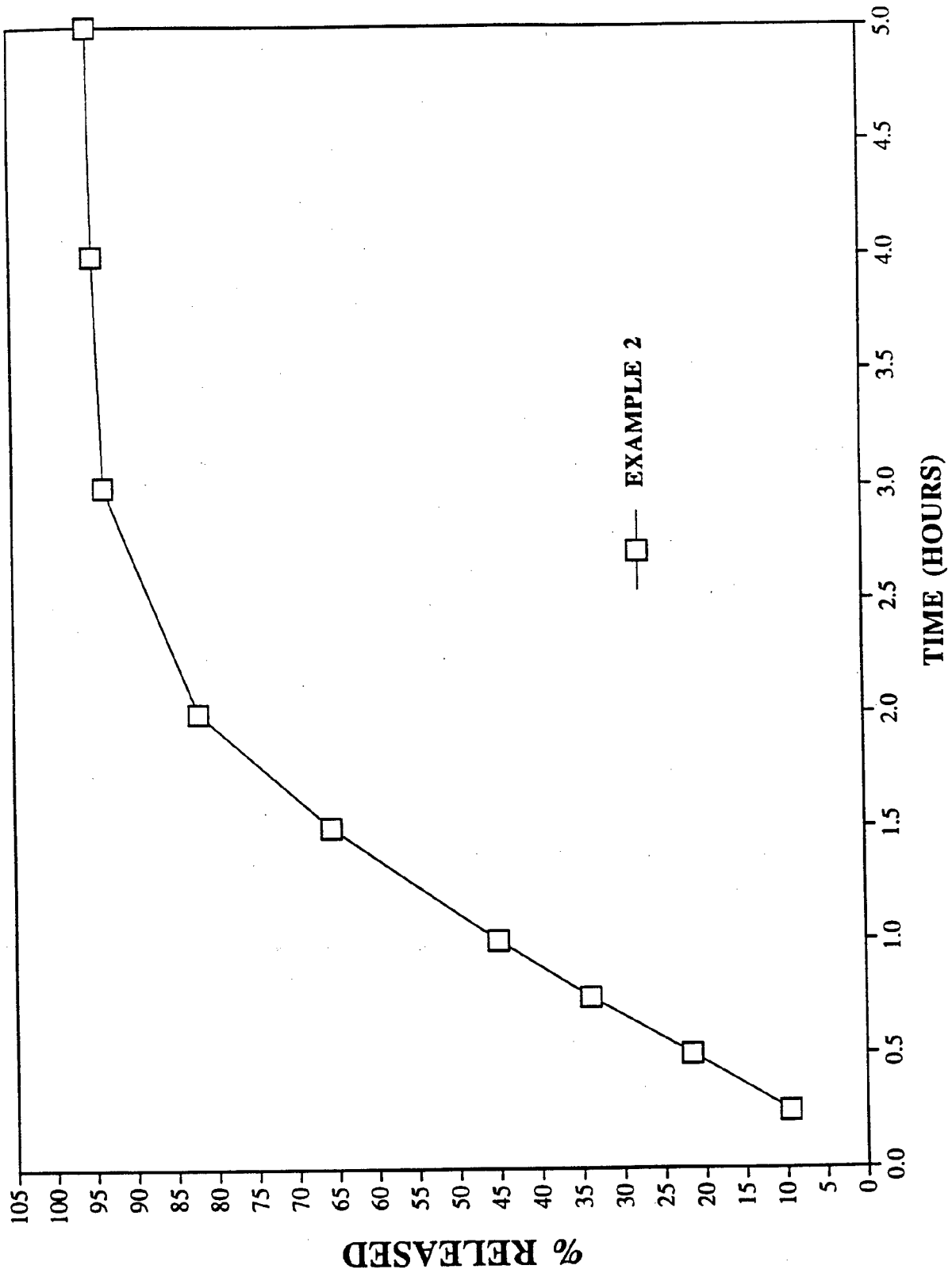
TIME (HOURS)
EXAMPLE 1

Figure 2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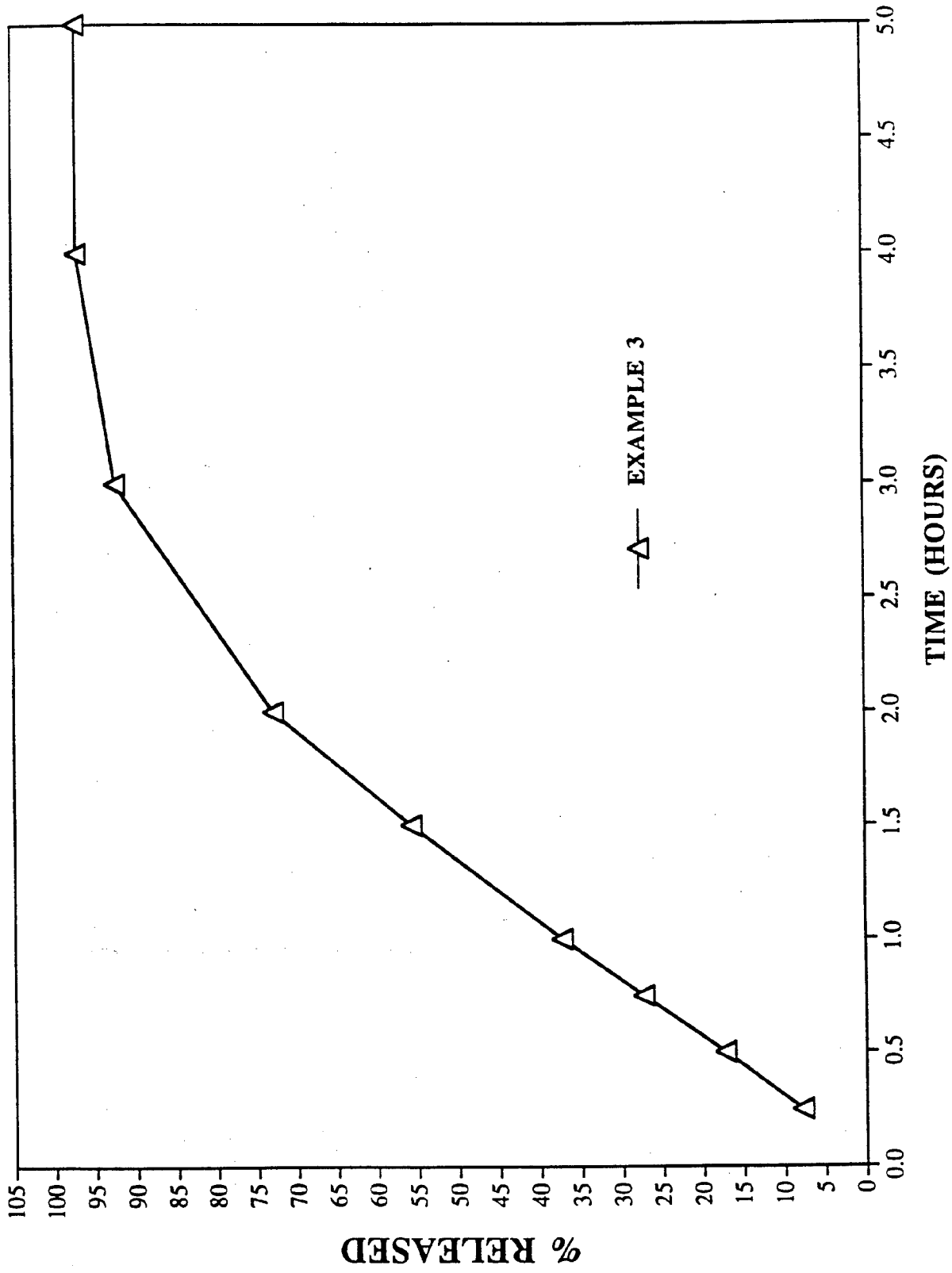
TIME (HOURS)
EXAMPLE 2

Figure 3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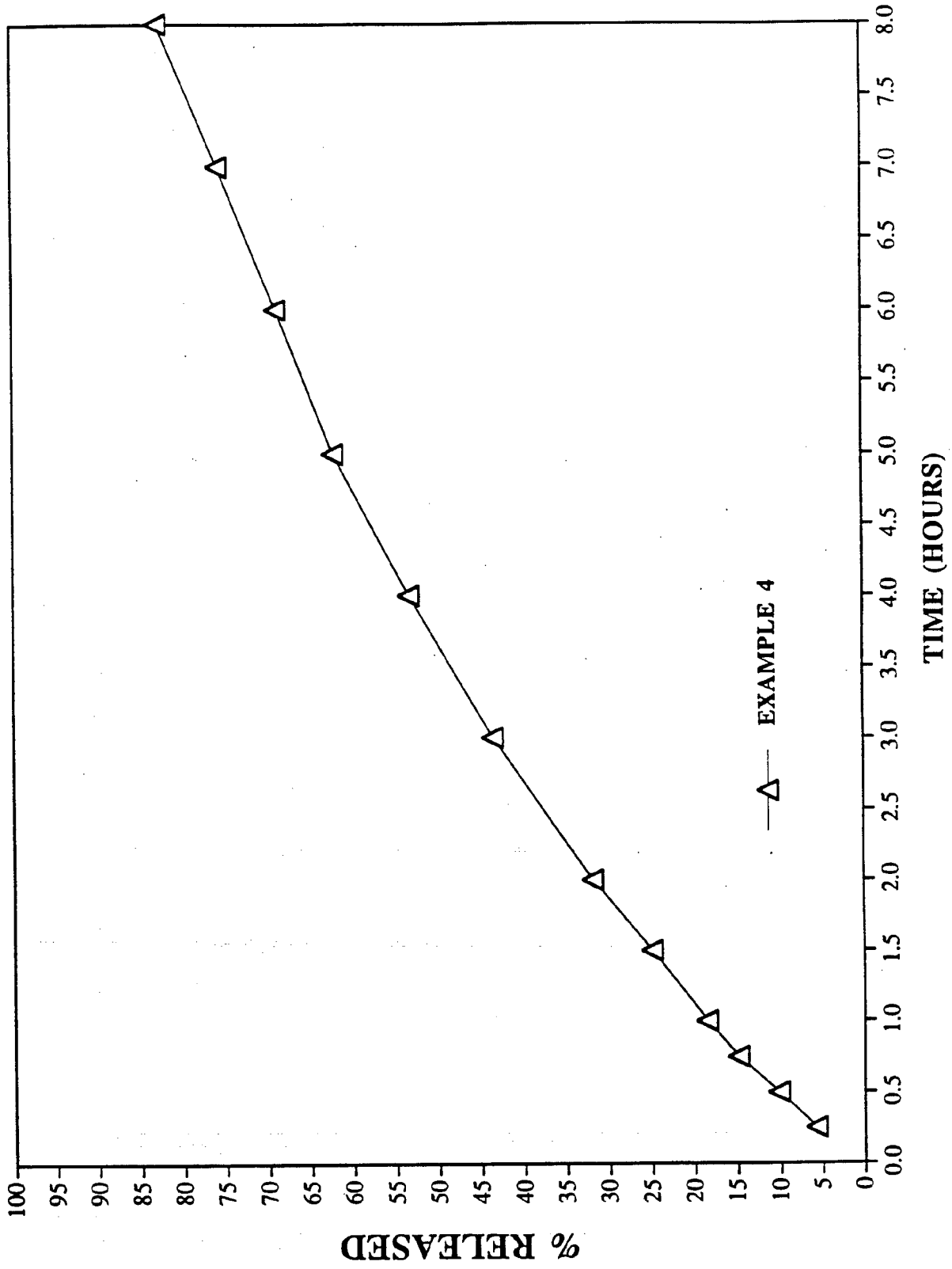
TIME (HOURS)
EXAMPLE 3

Figure 4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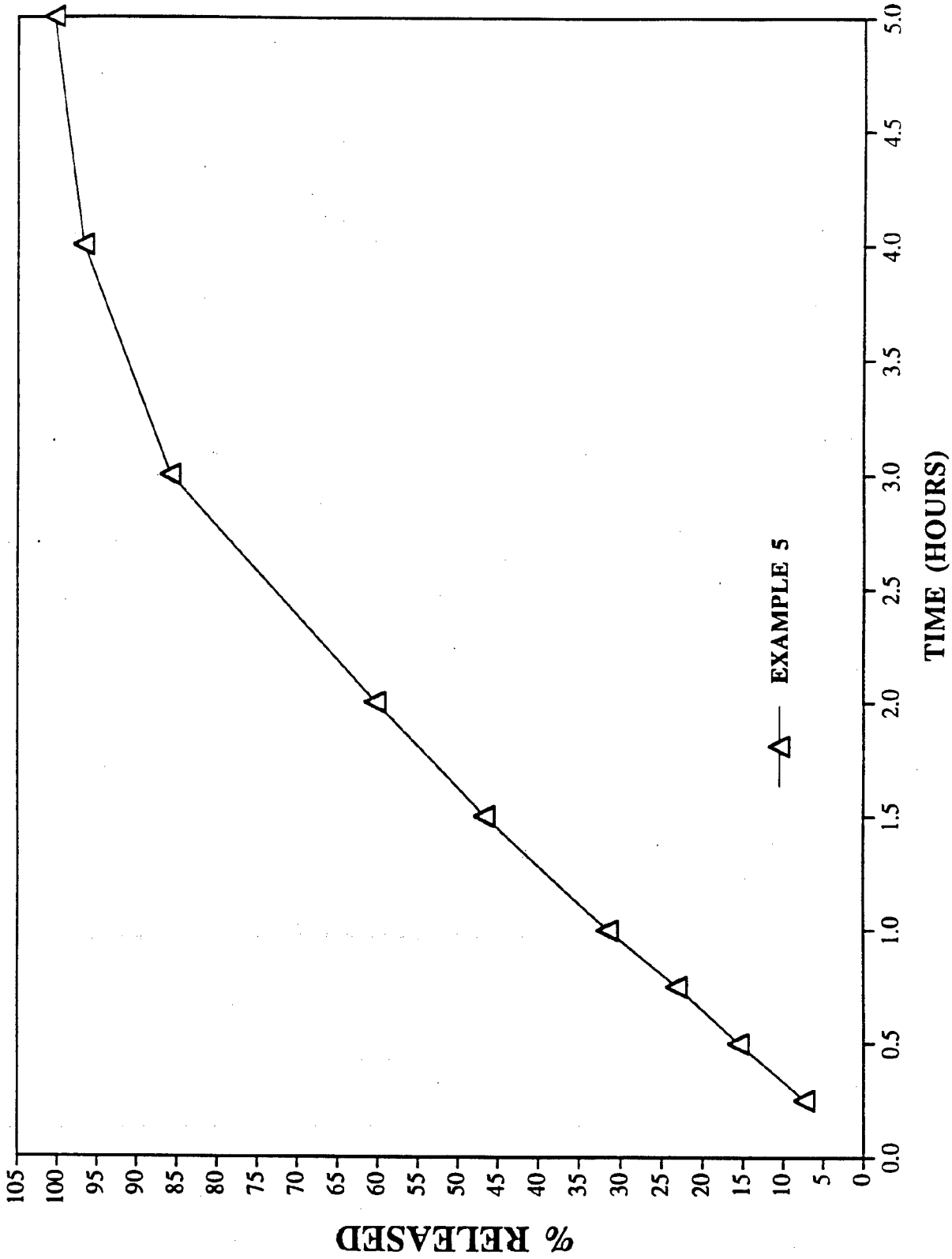
TIME (HOURS)
EXAMPLE 4

Figure 5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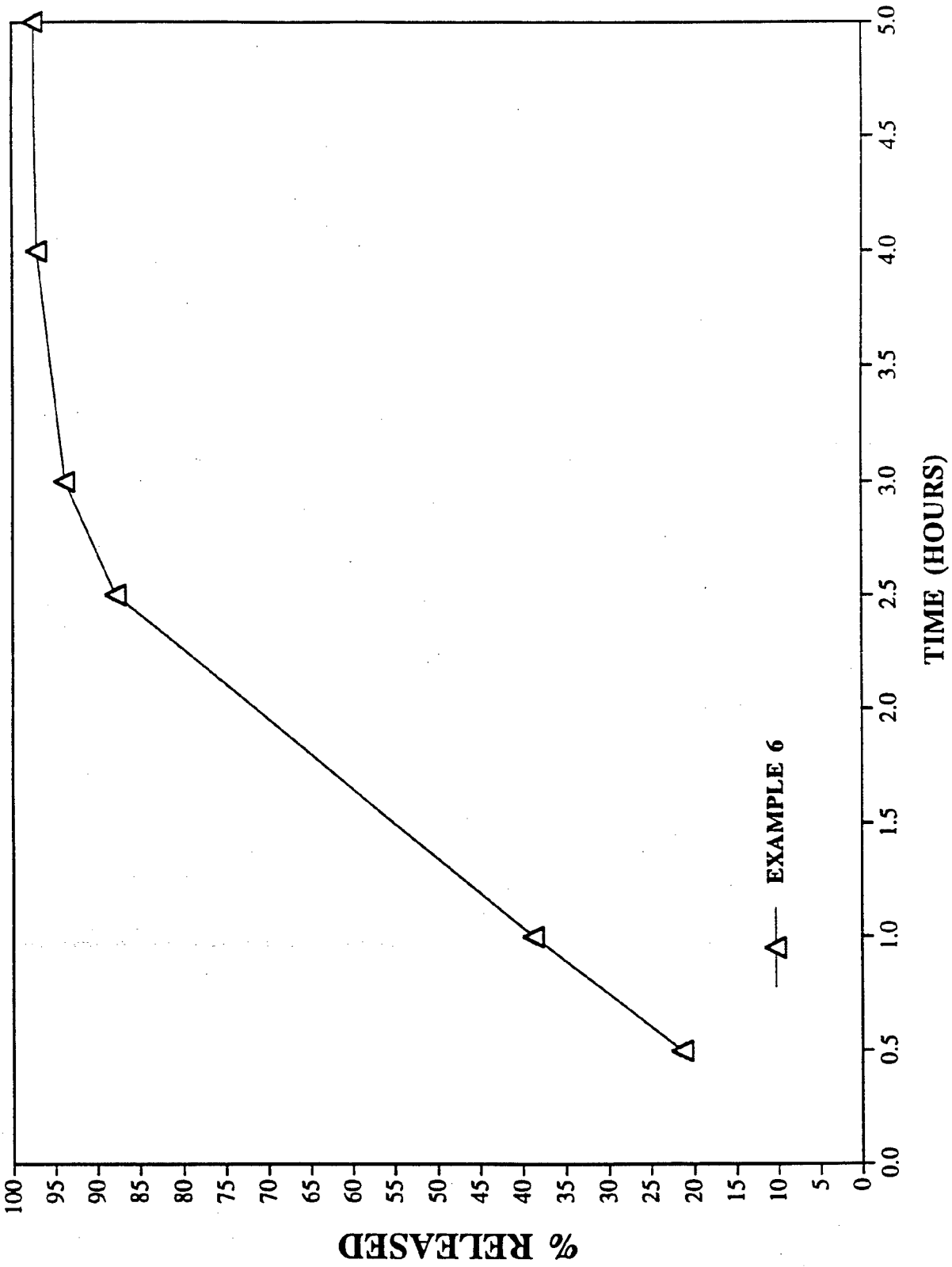
TIME (HOURS)
EXAMPLE 5

Figure 6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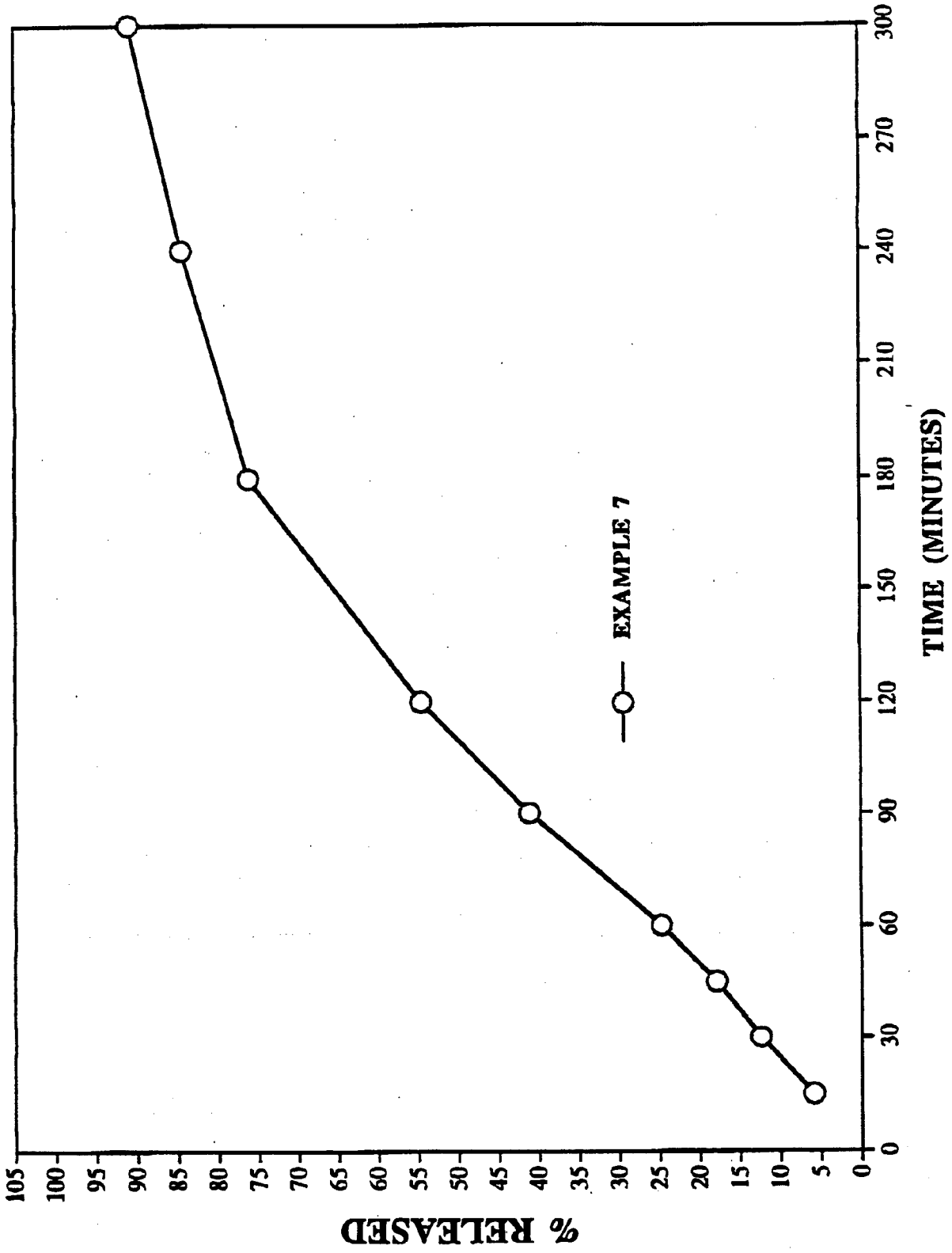
TIME (HOURS)
EXAMPLE 6

FIGURE 7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EXAMPLE 7
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TIME (MINUTES)

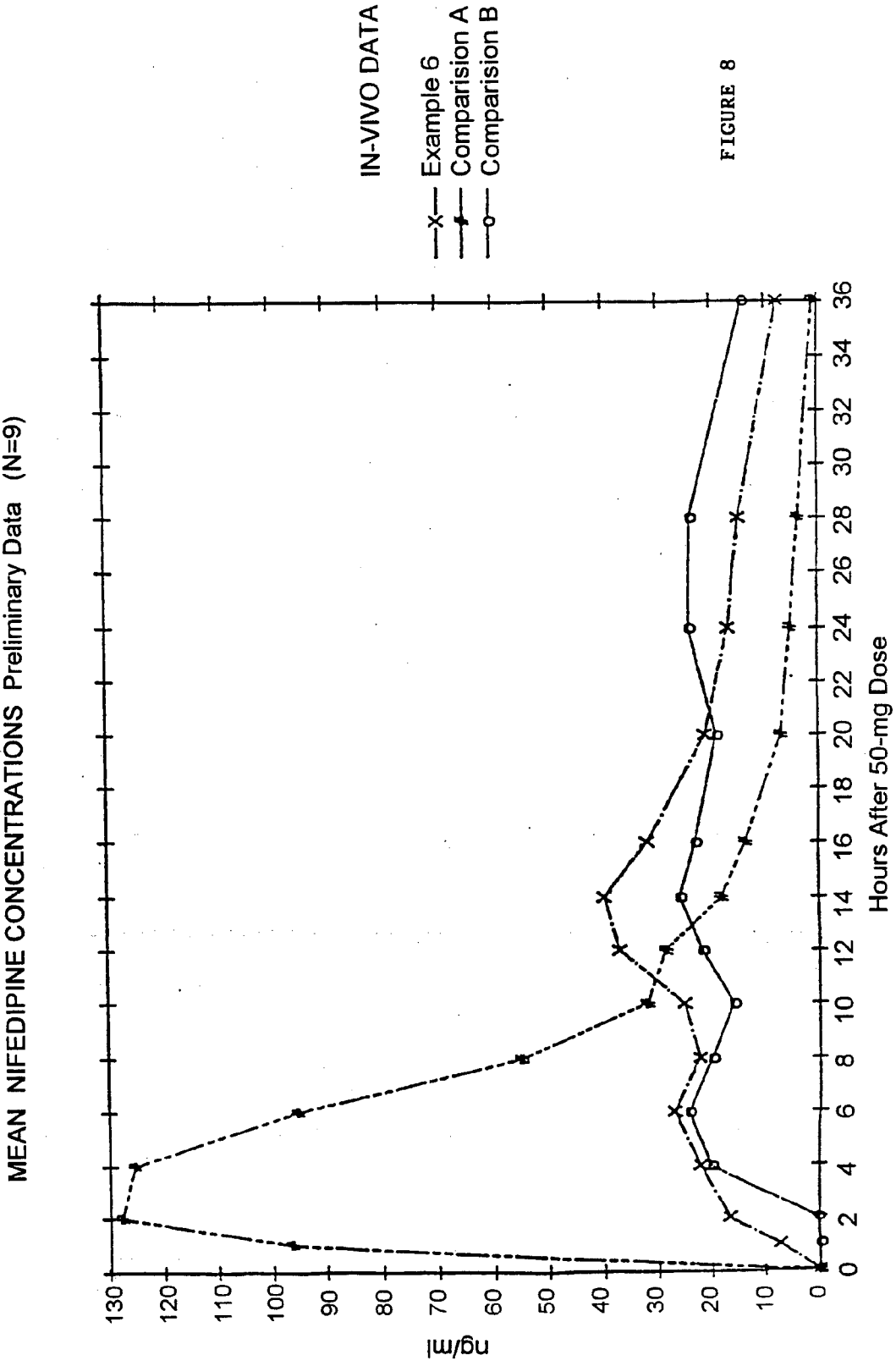

FIGURE 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 93/00462

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.[5] A61K 9/16, 9/52, 9/22, 31/44

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61K 9/16, 9/52, 9/26, 9/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)
DERWENT: low()solubil: and polymer:; nifedipine# and polymer#
JAPIO: low()solubil: and polymer:; nifedipine# and polymer#

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	AU,B,49594/85 (588258) (PHARMATEC S.P.A.) 8 April 1986 (08.04.86) See entire document	1-6, 9, 10, 15, 20-23, 25-27, 30-32
X	WO,A,89/02738 (APS RESEARCH LTD.) 6 April 1989 (06.04.89) See entire document	1, 2, 5, 6, 10, 13, 23, 25, 27, 30, 31
P, X	WO,A,93/13773 (ETHICAL PHARMACEUTICALS LTD.) 22 July 1993 (22.07.93) See entire document	1, 2, 5, 6, 9, 10, 15, 23, 25, 27, 30, 31

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

[X] See patent family annex.

* Special categories of cited documents :

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X	AU,B,68207/87 (592618) (ELAN CORPORATION P.L.C.) 14 July 1988 (14.07.88) See entire document	1-6, 10, 30-32
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X	Patent Abstracts of Japan, C-353, page 35, JP,A,61-17510 (TOYO BOSEKI K.K.) 25 January 1986 (25.01.86) Abstract	1, 2, 5, 6, 10, 23, 25, 30
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(54) Title: ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

(57) Abstract

The present invention relates to a method of increasing the absorption of a compound via the ocular, nasal, nasolacrimal or inhalation route into the circulatory system of a patient. In particular, a method comprising administering with the compound an absorption enhancer comprising a nontoxic, nonionic alkyl glycoside is provided. Additionally provided are methods of raising or lowering the blood glucose level by administering glucagon or insulin, respectively, with such absorption enhancers. Finally, compositions for raising or lowering the blood glucose level are provided.

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ABSORPTION ENHANCERS FOR DRUG ADMINISTRATION

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a method of increasing the absorption of a compound via the ocular, nasal, nasolacrimal or inhalation route into the circulatory system of a patient. In particular, a method comprising administering with the compound an absorption enhancer comprising a nontoxic, nonionic alkyl glycoside is provided. Additionally provided are methods of raising or lowering the blood glucose level by administering glucagon or insulin, respectively, with such absorption enhancers. Finally, compositions for raising or lowering the blood glucose level are provided.

BACKGROUND ART

The revolution in biotechnology has impacted on the pharmaceutical industry and on the practice of medicine by making available a variety of previously known and newly discovered proteins, e.g., insulin, growth hormone, interferons; peptides, e.g., cyclosporine, enkephalins and other synthetic peptides; as well as macromolecules, e.g., heparin and derivatives; drugs which open up an entirely new dimension to the treatment of disease. A serious limitation to the development and use of such agents, however, is the ability to deliver them safely and efficiently to their therapeutic site of action (Lee, V. H. L. et al., in "Peptide and Protein Drug Delivery," V.H.L. Lee ed. Marcel Dekker, New York, pp. 1-56 (1991)). Because these drugs are usually available in only small amounts, are expensive and are biologically fragile - subject to denaturation and degradation - a rapid and efficient route of delivery is an important requirement for their successful use in therapy. Unfortunately, for the most part, the practical delivery of such agents has been limited to injectable routes such as intravenous, intramuscular and subcutaneous administration. Insulin is the classic example of such an agent whose obligatory use in insulin-dependent diabetes mellitus requires administration via injection.

In the case of other established macromolecular drugs, such as heparin, the requirement for delivery by injection and the availability of alternative, but far from ideal agents, such as the oral anticoagulants, has restricted the use of the injectable agent to the clinic or hospital, thus denying its benefits to a large outpatient population. Although many attempts have been made to safely and efficiently administer insulin, heparin and other macromolecular drugs by non-injectable routes, none have proved successful, and it has become apparent that the success of such attempts depends on the discovery of a safe and efficient agent to enhance absorption of the macromolecules (*see* Lee et al.).

Buccal absorption of insulin is minimal in the absence of a surfactant agent, but it has been shown to be improved with penetration-enhancers such as glycocholate and Brij 35. However, the low bioavailability observed and the possible toxicity of the enhancing agents used previously have made this route impractical (Oh, C. K. et al, *Meth. Find. Exp. Clin. Pharmacol.*, 12:205-212 (1990)). Similar findings have been reported for insulin absorption across the rectal mucosa (Rytting, J. H. et al., (V.H.L. Lee, ed.) Marcel Dekker, New York pp. 579-594 (1991)). However, it has recently been reported that dodecylmaltoside was effective in promoting the absorption of high molecular weight sugar compounds, such as dextrans, and other molecules, such as carboxyfluoroscein, across the rectal mucosa of rats without producing any apparent histological change to the tissue (Murakami, M. et al., *Int. J. Pharm.*, 79:159-169 (1992)). Hovgaard et al., (*J. Controlled Release*, 19:99-108 (1992)) reported the use of high concentrations of dodecyl maltoside to increase the absorption of insulin across the rectal mucosa in rats. High concentrations were found to be necessary for rectal absorption (3.2% -12.8% dodecyl maltoside). It was concluded by Hovgaard *et al.* that rectal absorption enhancers function at least in part because they render the insulin-enhancer complex more resistant to enzymatic degradation by intestinal digestive enzymes. The use of dodecyl maltoside in the reported concentrations would be too irritating and toxic to the much more sensitive ocular and nasal mucosa and thus unsuitable for ocular and nasal absorption enhancers.

A synthetic analogue of calcitonin, a hypocalcemic peptide has been shown to be effectively absorbed percutaneously in the rat by applying it in transdermal dosage form as a gel containing a combination of bile salts and the alkyl glycosides octylglucoside or octylthioglucoside (Ogiso, T. et al., *Chem. Pharm. Bull.*, 39:449-453 (1991)).

We had previously shown that systemic delivery of insulin via the ocular and nasal-lacrimal route in amounts sufficient to lower blood sugar in experimentally diabetic rats was made possible by including 1% saponin in the eye drops with the insulin (Pillion, D. J. et al., *Invest. Ophthalmol. Vis. Sci.*, 32:3021-3027 (1991)). However, saponins, which have also been used by others to promote ocular absorption of insulin (Chiou, G. C. Y. et al., *J. Pharm. Sci.*, 78:815-818 (1989); Chiou, C. Y. et al., *J. Ocular Pharmacol.* 5:81-91 (1989); U.S. Patent No. 5,182,258 (Chiou *et al.*), are a large and complex class of compounds, derived from plants, which are difficult to prepare in pure form and have deleterious properties such as being irritants (Price, K.R. et al., *CRC Crit. Rev. Food Sci. Nutr.*, 26:27-135 (1987)). Another surfactant, Tween 20, which has the same 12 carbon alkyl side chain as dodecylmaltoside, but which has a polyoxyethylene moiety in place of maltose, has been reported to be almost without effect in allowing absorption of insulin in rabbit eyes (Chiou, et al., *J. Pharm. Sci.*,) Furthermore, saponin, fusidic acid, EDTA, polyoxyethylene-9-lauryl ether, glycocholate, taurocholate, deoxycholate and decamethonium as ocular absorption enhancers have met with limited success in promoting the ocular absorption of insulin (Pillion et al., Chiou et al., (*J. Pharm. Sci.*), Chiou et al. (*J. Ocular Pharmacol.*) and Yamamoto et al., *J. Pharmacol. Exptl. Ther.*, 249:249-255 (1989)), but the toxicity of these agents makes their therapeutic usage problematic.

Intranasal administration of insulin in the form of a nasal spray with bile salts or laureth-9 as absorption enhancers has been tested in clinical trials with normal and diabetic subjects, but also with only limited success (Moses, A. C. et al., *Diabetes*, 32:1040-1047 (1983); Gordon, G. S. et al., *Proc.*

Natl. Acad. Sci. USA, 82:7419-7423 (1985); Salzmann, R. et al., *New Engl. J. Med.*, 312:1078-1084 (1985)). The major limiting factors which have prevented the practical development of this route for general use is the low efficiency of absorption across the nasal mucosa and the local and systemic toxicity of the penetration-enhancing agents used (Moses et al., Gordon et al., Salzmann et al and Chadwick, U.S. et al., *Gut*, 17:10-17 (1976)). Aerosolized insulin has been absorbed via the respiratory route, but only at low efficiency, probably because no absorption enhancer was employed (Wigley, F. M. et al., *Diabetes*, 20:552-556 (1971).

Dodecylmaltoside and other alkyl glycosides can readily be obtained in pure form and have well defined, simple structures (Neugebauer, J., "A Guide to the Properties and Uses of Detergents in Biology and Biochemistry," Calbiochem Corporation (1988)). They are mild nonionic surfactants which have generally been shown to be nontoxic to several different cell types (DiCorleto, P. E. et al., *J. Immunol.*, 143:3666-3672 (1989) and LeGrue, S. J. et al., *J. Natl. Cancer Inst.*, 69:131-136 (1982)). Octylglucoside had no effect on the viability or morphology of monocytes or endothelial cells (DiCorleto et al.) and was non-cytolytic to intact mouse fibrosarcoma cells (LeGrue et al.) Orally administered alkyl glycosides, including octyl β-D-glucoside and dodecyl β-D-maltoside, have also been shown to be metabolized to nontoxic metabolites by cleavage to sugars and long chain alcohols which enter into the pathways of carbohydrate and lipid metabolism. It was suggested that these compounds would be suitable for use as food additives because of their lack of toxicity (Weber, N. et al., *J. Nutr.*, 114:247-254 (1984)). In contrast, other agents which have been shown to enhance the systemic absorption of insulin, such as bile salts or laureth-9, are known to be irritating to mucosal surfaces and are not metabolized to simple products in the body (Moses et al., Gordon et al., and Salzmann et al.). In the case of bile salts, it is known that they are toxic to the gastrointestinal mucosa when administered orally and

that they cause ultrastructural abnormalities of the nasal mucosa when used to administer insulin by this route (Moses et al., Gordon et al., and Chadwick et al.).

Thus, many attempts have been unsuccessfully made to obtain a suitable, effective absorption enhancer for drugs, and there is a great need for such an enhancer. The ideal absorption or penetration enhancer would preserve the biological activity of the protein or other drug and thus should be nonreactive and non-denaturing. It should enhance the passage of the drug through membrane barriers without damaging the structural integrity and biological functions of the membrane. Most importantly, both it and its metabolites should be nonirritating and nontoxic, both at the site of application, and also systemically, since it is likely that any enhancer of drug absorption will itself be absorbed and have to be metabolized and/or cleared from the body. Such an absorption enhancer is provided herein.

SUMMARY OF THE INVENTION

The present invention relates to a method of increasing absorption of a compound into the circulatory system of a subject comprising administering via the ocular, nasal, nasolacrimal, or inhalation route the compound and an absorption increasing amount of a suitable nontoxic, nonionic glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide.

The present invention also relates to a method of lowering blood glucose level in a subject comprising administering via the ocular, nasal, nasolacrimal or inhalation route, a blood glucose-reducing amount of a composition comprising insulin and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of insulin and lowering the level of blood glucose.

The instant invention further relates to a method of raising blood glucose level in a subject comprising administering via the ocular, nasal, nasolacrimal or inhalation route a blood glucose-raising amount of a suitable composition comprising glucagon and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of glucagon and raising the level of blood glucose.

The present invention also relates to a composition comprising (a) a nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, in concentration in the range of 0.01% to 1.0%, capable of increasing absorption of a compound into the circulatory system of a patient and (b) an agent selected from the group consisting of insulin and glucagon.

Accordingly, it is an object of the present invention to provide a method of increasing the absorption of a compound into the circulatory system of a subject by utilizing the ocular, nasal and nasolacrimal or inhalation route.

Another object of the present invention is to provide compositions and methods for raising or lowering the blood glucose level in a subject utilizing the provided method for increasing absorption of compounds, and thus treating hypoglycemia or diabetes mellitus, respectively.

Finally, an object of the present invention is to provide compositions for raising and lowering blood glucose levels.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following detailed description of specific embodiments and the Examples included therein.

The present invention provides a method of increasing absorption of a compound into the circulatory system of a subject comprising administering via the ocular, nasal, nasolacrimal, or inhalation route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide. The compound and the alkyl glycoside can be mixed prior to administration, or they can be administered sequentially, in either order. It is preferred that they be mixed prior to administration.

As used in the claims, "a" can mean one or more.

As used herein, "hypoglycemia" includes a hypoglycemic crisis.

"Nontoxic," as used herein, means that the alkyl glycoside molecule has a sufficiently low toxicity to be suitable for human administration. Preferred alkyl glycosides are nonirritating to the tissues to which they are applied. Any alkyl glycoside should be of minimal or nontoxicity to the cell, such as not to cause damage to the cell. Toxicity for any given alkyl glycoside may vary with the concentration of alkyl glycoside used. It is also beneficial if the alkyl glycoside chosen is metabolized or eliminated by the body and if this metabolism or elimination is done in a manner that will not be harmfully toxic.

As used herein, "alkyl glycoside" refers to any sugar joined by a linkage to any hydrophobic alkyl, as is known in the art. The hydrophobic alkyl can be chosen of any desired size, depending on the hydrophobicity desired and the hydrophilicity of the saccharide moiety. A preferred range of alkyl chains is from 9 to 24 carbon atoms. An even more preferred range is from 9 to 14 carbon atoms.

As used herein, "saccharide" is inclusive of monosaccharides, oligosaccharides or polysaccharides in straight chain or ring forms. Oligosaccharides are saccharides having two or more monosaccharide residues.

As used herein, a "suitable" alkyl glycoside means one that fulfills the limiting characteristics of the invention, i.e., that the alkyl glycoside be nontoxic and nonionic, and that it increases the absorption of a compound when it is administered with the compound via the ocular, nasal, nasolacrimal or inhalation route. Suitable compounds can be determined using the methods set forth in the examples.

Also as used herein, "hydrophile-lipophile balance number" (HLB) is a characteristic of individual surfactants that can be either calculated or determined empirically, as previously described (Schick, M.J. *Nonionic Surfactants*, p. 607 (NY: Marcel Dekker, Inc. (1967)). HLB can be calculated by the formula: 20 x MW hydrophilic component/(MW hydrophobic component + MW hydrophilic component), where MW = molecular weight (Rosen, M.J., *Surfactants and Interfacial Phenomena*, pp. 242-245, John Wiley, New York (1978)). The HLB is a direct expression of the hydrophilic character of the surfactant, i.e., the larger the HLB, the more hydrophilic the compound. A preferred surfactant has an HLB of from 10 to 20 and an even more preferred range of from 11 to 15.

Compounds whose absorption can be increased by the method of this invention include any compounds now known or later discovered, in particular drugs that are difficult to administer by other methods, for example, drugs that are degraded in the gastrointestinal (GI) tract or that are not absorbed well from the GI tract, or drugs that subjects could administer to themselves more readily via the ocular, nasal, nasolacrimal or inhalation route than by traditional self-administration methods such as injection. Some specific examples include peptides, polypeptides, proteins and other macromolecules, for example, peptide hormones, such as insulin and calcitonin, enkephalins, glucagon and hypoglycemic agents, such as tolbutamide and glyburide, and agents which are poorly absorbed by enteral routes, such as griseofulvin, an antifungal agent.

The saccharide can be chosen, for example, from any currently commercially available saccharide species or can be synthesized. The saccharide can be a monosaccharide, a disaccharide, an oligosaccharide or a polysaccharide, or a combination thereof to form a saccharide chain. Some examples of the many possible saccharides to use include glucose, maltose, maltotriose, maltotetraose, sucrose and trehalose. Preferable saccharides include maltose, sucrose and glucose.

Additionally, various oxygen atoms within the compounds can be substituted for by sulfur in order to decrease susceptibility to hydrolytic cleavage by glycohydrolases in the body (Defaye, J. and Gelas, J. in *Studies in Natural Product Chemistry* (Atta-ur-Rahman, ed.) Vol. 8, pp. 315-357, Elsevier, Amsterdam, 1991). For example, the heteroatom of the sugar ring can be either oxygen or sulfur, or the linkage between monosaccharides in an oligosaccharide can be oxygen or sulfur (Horton, D. and Wander, J.D., "Thio Sugars and Derivatives," *The Carbohydrates: Chemistry and Biochemistry*, 2d. Ed. Vol. IB, (W. Reyman and D. Horton eds.), pp. 799-842, (Academic Press, N.Y.), (1972)). Oligosaccharides can have either α (alpha) or β (beta) anomeric configuration (see Pacsu, E., et al. *in Methods in Carbohydrate Chemistry* (R.L. Whistler, et al., eds.) Vol. 2, pp. 376-385, Academic Press, New York 1963).

Many alkyl glycosides can be synthesized by known procedures, i.e., chemically, as described, e.g., in Rosevear et al., *Biochemistry* 19:4108-4115 (1980) or Koeltzow and Urfer, *J. Am. Oil Chem. Soc.*, 61: 1651-1655 (1984), U.S. Patent No. 3,219,656 and U.S. Patent No. 3,839,318 or enzymatically, as described, e.g., in Li et al., *J. Biol. Chem.*, 266:10723-10726 (1991) or Gopalan et al., *J. Biol. Chem.* 267:9629-9638 (1992).

The linkage between the hydrophobic alkyl and the hydrophilic saccharide can include, among other possibilities, a glycosidic, thioglycosidic (*Horton*), amide (*Carbohydrates as Organic Raw Materials*, F.W. Lichtenthaler ed., VCH Publishers, New York, 1991), ureide (Austrian Pat. 386,414 (1988);

Chem. Abstr. 110:137536p (1989); see Gruber, H. and Greber, G., "Reactive Sucrose Derivatives" in *Carbohydrates as Organic Raw Materials*, pp. 95-116) or ester linkage (*Sugar Esters: Preparation and Application*, J.C. Colbert ed., (Noyes Data Corp., New Jersey), (1974)).

Examples from which useful alkyl glycosides can be chosen for the therapeutic composition include: alkyl glycosides, such as octyl-, nonyl-, decyl-, undecyl-, dodecyl-, tridecyl-, tetradecyl, pentadecyl-, and octadecyl α- or β-D-maltoside, -glucoside or -sucroside (synthesized according to *Koeltzow and Urfer*; Anatrace Inc., Maumee, Ohio; Calbiochem, San Diego, California; Fluka Chemie, Switzerland); alkyl thiomaltosides, such as heptyl, octyl, dodecyl-, tridecyl-, and tetradecyl-β-D-thiomaltoside (synthesized according to Defaye, J. and Pederson, C., "Hydrogen Fluoride, Solvent and Reagent for Carbohydrate Conversion Technology" in *Carbohydrates as Organic Raw Materials*, 247-265 (F. W. Lichtenthaler, ed.) VCH Publishers, New York (1991); Ferenci, T., J. *Bacteriol.*, 144:7-11 (1980)); alkyl thioglucosides, such as heptyl- or octyl 1-thio α- or β-D-glucopyranoside (Anatrace, Inc., Maumee, Ohio; see Saito, S. and Tsuchiya, T. *Chem. Pharm. Bull.* 33:503-508 (1985)); alkyl thiosucroses (synthesized according to, for example, Binder, T.P. and Robyt, J.F., Carbohydr. Res. 140:9-20 (1985)); alkyl maltotriosides (synthesized according to *Koeltzow and Urfer*); long chain aliphatic carbonic acid amides of sucrose β-amino-alkyl ethers; (synthesized according to Austrian Patent 382,381 (1987); *Chem. Abstr.*, 108:114719 (1988) and *Gruber and Greber* pp. 95-116); derivatives of palatinose and isomaltamine linked by amide linkage to an alkyl chain (synthesized according to Kunz, M., "Sucrose-based Hydrophilic Building Blocks as Intermediates for the Synthesis of Surfactants and Polymers" in *Carbohydrates as Organic Raw Materials*, 127-153); derivatives of isomaltamine linked by urea to an alkyl chain (synthesized according to *Kunz*); long chain aliphatic carbonic acid ureides of sucrose β-amino-alkyl ethers (synthesized according to *Gruber and Greber*, pp. 95-116); and long chain aliphatic carbonic acid amides of sucrose β-amino-alkyl ethers (synthesized according to *Austrian Patent* 382,381 (1987), *Chem. Abstr.*, 108:114719 (1988) and *Gruber and Greber*, pp. 95-116).

Some preferred glycosides include maltose, sucrose, and glucose linked by glycosidic linkage to an alkyl chain of 9, 10, 12 or 14 carbon atoms, i.e., nonyl-, decyl-, dodecyl- and tetradecyl sucroside, glucoside, and maltoside. These compositions are nontoxic, since they are degraded to an alcohol and an oligosaccharide, and amphipathic.

The above examples are illustrative of the types of glycosides to be used in the methods claimed herein; the list is not exhaustive. Derivatives of the above compounds which fit the criteria of the claims should also be considered when choosing a glycoside. All of the compounds can be screened for efficacy following the methods taught in the examples.

Preferred concentrations of alkyl glycosides are those within the range of 0.01-1%, as such low concentrations reduce any potential irritability or damage to the tissues while still increasing absorption. Even more preferred are concentrations within the range of 0.125-0.5%. From a medical standpoint, the less absorption enhancer used, that is still as effective as desired, the better for the subject.

The method of this invention can also include the administration, along with the alkyl glycoside and a protein or peptide, a protease or peptidase inhibitor, such as aprotinin, bestatin, alpha$_1$ proteinase inhibitor, recombinant secretory leucocyte protease inhibitor, captopril and other angiotensin converting enzyme (ACE) inhibitors and thiorphan, to aid the protein or peptide in reaching its site of activity in the body in an active state (i.e., with degradation minimal enough that the protein is still able to function properly). The protease or peptidase inhibitor can be mixed with the alkyl glycoside and compound and then administered, or it can be administered separately, either prior to or after administration of the glycoside and compound.

The amount of compound administered will, of course, be dependent on the subject being treated, the subject's weight, the severity of symptoms and the judgment of the prescribing physician. Generally, however, dosage will approximate that which is typical for known methods of administration of the specific compound. For example, for intranasal administration of insulin, an approximate dosage would be about 0.5 unit/kg regular porcine insulin (Moses *et al.*). Dosage for compounds affecting blood glucose levels optimally would be that required to achieve proper glucose levels, for example, to a normal range of about 5-6.7 mM. Additionally, an appropriate amount may be determined by one of ordinary skill in the art using only routine testing given the teachings herein (see Examples).

The compound can be administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained release format. The spray and the aerosol can be achieved through use of the appropriate dispenser. The sustained release format can be an ocular insert, erodible microparticulates, swelling mucoadhesive particulates, pH sensitive microparticulates, nanoparticles/latex systems, ion-exchange resins and other polymeric gels and implants (Ocusert, Alza Corp., California; Joshi, A., S. Ping and K. J. Himmelstein, Patent Application WO 91/19481). These systems maintain prolonged drug contact with the absorptive surface preventing washout and nonproductive drug loss.

Also provided is a method of lowering blood glucose level in a subject comprising administering via the ocular, nasal, nasolacrimal or inhalation route, a blood glucose-reducing amount of a composition comprising insulin and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of insulin and lowering the level of blood glucose. A "blood glucose-reducing amount" of such a composition is that amount capable of producing the effect of reducing blood glucose levels, as taught herein. Preferred is an amount that decreases blood glucose to

normoglycemic or near normoglycemic range. Also preferred is an amount that causes a sustained reduction in blood glucose levels. Even more preferred is an amount sufficient to treat diabetes mellitus by lowering blood glucose level. Thus, the instant method can be used to treat diabetes mellitus. Preferred alkyl glycosides are the same as those described above and exemplified in the Examples.

Also provided is a method of raising blood glucose level in a subject comprising administering via the ocular, nasal, nasolacrimal or inhalation route a blood glucose-raising amount of a suitable composition comprising glucagon and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of glucagon and raising the level of blood glucose. A "blood glucose-raising amount" of such a composition is that amount capable of producing the effect of raising blood glucose levels. Preferred is an amount that increases blood glucose to normoglycemic or near-normoglycemic range. Also preferred is an amount that causes a sustained raising of blood glucose levels. Even more preferred is an amount sufficient to treat hypoglycemia by raising blood glucose level. Thus this method can be used to treat hypoglycemia. Preferred alkyl glycosides are the same as those described above and exemplified in the Examples.

Also provided is a composition comprising (a) a nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, in concentration in the range of 0.01% to 1.0%, capable of increasing absorption of a compound into the circulatory system of a patient and (b) an agent selected from the group consisting of insulin and glucagon. When this composition includes insulin, it can be used to cause the known effect of insulin in the bloodstream, i.e., lower the blood glucose levels in a subject, by administering it by, for example, the administration means of this invention, i.e.,

via the ocular, nasal, nasolacrimal or inhalation route. Such administration can be used to treat diabetes mellitus, using the concentrations of insulin known to those of skill in the art to properly lower blood glucose.

Similarly, when this composition includes glucagon, it can be used to cause the known effect of glucagon in the bloodstream, i.e., to raise the blood glucose levels in a subject. Such administration can therefore be used to treat hypoglycemia, including hypoglycemic crisis.

The present invention is more particularly described in the following examples which are intended as illustrative only since numerous modifications and variations therein will be apparent to those skilled in the art.

EXAMPLES

Hypoglycemic Effects of Insulin Delivered by the Ocular Route

All of the experimental results described were obtained in normal rats in which blood glucose values have been elevated as a consequence of anesthesia produced by xylazine/ketamine. This mimics the hyperglycemic state seen in diabetic animals and humans. The elevated levels of D-glucose that occur in response to anesthesia provide an optimal system in which to measure any systemic hypoglycemic action of insulin-containing eye drops. Hence, anesthetized rats given eye drops containing insulin can be compared to anesthetized animals given eye drops without insulin, and the differential systemic responses should accurately reflect the effect of insulin absorbed via the ocular route of administration.

Adult male Sprague-Dawley rats (250-350g) were fed ad libitum, and experiments were conducted between 10:00 a.m. and 3:00 p.m. Rats were anesthetized with a mixture of xylazine (7.5 mg/kg) and ketamine (50 mg/kg) given intraperitoneally (IP) and allowed to stabilize for 50-90 min before the administration of eye drops. Anesthesia of a normal rat with xylazine/ketamine

produces an elevation in blood glucose values which provides an optimal state to determine the systemic hypoglycemic action of insulin-containing eye drops. Blood D-glucose values were measured by collecting a drop of blood from the tail vein at 5-10 min intervals throughout the experiment and applying the blood to glucometer strips (Chemstrip bG) according to directions provided with the instrument (Accu-Chek II, Boehringer Mannheim Diagnostics; Indianapolis, IN). Blood D-glucose values ranged from 200 to 400 mg/dl in anesthetized nondiabetic rats.

At time 0, after a 50-90 min stabilization period, rats were given 20 μl of eye drops composed of phosphate-buffered saline with or without 0.2% regular porcine insulin and 0.125-0.5% of the absorption enhancer to be tested. Eye drops were instilled at time 0 using a plastic disposable pipette tip with the eyes held open, and the rat was kept in a horizontal position on a warming pad (37°C) throughout the protocol. The rats were given additional anesthesia if they showed signs of awakening. Rats received in each eye 20 μl of 0.125-0.5% absorption enhancer in phosphate buffered saline, pH 7.4 with (experimental) or without (control) 0.2% (50 U/ml) regular porcine insulin (Squibb-Novo, Inc.) for a total of 2 U per animal. Octyl β-D-maltoside, decyl-β-D-maltoside, dodecyl-β-D-maltoside, tridecyl-β-D-maltoside and tetradecyl-β-D-maltoside were obtained from Anatrace, Inc. (Maumee, Ohio). Hexylglucopyranoside, heptylglucopyranoside, nonylglucopyranoside, decylsucrose and dodecylsucrose were obtained from Calbiochem, Inc. (San Diego, Calfornia); Saponin, BL-9 and Brij 78 were obtained from Sigma Chemical Co. (St. Louis, Missouri).

When rats received eye drops containing saline only, 0.2% regular porcine insulin in saline only, or absorption enhancer only, the level of D-glucose in the blood remained elevated. However, when rats received eye drops containing 0.2% regular porcine insulin and several alkylmaltoside or alkylsucrose compounds, a pronounced decrease in blood D-glucose values occurred and was maintained for up to two hours. Insulin administered ocularly with 0.5% dodecyl-β-D-maltoside (see Table 1) or 0.5% decyl-β-D-maltoside

(see Table 3) results in a prompt and sustained fall in blood glucose levels which are maintained in the normoglycemic (80-120 mg/dl) or near-normoglycemic (120-160 mg/dl) range for the two hour duration of the experiment. Therefore, two alkylmaltosides are effective in achieving sufficient absorption of insulin delivered via the ocular route to produce a prompt and sustained fall in blood glucose levels in experimentally hyperglycemic animals. These agents, therefore, can be useful to achieve systemic absorption of insulin and other peptide, protein, e.g., glucagon and macromolecular drugs, e.g., heparin delivered via the ocular route in the form of eye drops.

Several other alkylmaltosides also proved effective as absorption enhancers for ocular administration of insulin including 0.5% tridecylmaltoside (see Table 3) and 0.125% (Table 2) and 0.5% tetradecyl maltoside. Based on these studies it appears that alkylmaltosides with the longer alkyl chains, i.e., dodecyl-, tridecyl- and tetradecyl-β-D-maltosides, and hence, with the greater hydrophobic/hydrophilic structural balance are more effective as absorption enhancers than those with shorter alkyl chains which produce less, e.g., decylmaltoside, or no, e.g., octylmaltoside, activity. It should be noted that the most effective alkylmaltosides produce effects comparable to or greater than those seen with other absorption enhancers such as saponin, with the added advantage that they can be metabolized to nontoxic products following systemic absorption.

The effects of the alkylmaltosides as absorption enhancers are dose-dependent, as can be seen by examining the effects of different concentrations ranging from 0.125-0.5% in producing a hypoglycemic effect when combined with insulin. Whereas, 0.5% and 0.375% dodecylmaltoside appear equally effective in achieving systemic absorption of insulin and reduction of blood glucose levels, 0.25% has a smaller and more transient effect and 0.125% is ineffective (Table 1). Similarly, tridecylmaltoside also shows a dose-dependent effect in lowering blood glucose concentrations when combined with insulin, but the effect achieved with even 0.25% of the enhancer is sustained for

the two hour time course of the experiment. The dose-dependent effects of the alkylmaltosides suggest that they achieve enhancement of protein absorption via the ocular route in a graded fashion proportional to the concentration of the agent.

TABLE 1

Effect of Eye Drops Containing Insulin Plus Various Concentrations of Dodecyl Maltoside on Blood Glucose Values (in mg/dl) in Rat

	Dodecyl Maltoside Concentration			
	.125%	.25%	.375%	.50%
Time (min)	Blood Glucose Concentrations (mg/dl)			
-20	305 ± 60	271 ± 38	305 ± 51	375 ± 9
-10	333 ± 58	295 ± 32	308 ± 27	366 ± 12
0	338 ± 67	323 ± 62	309 ± 32	379 ± 4
30	349 ± 64	250 ± 48	212 ± 18	297 ± 18
60	318 ± 38	168 ± 22	134 ± 4	188 ± 25
90	325 ± 57	188 ± 55	125 ± 12	141 ± 13
120	342 ± 78	206 ± 63	119 ± 19	123 ± 5

The absorption enhancing effects of the alkyl saccharides are not confined to the alkylmaltosides alone since dodecylsucrose (0.125%, 0.25%, 0.375%) also shows a dose-dependent effect in producing ocular absorption of insulin and hence a reduction in blood glucose levels, even at 0.125% (from 335 mg/dl ± 26 mg/dl at time 0 min. to 150 mg/dl ± 44 mg/dl at time 120 min.). 0.5% decylsucrose was also effective in reducing blood glucose levels, but as shown for the alkylmaltosides, a reduction in the length of the alkyl chain, and hence the hydrophobic properties of the molecule, appears to reduce the potency of the alkylsucrose compounds. However, a significant and sustained reduction in blood glucose levels is achieved with 0.5% decylsucrose (from 313 mg/dl ± 15 mg/dl at time 0 min. to 164 mg/dl ± 51 mg/dl at time 120 min.).

The absorption enhancing abilities of alkylsaccharides with two distinct disaccharide moieties suggests that it is the physicochemical properties of the compounds which are crucial to their activity and that other alkylsaccharides, e.g., dodecyllactose, have the right balance of properties to be equally or more effective as absorption enhancers while retaining the metabolic and nontoxic properties of the alkylsaccharide enhancing agents.

Studies with alkylglucosides were also conducted; 0.5% hexylglucoside and 0.5% heptylglucoside were ineffective at promoting insulin absorption from the eye, but 0.5% nonylglucoside effectively stimulated insulin absorption and reduced blood glucose levels (from 297 mg/dl to 150 mg/dl). This result once again showed that the alkyl chain length, as well as the carbohydrate moiety, play critical roles in effectively enhancing insulin absorption.

It should be noted that no damaging effects to the ocular surface were observed with any of the alkylmaltoside or alkylsucrose agents employed in these studies. Furthermore, the prompt and sustained hypoglycemic effects produced by these agents in combination with insulin suggest that these absorption enhancers do not adversely affect the biological activity of the hormone, in keeping with their nondenaturing, mild surfactant properties. Finally, since we have observed previously with other absorption enhancers that insulin administration via eye drops results in significant absorption of the hormone via the nasolacrimal drainage system, therapeutically effective administration of insulin with alkylmaltosides, alkylsucrose and like agents by intranasal administration was tested.

Hypoglycemic Effects of Insulin Delivered Intranasally

Tetradecylmaltoside in combination with insulin also produced a drop in blood D-glucose levels when administered in the form of a drop intranasally as well as via a drop by the ocular route. A rat administered eyedrops containing 0.2% regular porcine insulin with 0.125%

tetradecylmaltoside produced a prompt and prominent drop in blood glucose levels which were then further decreased by administration of a nose drop containing the same concentration of insulin with 0.5% tetradecylmaltoside (Table 2). The protocol of the experiment was the same as described for ocular administration.

TABLE 2

Effect of Insulin Eye Drops Containing 0.125% Tetradecyl Maltoside and Nose Drops Containing 0.5% Tetradecyl Maltoside on Blood Glucose Values in Rats

Time (min)	Blood Glucose (mg/dl)
-20	319
-10	311
Eye drops added	
0	322
15	335
30	276
45	221
60	212
75	167
90	174
105	167
120	208
Nose Drops added	
135	129
150	74
165	76
180	68

Hyperglycemic Effects of Glucagon Delivered by the Ocular Route

Our previous studies demonstrated that insulin absorption from the eye was stimulated by saponin, BL-9 and Brij-78; the latter two reagents were ineffective at stimulating the absorption of glucagon from the eye, whereas saponin was effective. Glucagon absorption from the eye was measured in rats given eye drops containing various surfactants plus glucagon (30μg) (Eli Lilly, Indianapolis, Indiana) by monitoring an elevation in blood D-glucose levels. In these experiments, rats were anesthetized with sodium pentobarbital rather than xylazine/ketamine; this modification of the procedure resulted in basal blood glucose levels in the normoglycemic range and made it possible to readily monitor the hyperglycemic action of any glucagon absorbed from the eye. Once again, paired animals that received eye drops containing the surfactant agents only, or glucagon only, could be compared to animals receiving eye drops with surfactant agents and glucagon. When eyedrops containing 0.5% saponin plus glucagon were administered to rats, the level of D-glucose in blood rose significantly, but no such effect was observed with eye drops containing 0.5% BL-9 or 0.5% Brij-78 plus glucagon. Interestingly, when eye drops containing dodecylsucrose, decylmaltose or tridecylmaltose plus glucagon were administered to rats which had previously been treated with eyedrops containing these surfactant agents plus insulin, the glucagon was absorbed and blood D-glucose values were significantly increased (Table 3). This result confirms that certain alkylsaccharides can stimulate glucagon absorption from the eye, just as they stimulate insulin absorption. Additionally, the use of glucagon eyedrops to treat a hypoglycemic crisis is now possible provided that an appropriate surfactant agent is included in the eye drop formulation.

TABLE 3

Effect of Eye Drops Containing Insulin or Glucagon and 0.5% Decyl Maltoside, 0.5% Dodecyl Sucrose, or 0.5% Tridecyl Maltoside on Blood Glucose Values in Rats

	Surfactant Agent		
	Dodecyl Sucrose	Decyl Maltoside	Tridecyl Maltoside
Time (min)	Blood Glucose Concentration (mg/dl)		
-20	266	249	255
-10	305	287	307
Insulin eye drops added			
0	351	337	323
10	347	304	309
20	252	292	217
30	161	221	131
40	120	164	100
50	105	138	87
60	114	114	107
70	113	104	115
80	104	110	79
90	86	120	85
100	113	92	76
110	107	81	74
120	112	87	75
Glucagon eye drops added			
130	111	95	82
140	143	99	121
150	202	132	148
160	247	157	173
170	242	171	162
180	234	180	162
190	211	189	156

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

Although the present process has been described with reference to specific details of certain embodiments thereof, it is not intended that such details should be regarded as limitations upon the scope of the invention except as and to the extent that they are included in the accompanying claims.

What is claimed is:

1. A method of increasing absorption of a compound into the circulatory system of a subject comprising administering via the ocular, nasal, nasolacrimal, or inhalation route the compound and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide.

2. The method of Claim 1, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

3. The method of Claim 1, wherein the alkyl has from 9 to 24 carbons.

4. The method of Claim 1, wherein the alkyl glycoside further has a hydrophile-lipophile balance number in the range of about 10 to 20.

5. The method of Claim 1, wherein the linkage is selected from the group consisting of a glycosidic linkage, a thioglycosidic linkage, an amide linkage, a ureide linkage and an ester linkage.

6. The method of Claim 1, wherein the saccharide has a ring structure containing at least one sulfur atom.

7. The method of Claim 1, wherein the monosaccharide residues of the saccharide are linked by a sulfur atom.

8. The method of Claim 3, wherein the alkyl has from 9 to 14 carbon atoms.

9. The method of Claim 8, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

10. The method of Claim 1, wherein the compound is a protein or a peptide.

11. The method of Claim 10, wherein the protein or peptide drug is selected from the group consisting of insulin and glucagon.

12. The method of Claim 10, and further comprising administering a protease or peptidase inhibitor.

13. The method of Claim 1, wherein the compound is administered in a format selected from the group consisting of a drop, a spray, an aerosol and a sustained-release format.

14. A method of lowering blood glucose level in a subject comprising administering via the ocular, nasal, nasolacrimal or inhalation route, a blood glucose-reducing amount of a composition comprising insulin and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of insulin and lowering the level of blood glucose.

15. The method of Claim 14, wherein the alkyl glycoside has a concentration in the range of about 0.01% to 1.0%.

16. The method of Claim 14, wherein the alkyl has from 9 to 24 carbons.

17. The method of Claim 16, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

18. The method of Claim 14, wherein the lowering of the blood glucose level is sufficient to treat diabetes mellitus.

19. A method of raising blood glucose level in a subject comprising administering via the ocular, nasal, nasolacrimal or inhalation route a blood glucose-raising amount of a suitable composition comprising glucagon and an absorption increasing amount of a suitable nontoxic, nonionic alkyl glycoside

having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, thereby increasing the absorption of glucagon and raising the level of blood glucose.

20. The method of Claim 19, wherein the alkyl glycoside has a concentration in the range of 0.01% and 1.0%.

21. The method of Claim 19, wherein the alkyl has from 9 to 24 carbons.

22. The method of Claim 21, wherein the saccharide is selected from the group consisting of maltose, sucrose and glucose.

23. The method of Claim 19, wherein the raising of blood glucose level is sufficient to treat hypoglycemia.

24. A composition comprising (a) a nontoxic, nonionic alkyl glycoside having a hydrophobic alkyl joined by a linkage to a hydrophilic saccharide, in concentration in the range of 0.01% to 1.0%, capable of increasing absorption of a compound into the circulatory system of a patient and (b) an agent selected from the group consisting of insulin and glucagon.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	INTERNATIONAL JOURNAL OF PHARMACEUTICS, Volume 79, issued 1992, Murakami et al, "Assessment of Enhancing Ability of Medium-Chain Alkyl Saccharides as new Absorption Enhancers in Rat Rectum", pages 159-169.	1-24
X	JOURNAL OF CONTROLLED RELEASE, Volume 19, issued 1992, Hovgaard et al, "Insulin Stabilization and GI Absorption", pages 99-108.	1-24
X	CHEMICAL PHARMACOLOGICAL BULLETIN, Volume 39, No. 2, issued 1991, Ogiso et al, "Percutaneous Absorption of Elcatonin and Hypocalcemic Effect in Rat", pages 449-453.	1-24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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(54) Title: TOCOPHEROL COMPOSITIONS FOR DELIVERY OF BIOLOGICALLY ACTIVE AGENTS

(57) Abstract

The present invention provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions. Such compositions are particularly suitable for transmucosal, and especially intranasal or rectal administration, or administration via the oral cavity.

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Tocopherol compositions for delivery of biologically active agents

The present invention is directed to new pharmaceutical compositions for delivery of biologically active agents. More particularly, the invention concerns the use of a tocopherol or a derivative thereof to prepare compositions having low irritability suitable for administration to mucosal membranes and which may be used efficiently to administer drugs, which are substantially insoluble or only sparingly soluble in water.

For systemic action, drugs are normally administered by mouth and are then absorbed in the gastrointestinal tract. However, this mode of administration is not suitable in all circumstances, for example in the case of drugs which are metabolised to any significant degree by the liver or which are poorly absorbed. In other cases, the oral route may be impractical, for example in patients suffering from nausea or who are unconscious. Before surgery, oral administration is not advisable because of the risk of vomiting and in many cases, a more rapid effect may be required than can be achieved by the oral route.

In these circumstances the parenteral route is frequently used, most notably intravenous or intramuscular injection. However, whilst this provides a convenient way of achieving a strong and rapid systemic effect, it has a number of disadvantages including the requirement for sterile equipment and trained personnel. It is also unpleasant to the patient.

Moreover, in cases where a systemic effect is not required, local administration may be preferable, for example to avoid side effects, to reduce the dosage, or

simply to facilitate the administration.

Such problems have lead in recent years to an increasing interest in developing formulations for the topical administration of drugs, and in particular for topical administration involving absorption from mucous membranes.

Topical administration has the advantage that drugs may be administered readily and simply to achieve a systemic or dermal, regional or localised effect, as required. However, topical absorption of drugs through the skin can be slow, and in many cases transmucosal routes of delivery are preferred. Since it may be performed by untrained personnel and permits therapeutic plasma levels of drugs rapidly to be achieved, intranasal administration has received particular attention in this regard.

For topical delivery, biologically active drugs are normally administered in the form of aqueous solutions. However, many biologically active compounds are substantially insoluble or only sparingly soluble in water and in such cases, organic solvents are required to dissolve these agents. The problem here is that mucosal tissues are generally very sensitive and such solvents are frequently too irritant to be of clinical use. Thus for example, Lau and Slattery [Int. J. Pharm. 1989, p. 171-74] attempted to administer the benzodiazepines diazepam and lorazepam by dissolving these compounds in a range of solvents including: triacetin, DMSO, PEG 400, Cremophor EL, Lipal-9-LA, isopropyladipate and azone dodecyle-aza-cycloheptane-2-one. Whilst many of the solvents dissolved diazepam and lorazepam in the desired concentrations, when administered to the nose they were too irritant to be of use. Thus, Cremophor EL was found to be the least irritative for mucosal tissue, but nasal absorption using this solvent is rather slow and peak concentration is low relative to that found after iv. administration.

Triglycerides such as vegetable oils are generally non-irritant, but usually these oils are too poor as solvents to be of any use.

Attempts have been made to develop various other vehicles for transmucosal delivery of drugs, such as benzodiazepines, having limited water solubility. Thus, for example WO 86/04233 of Riker discloses a pharmaceutical composition wherein the drug (eg. diazepam) is dissolved in a mixture of propellant and co-solvent eg. glycerolphosphatide. The composition requires a pressurized system and at least one halogenated hydrocarbon aerosol propellant.

In US Patent 4,863,720 of Burghardt, a sublingual sprayable pharmaceutical preparation is disclosed, in which the active drug can be a benzodiazepine, optionally comprising polyethylene glycol (PEG) and requiring ethanol, di- and/or triglyceride of fatty acids and a pharmaceutically acceptable propellant gas.

US Patent 4,950,664 of Rugby-Darby describes the nasal administration of benzodiazepines in a pharmaceutically acceptable nasal carrier. The carrier may be a saline solution, an alcohol, a glycol, a glycol ether or mixtures thereof.

In PCT WO 91/16929 of Novo Nordisk, glycofurols or ethylene glycols are suggested as carriers for a variety of drugs, including benzodiazepines, which may be used on mucous membranes.

Another solution proposed to this problem, has been the use of micelles or liposomes, but these are frequently difficult to produce on a technical scale.

A further constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to administer more than about 0.1 ml per dose per nostril. Therefore, a great need exists for solvents, in which, on the one hand the solubility of the active drug is high, and which, on the other hand, are non-irritating to the

mucosa.

The aim of the present invention is to provide a solution to the above mentioned problems.

Tocopherols and their derivatives such as esters for example, are widely used in vitamin supplementation and as antioxidants in the food industry and in many pharmaceutical compositions. However, although in a few cases, a potential use in formulating pharmaceutical compositions has been reported, tocopherols and derivatives thereof have not generally previously been proposed as drug carriers.

Thus for example, European Patent Application No. 539,215 of Stafford-Miller suggests a possible use of Vitamin E and its derivatives as penetration enhancers in topical compositions.

WO 89/03689 of The Liposome Co., describes a liposome system based on acid derivatives of α-tocopherol in a low pH aqueous medium for delivery of drugs which tolerate, or require, acid conditions.

The present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues.

As will be described in more detail below, it has also been found that certain tocopherol derivatives are efficient, non-irritant emulsifiers for such drugs, when dissolved in a tocopherol-based solvent.

In one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions.

A further aspect of the invention provides a composition for delivery of a substantially insoluble or

sparingly soluble biologically active agent, comprising said agent dissolved in a tocopherol or a derivative thereof.

Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol (chemical name: 2,5,7,8-tetramethyl-2-(4',8',12'-trimethyldecyl)-6-chromanole) is the most active and widely distributed in nature, and has been the most widely studied. Other members of the class include beta, gamma, and delta tocopherols but these are not used in pure form in therapeutics, although they are present in foodstuffs. Tocopherols occur in a number of isomeric forms, the D and DL forms being most widely available.

As used herein, the term "tocopherol" includes all such natural and synthetic tocopherol or Vitamin E compounds.

The melting point of natural α-tocopherol is between 2.5 and 3.5°C. α-Tocopherol is a viscous oil at room temperature, is soluble in most organic solvents, but insoluble in water.

Although tocopherols are available naturally in foodstuffs and may be extracted from plants, α-tocopherol is now mainly produced synthetically.

Any of the forms or isomers of tocopherols and their derivatives, eg. esters may be used according to the present invention. Thus for example, α-tocopherol can be used as such or in the form of its esters such as α-tocopherol acetate, linoleate, nicotinate or hemi succinate-ester, many of which are available commercially.

A special article of commerce is called Tenox GT-2 and consists of 70% tocopherol of natural origin, which has been concentrated from vegetable oil. This oil has a mild odour and a gentle taste.

The compositions of the present invention are particularly suited for application to mucous membranes

in animals or humans, to deliver systemically substantially insoluble or sparingly soluble biologically active agents in a manner which ensures that a clinical effect is reached at least as rapidly as by conventional oral administration, with for instance tablets.

Thus, the compositions of the invention may be used for controlled release delivery of bioactive agents to achieve a beneficial or therapeutic effect over a prolonged period of time.

The compositions of the invention may also be applied to achieve a local effect, where desired, on the mucous membranes or the underlying tissue.

However, whilst the beneficial effects of the invention are particularly apparent in transmucosal delivery, the utility of the invention is not limited and compositions according to the invention may also be administered topically to all body surfaces, including the skin and all other epithelial or serosal surfaces, as well as parenterally or enterally, eg. as implants or by intravenous, intramuscular or subcutaneous injection, by infusion, or orally.

Transmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes for example in the nose, vagina, rectum, ears, eyes, oral cavity, lungs, genito-urinary tracts, and gastro-intestinal tract. Nasal, rectal and oral cavity administrations are particularly preferred.

The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent. However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application.

Viscosity can be reduced by addition of co-solvents such as ethanol, but this is less desired, since

solutions of this kind tend to be irritating to certain mucosal tissues.

Alternatively, the tocopherol solutions may be emulsified, to obtain formulations of lower viscosity. This may be achieved in known manner, by mixing the tocopherol-based "oil phase" containing the dissolved bioactive agent with an appropriate aqueous phase, eg. water, saline or buffer solutions.

Methods and appropriate aqueous media for obtaining emulsions are well known in the art and described in the literature. Emulsions according to the invention may be oil-in-water (O/W) or water-in-oil (W/O) emulsions. Generally speaking, O/W emulsions may be achieved when the oil phase contains up to about 70% lipids. W/O emulsions are formed when the oil phase exceeds c.a. 70%.

For nasal administration, due to the small administration volume required, it has generally been found that a high concentration of the oil (or lipid) phase is required. Emulsions with high lipid content are technically difficult to achieve and may be unstable. It may therefore be necessary to employ an emulsifier in order to form a stable emulsion. A wide range of emulsifiers are well known, both in the food and pharmaceutical arts, and are widely described in the literature. However, stability and viscosity may still be a problem, where very high contents of the oil phase are required. Moreover, some of the more widely available commercial emulsifiers, eg. phospholipids, polysorbates or various sorbitan esters of fatty acids may be irritating to the more sensitive mucosal tissues, such as those of the nose.

The inventors have surprisingly found however that tocopherol derivatives, particularly certain esters, may themselves form efficient, non-irritating emulsifiers to enable stable emulsions to be formed, even where high lipid levels are involved eg. about 50-70%. Particular

mention may be made in this regard of Vitamin E TPGS which is a water soluble derivative of Vitamin E and consists of α-tocopherol, which is esterified with succinic acid, the other acidic group of the latter being esterified with polyethylene glycol 1000. Vitamin E TPGS is an almost odourless waxy amphiphilic substance with a molecular weight about 1513. The melting point is about 36°C and its solubility in water is about 20%.

Stable emulsions may readily be achieved according to the invention using a range of tocopherols or derivative compounds as solvents, with Vitamin E TPGS as emulsifier, and any suitable aqueous medium.

A further aspect of the invention thus provides a composition suitable for delivery of substantially insoluble or sparingly soluble biologically active agents, comprising a tocopherol or a derivative thereof, and Vitamin E TPGS as emulsifier.

The tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers.

It has furthermore surprisingly been shown that various other solvents may be used in the emulsion system described above, without compromising the stability of the emulsion.

When the emulsion according to the present invention is of the oil-in-water type, it is desirable that the droplet size is as small as possible. It has been shown that by using systems according to the invention, for example, α-tocopherol, water, Vitamin E TPGS and bioactive agent, it is possible to form stable emulsions with an initial droplet size in the range 0.01-100 μm, preferably 0.01-50 μm, most preferably 0.1-20 μm.

The compositions which may be prepared according to the present invention, may contain any biologically

active agent which is insoluble or sparingly soluble in water, ie. with a solubility in water (w/v) which is 3% or less. For example such agents may include any bioactive agent which has less than 1% (w/v) solubility in water. Representative active agents from a range of different therapeutic groups are listed below, by way of exemplification.

Hormones and hormone-like substances of the steroid-group:

Corticosteroids such as cortisone, hydrocortisone, prednolone, prednisolone, triamcinolone acetonide, dexamethasone, flunisolide, budesonide, toxicorole pivalate, betametasone, beclomethasone dipropionate, fluticasone etc;

Sex-hormones such as: estradiol, progesterone, testosterone etc;

Antibiotics: Tetracyclines such as tetracycline, doxycycline, oxytetracycline, chloramphenicol etc; Macrolides such as erythromycin and derivatives, etc;

Antivirals: such as acyclovir, idoxuridine, tromantadine etc;

Antimycotics: Miconazole, ketoconazole, fluconazole, itraconazole, econazole, terconazole, griseofulvin, and polyenes such as amphotericin B or nystatine etc;

Anti-amoebics: Metronidazole, metronidazole benzoate and tinidazole etc;

Anti-inflammatory drugs: NSAID's such as indomethacin, ibuprofen, piroxicam, diclofenac etc;

Anti-allergics: Disodium cromoglycate etc;

Immunosuppressive agents: cyclosporins etc;

Coronary drugs: including vasodilators such as nitroglycerin, isosorbide dinitrate, Calcium-antagonists such as verapamile, nifedipine and diltiazem, Cardiac-glycosides such as digoxine.

Analgesics: eg. morphine, buprenorphine, etc;

Local anaesthetics: eg. lidocaine, etc;

Anxiolytics, sedatives & hypnotics: diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lormetazepam, brotizolam, clobazam, clonazepam, lorazepam, oxazepam, buspirone, etc;

Migraine relieving agents: sumatriptan, ergotamines and derivatives etc;

Drugs against motion sickness: eg. cinnarizine, anti-histamines, etc;

Anti-emetics: eg. ondansetron, tropisetron, granisetrone, metoclopramide, etc.

Others: such as disulfiram, vitamin K, etc.

The emulsions according to the present invention are especially suitable for nasal application because of their low index of irritability and are therefore particularly well suited to the delivery of biologically active drugs influencing the central nervous system (CNS).

Other biologically active agents which may be used include peptides, hormones, etc. The active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w).

Generally speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative solvent. The emulsion used in compositions of the invention may contain 1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w).

As mentioned above, the emulsions of the present invention can be prepared by conventional means, by heating the oil and aqueous phases separately, and then mixing the two phases. The active ingredient can be dissolved in the lipid fraction of the tocopherol solvent and other solvents may be added if desired. The emulsifier, eg. Vitamin E TPGS, and optionally other emulsifiers, can be added to either the oil and/or the water phase. The water phase is then vigorously mixed with the oil phase. Mixing, eg. stirring may be continued as required eg. for up to 2 hours. Depending on the viscosity of the emulsion, a magnetic stirrer, a low shear mixer or the like can be used. If necessary, the emulsion can be processed by a low shear mixer and a high pressure homogenizer to achieve the desired droplet size. The formulations may be inspected microscopically to measure the droplet size and to be sure that no precipitation has taken place. The type of emulsion formed may be determined readily by a colour test using an oil- and/or water-soluble dye. To confirm the result, it may be examined whether the emulsion is easy to wash off with water or not. An O/W emulsion is coloured with the water-soluble dye and is very easy to wash off with water. A W/O emulsion is coloured with

the oil-soluble dye and is very difficult to wash off with water.

In a further aspect, the present invention thus provides a method of preparing a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising dissolving said agent in an amount of a tocopherol or a derivative thereof, sufficient to dissolve said agent.

In a preferred aspect, the method of the invention further comprises forming an emulsion of said tocopherol/biologically active agent solution, by mixing with an aqueous phase, optionally in the presence of an emulsifier, preferably vitamin E TPGS.

The compositions of the invention may take any of the conventional pharmaceutical forms known in the art, and may be formulated in conventional manner, optionally with one or more pharmaceutically acceptable carriers or excipients. Thus for example the compositions may take the form of ointments, creams, solutions, salves, emulsions, lotions, liniments, aerosols, sprays, drops, pessaries, suppositories, tablets, capsules or lozenges.

In a still further aspect, the present invention provides the use of a tocopherol or a derivative thereof for the preparation of a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent to a human or non-human animal subject.

Alternatively viewed, the invention can be seen to provide a method of treatment of a human or non-human animal subject by delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising administering to said subject a composition of the invention as hereinbefore defined.

The formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added:

Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin.

To optimize the stability of the emulsions, it may be appropriate to add surfactants such as Vitamin E TPGS poloxamers (eg. Pluronic®), cetearyl glucoside, polysorbates or sorbitan esters of fatty acids, or any of the other surfactants well known in the art, or other stabilisers such as xanthan gum, or propylene glycol alginate.

It is also possible to enhance the bioadhesive properties of the formulations according to the present invention by addition of bioadhesive polymers such as:

- polyacrylic polymers such as carbomer and carbomer derivatives, eg. Polycarbophil or Carbopol etc;
- cellulose derivatives such as hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropyl-cellulose or sodium carboxymethylcellulose etc;
- natural polymers like gelatin, sodium alginate, pectin etc;
- more generally, any physiologically acceptable polymer showing bioadhesive characteristics may be used.

To ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives such as benzalkonium chloride, sodium edetate, sorbic acid, potassium sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable.

The invention will now be described in more detail in the following non-limiting Examples, with reference to the drawings in which:

Figure 1 is a graph showing mean serum concentrations (ng/ml) against time (minutes) after intranasal administration of 2.5 mg diazepam

(Formulation C) -▲- Desmethyldiazepam -■- Diazepam;

Figure 2 is a graph showing mean serum concentrations (ng/ml) against time (minutes) after oral administration of 2.0 mg diazepam (Formulation D) -■- Desmethyldiazepam -♦- Diazepam;

EXAMPLES

As already mentioned, administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 µl). The first example has a very high concentration of diazepam, and it is possible to administrate diazepam to the nose and to achieve a rapid clinical effect.

Example 1

A diazepam nosedrop preparation is made as follows: (100 g)

5 g of diazepam is mixed with 44 g of Tenox GT2, and 22 g of triacetin, and 5 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.45 g of Pluronic F-68 (poloxamer 188) and 0.01 g of benzalkonium chloride are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed into the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion was a pale yellow o/w emulsion, where the mean droplet size was about 1-2 µm.

This formulation (1) was tested in 8 rabbits in a randomized cross-over study compared with a commercially available diazepam formulation, Stesolid® 5mg/ml for

injection, (2).

Formulation 1 was given intranasally (i.n.) with a Eppendorf Multipette ® 4780. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits receive a volume that equals 2 mg diazepam, 40µl of formulation 1. After each administration the actual dose received is estimated by visual inspection of the pipette tip and the rabbit nostrils. Only applications volumes estimated to 80% are accepted.

Formulation 2 was given as an ear-vein infusion during ½ minute. The rabbits received 0.4 ml Stesolid® 5mg/ml (equals 2 mg diazepam). The rabbits were placed in a supine position for half a minute to attain the same experimental conditions as for i.n. dosing.

The rabbits were then tested with respect to pharmacodynamic response in the following way:

- Hind legs to one side and the rabbit must stay in this position even after a firm tip with a finger on the hip. The test is immediately repeated with both legs placed on the other side.

The rabbits were tested approximately once per minute until positive pharmacodynamic response, and thereafter tested every 2 minutes. Total test period is 20 minutes. The same person has dosed and tested all the rabbits in the present study.

The time to pharmacodynamic response is 4.4 minutes (mean, n=8) using formulation 1 and 1.6 minutes (mean, n=8) using formulation 2.

Example 2

A diazepam nosedrop preparation is made as follows: (100 g)

5 g of diazepam is mixed with 45.4 g of Tenox GT2, and 22.7 g of triacetin, and 15 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.45 g of Pluronic F-68 (poloxamer 188) and 0.01 g of benzalkonium chloride are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a clear orange w/o emulsion.

A less concentrated formulation of diazepam is required for the rectal administration, but still it can be very difficult to find an acceptable vehicle with low irritation.

Example 3

A diazepam enema preparation is made as follows: (100 g)

1 g of diazepam is mixed with 40 g of α-tocopherol, and 15 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. 5 g of ethanol is added to the oil phase immediately before mixing with the water phase. To the water phase, 2.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the

magnetic stirrer. The emulsion is a white o/w emulsion.

Cinnarizine is used for motion sickness. Like diazepam, the drug has a very low water solubility. It will be a great advantage if the patient can administer the drug easily and have a rapid effect.

Example 4

A cinnarizine nosedrop formulation is made as follows: (100 g)

5 g of cinnarizine is mixed with 64 g of α-tocopherol, and 8 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a white o/w emulsion.

Miconazole is used for the local treatment of infections caused by fungi. The next two formulations show formulations for use in the oral cavity and the vagina.

Example 5

A miconazole preparation for the oral cavity is made as follows: (100 g)

20 g of miconazole is mixed with 58.8 g of α-tocopherol, and 13 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. 5 g of ethanol is added to the oil phase immediately before

mixing with the water phase. To the water phase, 1.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is added very slowly to the oil phase under vigorously mixing by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a yellow to brown w/o emulsion.

Example 6

A miconazole vaginal cream is made as follows: (100 g)

5 g of miconazole is mixed with 38 g of α-tocopherol, and 38 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 2.5 g of Pluronic F-681 (poloxamer 188) and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a low shear mixer. Thereafter, the emulsion is cooled to room temperature still mixed by the low shear mixer. The emulsion is a glossy, beige w/o emulsion. The emulsion has a consistency as an ointment and is very sticky.

The following Examples are divided into three subsections covering 1) Solubility; 2) Compositions and 3) Pharmacology/toxicology.

Example 7

SOLUBILITY

For the following, non-limiting, sparingly soluble drugs in water, the solubility in α-tocopherol and sesame oil are listed in Table 1:

Sesame oil was chosen as the reference, because it is a very commonly used and well tolerated vegetable oil. The solubilities in sesame oil and α-tocopherol were investigated by visual inspection of the saturation point.

TABLE 1.

Active agent	g drug in 100 g of α-tocopherol	g drug in 100 g of sesame oil
Diazepam	12	2
Alprazolam	4 < x < 6	< 0.2
Midazolam	> 13	1 < x < 2
Cinnarizine	11 < x < 18	2 < x < 4
Metoclopramide	2 < x < 4	< 2
Budesonide	1 < x < 2	< 0.1
Miconazole	60	5 < x < 10
Metronidazole benzoate	12 < x < 14	< 2
Lidocaine	> 45	> 18
Disulfiram	5	3 < x < 4
Progesterone	> 30	2 < x < 4
Testosterone	16 < x < 18	0.6 < x < 1

All the investigated biologically active agents show a surprisingly high solubility in α-tocopherol.

COMPOSITIONS

In the following, non-limiting Examples, several drugs are shown in a number of different types of

administration forms.

The emulsions were prepared as follows:

The oil and the water phase were heated slowly until homogeneous phases were achieved.
The warm water phase was vigorously mixed into the oil phase. Then, the emulsion was slowly cooled to room temperature while stirring. The emulsion may be homogenized.

The preparation of the solutions was made as simple solution, in which the preparations were stirred until the drug was completely dissolved.

As already mentioned, administration of drugs with low water solubility to the nose is very difficult, because of the limited acceptable volume for the nose (about 100 µl). The following examples have very high concentration of diazepam, so it was possible to administer diazepam to the nose and to get a fast clinical effect.

Example 8

An O/W emulsion of diazepam as a nosedrop (100g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	59.000 g
	Vitamin E TPGS.	5.000 g
Water phase:	Disodium edetate	0.050 g
	Potassium sorbate	0.200 g
	Xanthan gum	0.025 g
	purified water to	100.000 g

The water phase was adjusted to pH 4.7 by 1N HCl.

Example 9

An O/W emulsion of diazepam as nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	58.000 g
	Sorbitan trioleate	0.500 g
	Fractionated coconut oil	5.000 g
Water phase:	Potassium sorbate	0.200 g
	Poloxamer 188	1.000 g
	Xanthan gum	0.030 g
	Polysorbate 80	0.500 g
	Purified water to	100.000 g.

The water phase was adjusted to pH 4.5 by 2N HCl.

Example 10:

An O/W emulsion of diazepam as nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	50.000 g
	Triacetin	10.000 g
	Cetearyl glucoside	2.000 g
	Methylparahydroxybenzoate (MPHB)	0.080 g
	Propylparahydroxybenzoate (MPHB)	0.040 g
Water phase:	Poloxamer 188	3.000 g
	Xanthan gum	0.030 g
	Purified water to	100.000 g.

Example 11:

A solution of diazepam, eg. as nosedrop, (25 g):

	Diazepam	1.250 g

α-Tocopherol	10.000 g
Triacetin	13.750 g

A less concentrated formulation of diazepam is needed for the rectal administration, but still it can be very difficult to find an acceptable vehicle with low irritation.

Example 12:

A solution of cinnarizine, eg. as drops for administration to the oral cavity (25g):

Cinnarizine	1.250 g
α-tocopherol	17.500 g
ethanol	1.250 g
fractionated coconut oil	5.00 g

A study has shown, that cinnarizine has a higher oral bioavailability, if it is dissolved in a vehicle before administration, [J. Pharm. Sci., vol 76, no. 4, p. 286-288, 1987], an example of such a vehicle could be α-tocopherol.

Example 13:

A solution of cinnarizine, eg. for oral administration in capsules, (25 g):

Cinnarizine	0.750 g
α-Tocopherol	24.250 g

Miconazole is used locally for treatment of infections caused by fungi. The following examples show formulations for the oral cavity and the vagina.

Example 14

A solution of miconazole e. g. as drops for administration to the oral cavity (25g).

Miconazole	6.250 g
α-Tocopherol	16.875 g
Ethanol	1.875 g

Budesonide is a very potential drug, and is used as a local corticoid, e. g. for rhinitis.

Example 15

An O/W emulsion of budesonide as nosedrop or nasal spray (50g).

Oily phase:	Budesonide	0.025 g
	α-tocopherol	12.500 g
	Vitamin E TPGS	5.000 g
Water phase:	Potassium sorbate	0.100 g
	Xanthan gum	0.020 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Example 16

A solution of budesonide as nosedrop (25g).

Budesonide	0.025 g
α-tocopherol	10.000 g
Sesame oil	14.975 g

Alprazolam is a benzodiazepine which is used for the treatment of e. g. anxiety, therefore a rapid effect is

desired in a easy way.

Example 17

An o/w emulsion of alprazolam as nosedrop or nasal spray (100g).

Oily phase:	Alprazolam	0.500 g
	α-tocopherol	20.000 g
	Vitamin E TPGS	10.00 g
Water phase:	Potassium sorbate	0.200 g
	Xanthan gum	0.050 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Example 18

A solution of alprazolam, e. g. as drops for administration in the oral cavity (25g).

alprazolam	0.125 g
α-tocopherol	13.750 g
sesame oil	11.125 g

Midazolam is a benzodiazepine tranquiliser with a sedative effect e.g., and is used for the treatment of anxiety and tension states, and as a sedative and for premedication. Midazolam has a very high first-pass effect after oral administration.

Example 19

An O/W emulsion of midazolam as nosedrop (50g).

Oily phase:	Midazolam	1.250 g

	α-Tocopherol	29.500 g
	Vitamin E TPGS	2.500 g
Water phase:	Potassium sorbate	0.100 g
	Xanthan gum	0.013 g
	Poloxamer 188	0.750 g
	Disodium edetate	0.025 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Disulfiram is used in the treatment of chronic alcoholism.

Example 20

A solution of disulfiram, e. g. as an oral solution or for oral administration by capsules (25g).

	Disulfiram	1.125 g
	α-Tocopherol	23.875 g

Example 21

An O/W emulsion of lidocaine for treatment of e.g. insect bites (100 g).

Oily phase:	Lidocaine	5.000 g
	α-Tocopherol	40.000 g
	Cetearyl glucoside	4.000 g
	MPHB	0.080 g
	PPHB	0.040 g
Water phase:	Poloxamer 188	3.000 g
	Xanthan gum	0.030 g
	Purified water to	100.000 g

Example 22

PHARMACOLOGY:

Studies on rabbits:

Preparations containing CNS active and muscle relaxing drugs such as diazepam and midazolam were tested in a pharmacodynamic model in rabbits.

The model consists of the following tests:

Test 1:
- Hind legs to one side and the rabbit must stay in this position even after a firm tip with a finger on the hip. The test is immediately repeated with both legs placed on the other side.

Test 2:
- Hind legs stretched out backwards and the rabbit must stay in this position even after a firm tip with a finger on the hip.

Test 3:
- The rabbit must stay in a supine position, when placed in such a position.

After administration of the formulations (i.n., oral or i.v.) the rabbits were exposed to the three tests approximately once per minute until positive pharmacodynamic response, and thereafter every 2 minutes. The total test period was 20 minutes after i.n. and i.v. administration and 30 minutes after peroral administration.

The time elapsed from administration until the first positive response in test 1 was used to compare the

onset of action of the different formulations.

STUDY 1

This pharmacodynamic study compared the nasal formulation of Example 8 (C) containing 5% of diazepam to a commercially available diazepam formulation, Stesolid® 2mg tablet, Dumex (D). The study was run in 8 rabbits in a randomized cross-over study. The rabbits were tested for pharmacodynamic response as described previously, but the test period was 30 minutes after peroral administration to be sure to obtain a pharmacodynamic effect.

Formulation C was given intranasally (i.n.) with a laboratory pipette. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits received a volume equivalent to 2.5 mg diazepam. After each administration the actual dose received is calculated by subtraction of the weight of the pipette before and after administration. Only applications determined to 80% (2 mg diazepam) were accepted.

Formulation D was given as an oral administration using a stomach pump. The tablet was dissolved in 5 ml water immediately before administration. The tube was rinsed with 10 ml water.

The time to onset of pharmacodynamic response in test 1 is 4.5 minutes (median, n=7) using formulation C and 19.4 minutes (median, n=8) using formulation D.

STUDY 2

This pharmacokinetic study compared the nasal formulation of Example 8 (C) containing 5% of diazepam

to a commercially available diazepam formulation, Stesolid® 2mg tablet, Dumex (D). The study was run in 8 rabbits in a randomized cross-over study.

Formulation C was given intranasally (i.n.) as described in study 1.

Formulation D was given by oral administration as described in study 1 using a stomach pump.

Blood samples from the ear-vein were taken before administration (time = 0) and at 2, 5, 10, 15, 30, 45, 60, 75, 90, 120, 180 and 240 minutes.

Serum was analyzed for diazepam and the metabolite, desmethyldiazepam using Gas Chromatografy (GC). The limit of detection was 5ng/ml for both substances.

The pharmacokinetic parameters found for diazepam were t_{max} = 23 minutes (median, n=6), C_{max} = 68.2 ng/ml (median, n=6) after administration of formulation C and t_{max} = 45 minutes (median, n=6), C_{max} = 9.7 ng/ml (median, n=6) after administration of formulation D.

Figures 1 and 2 illustrate the mean serum concentrations of diazepam and desmethyldiazepam after administration of formulations C and D.

STUDY 3

This pharmacodynamic study compared Example 8(C) containing 5% of diazepam with Example 19 (E) containing 2.5% of midazolam. The study was using 6 rabbits.

Formulations C and E were given intranasally (i.n.) with a laboratory pipette. Each rabbit was held in a supine position during and one minute after i.n. dosing in one

nostril. The rabbits received a volume equivalent to 2.5 mg diazepam or 1.25 mg midazolam, respectively.

After each administration the actual dose received was calculated by subtraction of the weight of the pipette before and after administration. Only doses equivalent to 80% were accepted.

The time to onset of pharmacodynamic response in test 1 was 3.1 minutes (median, n=6) using formulation C containing diazepam and 2.5 minutes (median, n=6) using formulation E containing midazolam.

Example 23

TOXICOLOGY:

Local irritancy in humans:

The investigation was carried out in order to estimate irritation after nasal application of 10 mg of diazepam; 100 mg of the preparation from Example 8 in each nostril.

6 volunteers, 3 male and 3 female participated in the trial.

The investigator inspected both nostrils macroscopically for local irritation at the following times: Immediately after medication, at 30 minutes, and 1, 2, 4, and 6 hours.

In one volunteer the macroscopic inspection showed light blush of both nostrils immediately after medication. None of the six volunteers had local irritation of the nostrils 30 minutes after application, see table 2.

CONCLUSION

The total results of the trial have shown that preparation of Example 8 does not cause unacceptable irritation of the nostrils.

Table 2.

Individual local irritation of the nostrils after intranasal administration of 10 mg diazepam, (Example 8)

Volunteer no.	Local irritation											
	Immediately after medication		30 min		1 h		2 h		4 h		6 h	
	R	L	R	L	R	L	R	L	R	L	R	L
1	-	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-	-	-
4	Light blush	Light blush	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	-	-	-	-

R: right nostril
L: left nostril

Claims

1. Use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble or sparingly soluble biologically active agents.

2. Use as claimed in claim 1 in the manufacture of pharmaceutical compositions.

3. A composition for delivery of a substantially insoluble or sparingly soluble biologically active agent, comprising said agent dissolved in a tocopherol or a derivative thereof.

4. A composition as claimed in claim 3 wherein the tocopherol is α-tocopherol or an ester thereof.

5. A composition as claimed in claim 3 or claim 4 in a form suitable for transmucosal, topical, enteral or parenteral application.

6. A composition as claimed in claim 5, in a form suitable for intranasal, vaginal or rectal application or for administration via the oral cavity.

7. A composition as claimed in any one of claims 1 to 6 in the form of an emulsion.

8. A composition as claimed in claim 7, additionally comprising an emulsifying agent.

9. A composition as claimed in claim 8, wherein the emulsifying agent is a tocopherol derivative.

10. A composition as claimed in claim 9, wherein the emulsifying agent is a tocopherol ester.

11. A composition as claimed in claim 10, wherein the emulsifying agent is Vitamin E TPGS.

12. A composition suitable for delivery of substantially insoluble or sparingly soluble biologically active agents, comprising a tocopherol or a derivative thereof, and an emulsifier.

13. A composition as claimed in claim 12, wherein the emulsifier is Vitamin E TPGS.

14. A composition as claimed in any of claims 3 to 13, further comprising one or more additional components selected from solvents, surfactants, stabilizers, bioadhesive polymers, preservatives, and odour- or taste-masking agents.

15. A composition as claimed in any one of claims 3 to 14, wherein the biologically active agent is a benzodiazepine or an anti-mycotic.

16. A composition as claimed in claim 15, wherein the biologically active agent is diazepam, midazolam or miconazole.

17. A composition as claimed in any one of claims 3 to 16, wherein the content of the tocopherol or derivative thereof is from 1 to 99.99% (w/w).

18. A composition as claimed in claim 17, wherein the content of the tocopherol or derivative thereof is from 20 to 99.99% (w/w).

19. A composition as claimed in claim 17, wherein the content of the tocopherol or derivative thereof is from 40 to 99.99% (w/w).

20. A method of preparing a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising dissolving said agent in an amount of a tocopherol or a derivative thereof, sufficient to dissolve said agent.

21. A method as claimed in claim 20, further comprising forming an emulsion of said tocopherol/biologically active agent solution, by mixing with an aqueous phase.

22. A method as claimed in claim 21, wherein the emulsification step is performed in the presence of an emulsifying agent.

23. A method as claimed in claim 22, wherein the emulsifying agent is Vitamin E TPGS.

24. Use of a tocopherol or a derivative thereof for the preparation of a composition as claimed in any one of claims 3 to 18.

25. A method of treatment of a human or non-human animal subject by delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising administering to said subject a composition as defined any one of claims 3 to 11 or 14 to 18.

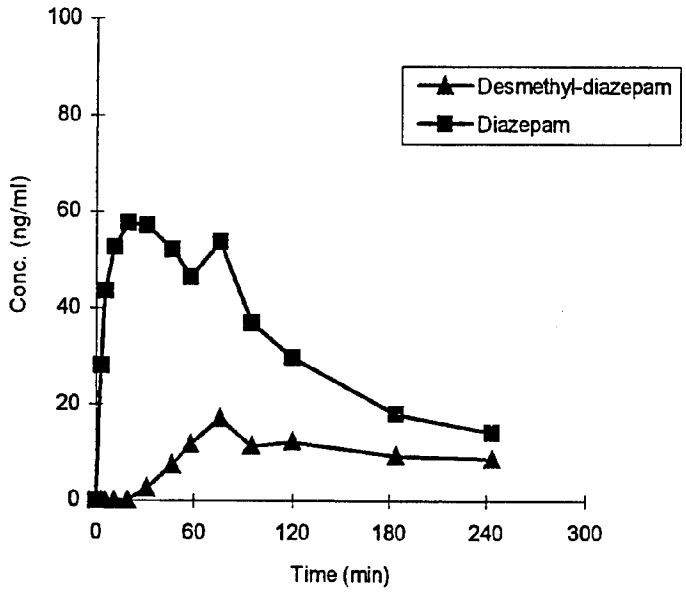
100
80
60
40
20
0
Conc. (ng/ml)
0
60
120
180
240
300
Time (min)
Desmethyl-diazepam
Diazepam

Fig. 1

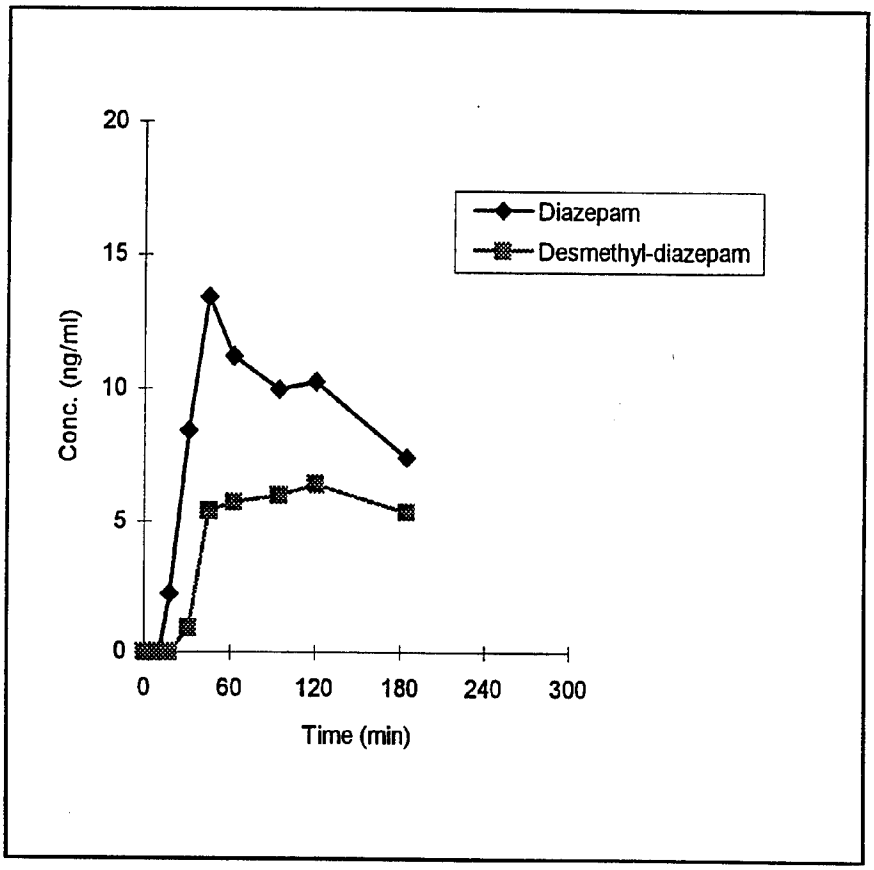
20
15
10
5
0
Conc. (ng/ml)
0
60
120
180
240
300
Time (min)
Diazepam
Desmethyl-diazepam

Fig. 2

INTERNATIONAL SEARCH REPORT

Internat l Application No
PCT/EP 95/01835

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO,A,89 03689 (THE LIPOSOME COMPANY) 5 May 1989 see the whole document ---	1-14, 17-25 15
X	WO,A,92 13531 (EASTMAN KODAK COMPANY) 20 August 1992 see the whole document ---	1-14, 17-25
P,Y	DATABASE WPI Section Ch, Week 9437, Derwent Publications Ltd., London, GB; Class B02, AN 94-302691 & WO,A,94 20143 (FUJISAWA PHARM CO LTD) 15 September 1994 see abstract -----	15

☐ Further documents are listed in the continuation of box C.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatı Application No
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8903689	05-05-89	CA-A-	1333360	06-12-94
		DE-A-	3883246	16-09-93
		DE-T-	3883246	02-12-93
		EP-A,B	0382779	22-08-90
		JP-T-	3500651	14-02-91
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		CA-A-	2079325	12-08-92
		EP-A-	0524308	27-01-93

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(54) Title: TOPICAL ACICLOVIR FORMULATIONS

(57) Abstract

Described are topical formulations for the administration of aciclovir. These formulations can be used in the preventive and therapeutic treatment of infections from *Herpes virus* and are characterised by the presence of sucrose esters as promoters of active ingredient absorption.

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TOPICAL ACICLOVIR FORMULATIONS

Field of invention

Object of the present invention are topical formulations useful in the treatment of viral infections of the skin and mucous membranes, which contain the active ingredient 9-(2-hydroxymethoxymethyl)guanine, known as aciclovir, and are characterised by the inclusion of sucrose esters as absorption promoters.

Previous art

Aciclovir, its salts and the esters derived from it, have long been known for their antiviral action, as extensively described in the British patent GB 1,523,865.

Several topical formulations containing aciclovir have been described in the previous art. In particular, patent EP 44,543 describes formulations of aciclovir in oil/water mixtures which contain at least 30% of a polyvalent alcohol miscible with water, and patent application WO 97/34,607 describes topical oil-in-water formulations containing at least 10% diethylene glycol monoethylether known by the commercial name Transcutol®.

The present invention relates to topical formulations for the administration of aciclovir, which contain a sucroester as an element promoting absorption of the active ingredient through the skin.

The sucroesters are sucrose esters obtained by reaction of sucrose with one or more fatty acids having a linear chain with an even number of carbon atoms ranging from 12 to 18, are widely used and have many applications in the pharmaceutical and food fields. These esters are commercially known by the name SUCROESTER® (Gattefossé S.A. - Saint Priest - France) or CRODESTA® (Croda Surfactants Ltd. - Goole - UK).

Sucroesters belong to the class of non-ionic surfactants, are endowed with good stability and do not undergo - after preparation of the finished products - any hydrolytic processes of a chemical or enzymatic nature. Being made up of a sugar with fatty acids, they are absolutely harmless compounds and not at all aggressive against the skin, thus being an excipient capable of meeting all of the cosmetic requirements of a topical preparation.

Description of invention

It has now been found, and it is an object of the present invention, that, when a sucrose ester is added to the ingredients of topical formulations for the administration of aciclovir via emulsified mixtures of lipids in water, these formulations become particularly effective in improving absorption and tolerance of aciclovir compared to both the commercial formulations and those described in the previous art.

The topical formulations which are an object of the invention comprise: from 0.1% to 10% w/w of aciclovir or any of its salts or any of its esters; from 0.1% to 40% w/w of a sucrose ester; from 20% to 40% w/w of water, incorporated in a mixture with an oily phase.

The lipidic component of the emulsion is made up of known materials and is emulsified with the aqueous component in accordance with processes known in the art. One or more emulsifying agents can be added to the ingredient of the lipidic phase, which can be a fat or an oil, to make the emulsion stable in time.

The ingredients of the oily phase are chosen predominantly on the basis of the cosmetic characteristics desired in the finished products since the solubility of aciclovir in oils and fats is confined to a limited range.

Example of the lipidic materials which can be used are linear or branched mono- or dialkylesters of esters of fatty acids such as, for example, isopropylmyristate and isopropylpalmitate, mixtures of cetyl and stearyl alcohol known by the commercial name Crodamol®, high-molecular-weight lipids such as white paraffin or liquid paraffin and other mineral oils.

Examples of emulsifiers and emulsion stabilising agents include cetyl alcohol, sodium lauryl sulphate, stearyl alcohol, polyoxyethylene alkylesters such as Brij® 72 and 721 and polyoxystearyl esters such as Steareth® 2 and 21.

In addition to water, the aqueous phase of the emulsion can also contain other ingredients such as glycerine and glycol. However, the amount of these ingredients is preferably lower than 30%.

Based on what described in the previous art (EP 044 543), an amount higher than 30% of polyalcohols such as glycerine and glycol is normally added to the

aqueous phase to be used for the emulsion in order to increase aciclovir solubility in the phase.

However, the presence of an amount of propylene glycol in amounts higher than 30% can cause poor-skin-tolerance reactions due to the dehydrating action peculiar to this glycol. This is particularly important when the topical preparation is to be applied onto areas of skin which is no longer sound, as is the case of lesions caused by *Herpes labialis*.

It has now been found, and it is an object of the invention, that the addition of esters of sucrose to the formulation ingredients allows these amounts of glycol in the formulation to be reduced far below 30%, at the same time increasing the therapeutic and cosmetic efficacy of the formulation thanks to the ability of sucroesters to act as promoters of the absorption of the active ingredient through the skin.

The sucroesters being substances which result from the combination of sucrose with normal food fats and, in particular, myristic acid, oleic acid, palmitic acid or stearic acid, they have a molecular structure with amphiphilic characteristics, both lipophilic and hydrophilic. These amphiphilic characteristics can be appropriately modulated using the sucroester most suitable for the various absorption requirements. In fact, the higher the number of sugar hydroxyls substituted by fatty acids, the more the lipophilic characteristics of sucroesters increase, and vice versa.

Thanks to the contemporary presence of hydrophilic and lipophilic groups in the molecule and the resulting ability of distribution in the skin layers with lipophilic characteristics (the horny layer) and the layers with hydrophilic characteristics (the dermis), the sucroesters are thus capable of acting as absorption promoters, helping permeation of substances which would otherwise be poorly absorbed.

Among the various types of sucroesters, the monoesters are particularly useful in helping formation of oil-in-water emulsions. The sucrose monoesters are scarcely soluble in cold water, while they are soluble in hot water, ethyl alcohol and acetone. Their amphiphilic characteristics are represented by HLB (Hydrophilic Lypophilic Balance) values which can range from 7 to 14. For example: sucrose

monopalmitate (HLB 14), sucrose mono/distearate (HLB 11), sucrose distearate (HLB 7).

For a typical implementation of the present invention, sucrose monopalmitate is preferred among the monoesters for its high HLB value which, in addition to helping formation of an oil-in-water emulsion, contributes to stabilising it.

The preferred composition ratios (w/w) for a formulation suitable for the administration of aciclovir according to the present invention include: sucrose monopalmitate 15%, aciclovir 5%, cetostearyl alcohol 3-10%, propylene glycol 5-30%, mineral oil 5-15%, Steareth® 21 2-5%, sodium lauryl sulphate 0.1-1%, purified water as needed to reach 100%.

Optionally, although it has been found that the addition of these preservatives is not strictly necessary for storage in time of the topical formulations described in the present invention, one or more preservatives such as, for example, p-oxybenzoates, sodium benzoate, benzalkonium chloride and the like, can be added to these formulations as a precautionary complement in case of long-term storage.

A process to prepare the above topical formulations, too, is an integrant part of the invention. This process consists in stirring aciclovir or any of its salts or esters, a sucrose ester, the active ingredients, the excipients making up the oily phase and those making up the aqueous phase in a suitable emulsifier, up to formation of an oil/water emulsion.

The method of formulating the emulsion can vary depending on the amount and nature of the ingredients and follows the processes known in emulsion formation described, for example, in A. R. Gennaro: "Remington: The Science and Practice of Pharmacy", 19th Ed., Ch. 21, 282-291, Mack Publ. Co. (1995).

The preferred method is that of hot(70°C)-suspending aciclovir in the aqueous phase together with the sucrose esters, sodium lauryl sulphate, propylene glycol and to finally add this mixture to the ingredients of the fatty phase kept in a melted state at a temperature of about 60 to 70°C. The emulsion forms after the addition of the aqueous phase to the vigorously-stirred oily phase.

The preferred apparatus for formation of the emulsion is a turboemulsifier, which

allows vigorous stirring under vacuum, thus avoiding incorporation of air and the consequent formation of bubbles in the final cream.

The topical formulation prepared in accordance with the invention can be used for the treatment or prevention of viral infections caused by *Herpes zoster, Herpes varicella* and type-1 or 2 *Herpes simplex*. In particular, it was found to be useful in cases of *Herpes labialis*. The formulation should be applied to the skin 1 to 6 times daily, preferably from 3 to 5 times.

It is also obvious that the formulations referred to in the present invention, even though they are conceived in particular for the administration of aciclovir and its derivatives, can easily adapt to the topical administration of other antiviral analogues of aciclovir such as, for example, famciclovir, penciclovir, valaciclovir and the like, or their synergetic combinations with other antiviral agents such as derivatives of guanine, vidarabine, citarabine and the like.

Provided below are some examples which are only meant to better describe the subject invention and show its advantages and applicability, but without being a limitation of same.

EXAMPLE 1

Aciclovir	5 %
Sucrose monopalmitate	15%
Cetostearyl alcohol	6.75%
Propylene glycol	20%
Sodium lauryl sulphate	0.75%
Poloxamer 407	1%
Mineral oil	5%
Stringy petrolatum	12.5%
Water	34%

An oily phase was prepared by melting a mixture made up of stringy petrolatum, mineral oil and cetostearyl alcohol at 60°C. An aqueous solution made up of sodium lauryl sulphate, Poloxamer® 407, propylene glycol, sucrose monopalmitate

and water in which micronised aciclovir had been hot(60°C)-dispersed was slowly added to the hot-stirred oily phase, and allowed to cool to ambient temperature. The cream which formed was filled into 10-gram aluminium tubes internally coated with epoxy resin.

EXAMPLE 2

Micronised aciclovir	5 %
Sucrose distearate	20%
Cetostearyl alcohol	6.75%
Propylene glycol	20%
Sodium lauryl sulphate	0.75%
Poloxamer® 407	1%
Mineral oil	5%
Stringy petrolatum	12.5%
Water q.s. to	100%

An oily phase was prepared by melting at 60°C made up of stringy petrolatum, mineral oil and cetostearyl alcohol. An aqueous phase made up of sodium lauryl sulphate, Poloxamer® 407, propylene glycol, sucrose distearate and water in which micronised aciclovir had been hot(70°C)-suspended, was added to the oily phase. Addition was slow with continuous hot-stirring, and cooling to ambient temperature was allowed. The cream which formed was filled into 5-gram aluminium tubes internally coated with epoxy resin.

EXAMPLE 3

Aciclovir	5%
Sucrose mono/distearate	15%
Stearyl alcohol	5%
Cetyl alcohol	5%
Propylene glycol	15%
Brij® 721	2,5%
Brij® 72	2,5%
Mineral oil	5%
Stringy petrolatum	12.5%
Water q.s. to	100%

An oily phase made up of stringy petrolatum, mineral oil, cetyl and stearyl alcohol was prepared by melting at 60°C. An aqueous solution made up of Brij® 721 and Brij® 72, propylene glycol, sucrose mono/distearate and water in which micronised aciclovir had been hot(60°C)-suspended, was added to the oily phase. Addition was slow with continuous hot-stirring, and cooling to ambient temperature was allowed.

EXAMPLE 4

A formulation having the following composition was prepared:

Micronised aciclovir	263 g
Sucroester® WE 15*	750 g
Cetostearyl alcohol	338 g
Propylene glycol	1000 g
Sodium lauryl sulphate	37 g
Poloxamer® 407**	50 g
Mineral oil	250 g
Stringy petrolatum	625 g
Water	1700 g

* Sucrose monopalmitate

** Copolymer of polyoxyethylene-polyoxypropylene

The ingredients of a fatty phase made up of stringy petrolatum, mineral oil and cetostearyl alcohol, were transferred into a Pressindustria-5L turboemulsifier. The temperature was brought to 60°C and the ingredients were allowed to melt for about 30 minutes. Water, sodium lauryl sulphate, Poloxamer® 407 were separately added into a 5-L dissolution tank and the mixture was heated to 70°C. After complete dissolution of the mixture, propylene glycol and sucrose monopalmitate were added and stirred for about 30 minutes at a temperature of 70°C. After achieving again complete dissolution, micronised aciclovir was added and suspended with stirring using an UltraTurrax® homogeniser, and a constant temperature was maintained. A 70 mmHg vacuum was created in the turboemulsifier and the turbine was started at 2800 rpm, stirring at 45 rpm. The homogeneous suspension made up of the aqueous phase at 65°C was slowly added to the stirred oily phase contained in the turboemulsifier, maintaining the temperature at 60°C, vacuum at 70 mmHg and stirring constant for 20 minutes. In the end cooling to ambient temperature was allowed for about 2 hours. The cream, with a homogeneous appearance, pH 7.1 and a viscosity of 12,000 cps, was filled into 5- or 10-gram tubes.

EXAMPLE 5

A sample of cream containing 5% aciclovir marketed by Glaxo-Wellcome with the name Zovirax® Cream and having the following per-cent w/w composition:

Aciclovir	5%
Cetostearyl alcohol	6.75%
Propylene glycol	40%
Sodium lauryl sulphate	0.75%
Poloxamer 407	1%
Mineral oil	5%
Stringy petrolatum	12.5%
Water	29.0%

was used a s a reference standard for permeation studies.

The cream described in Example 1 was compared with the above commercial cream Zovirax® using a percutaneous absorption apparatus (Crown Glass Company, New Jersey, USA) which uses continuous-flow Bronaugh cells to measure permeation through the skin of Guinea pigs (R. Bronaugh et al., Journal Pharmaceutical Sciences, 74, 64-67 (1985)).

The skin of Guinea pigs was mounted on Bronaugh cells having a surface of 0.3 sq.cm. to which an amount of cream equal to 200-250 mg was applied. A solution of phosphate buffer pH 7.4 was circulated for 48 hours and the various fractions were collected every 8 hours. The collected fractions were analysed by a reverse-phase HPLC method using a Waters-625 apparatus with a C18µ Bondapack column, injecting 20 µl, eluting with the mobile phase water:methanol:acetic-acid (840/160/1) at a rate of 1 ml/minute, determining absorption with a UV detector at 254 nm. The results of the permeation test are shown in Table 1 below:

TABLE 1

Formulation	Cumulative amount permeated in 48 hours
Cream Example 1	370.7 µg/sq.cm.
Zovirax® 5% Cream	274.8 µg/sq.cm.

It is obvious that the formulation in Example 1 could permeate through the skin layer in 48 hours an amount of aciclovir higher by at least 25% than the amount which was permeated by the commercial reference formulation Zovirax® 5% Cream. Based on this, the formulation which is an object of the invention allows improved drug permeation through the skin and induces improved drug absorption and, as a result, improved therapeutic efficacy.

CLAIMS

1. A pharmaceutical composition for the topical treatment of viral infections, comprising aciclovir, or any of its salts or esters, and a mixture of lipid ingredients in water, such composition containing from 0.1% to 40% w/w of a sucrose ester.

2. A pharmaceutical composition in accordance with claim 1, characterised by the fact that the mixture is an emulsion made up of a lipid phase, an aqueous phase, emulsifiers and emulsion-stabilising agents.

3. A pharmaceutical composition in accordance with claim 2, characterised by the fact that the ingredients of the lipid phase are chosen from a group made up of linear or branched mono- or dialkylesters of fatty acid esters, mixtures of cetyl and stearyl alcohol and high-molecular-weight lipids.

4. A pharmaceutical composition in accordance with claim 2, characterised by the fact that the ingredients of the aqueous phase include a total amount of glycerine and propylene glycol lower than 30% w/w.

5. A pharmaceutical composition in accordance with claim 2, characterised by the fact that the emulsifiers and emulsion-stabilising agents are chosen from a group made up of cetyl alcohol, sodium lauryl sulphate, stearyl alcohol, cetostearyl alcohol, polyoxyethylene alkylethers and polyoxy stearylethers.

6. A pharmaceutical composition in accordance with claim 1, characterised by the fact that the sucrose ester is a monoester of a fatty acid having an even number of carbon atoms.

7. A pharmaceutical composition in accordance with claim 6, characterised by the fact that the esterifying fatty acid is chosen from a group made up of myristic acid, oleic acid, palmitic acid and stearic acid.

8. A pharmaceutical composition in accordance with any preceding claim, comprising the following per-cent w/w ratios referred to the total weight of the composition: aciclovir, or any of its salts or any of its esters: from 0.1% to 10%; sucrose ester: from 0.1% to 40%; water in admixture with a phase of oily ingredients: from 20% to 40%.

9. A pharmaceutical composition in accordance with claim 1, comprising the following percent w/w ratios referred to the total weight of the composition:

aciclovir (5%), sucrose monopalmitate (15%), cetostearyl alcohol (6.75%), propylene glycol (20%), sodium lauryl sulphate (0.75%), Poloxamer ® 407 (1%), mineral oil (5%), stringy pertolatum (12.5%), water (34%).

10. A process for the preparation of the pharmaceutical composition described in claims 1-9, characterised by stirring: aciclovir or any of its salts or esters, a sucrose ester, the excipients making up the lipid phase and the excipients making up the aqueous phase in a turboemulsifier until a stable emulsion is obtained.

11. The use of a pharmaceutical composition in accordance with any preceding claim in preparing a medication useful in the treatment or prevention of viral infections caused by *Herpes zoster, Herpes varicella* and type-1 or 2 *Herpes simplex*.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 99/04606

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/52 A61K9/06 A61K9/107 A61K47/26

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 447 729 A (G.W.BELENDUIK ET AL.) 5 September 1995 (1995-09-05) claims 1,4-9,12,16 examples column 2, line 15 - line 43 ---	1-11
Y	WO 95 26715 A (DUMEX) 12 October 1995 (1995-10-12) claims 1,6,9,14,20,26,46 page 5, line 11 - line 14 page 8, line 23 - line 24 page 10, line 1 - line 4 page 19, line 6 ---	1-11
Y	WO 96 40144 A (PHARMAVENE) 19 December 1996 (1996-12-19) claims 1-9,14-22 ---	1-11
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 1999	26/10/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 99/04606

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 97 34607 A (GLAXO) 25 September 1997 (1997-09-25) cited in the application the whole document	1-11
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A	WO 95 16434 A (LIDAK) 22 June 1995 (1995-06-22) the whole document	1-11
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Déclaration en vertu de la règle 4.17 :
— *relative à la qualité d'inventeur (règle 4.17.iv)) pour US seulement*

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En ce qui concerne les codes à deux lettres et autres abréviations, se référer aux "Notes explicatives relatives aux codes et abréviations" figurant au début de chaque numéro ordinaire de la Gazette du PCT.

WO 03/055464 A1

(54) **Title:** MICRONIZED PHARMACEUTICAL OR NUTRACEUTICAL POWDER WITH IMMEDIATE RELEASE

(54) **Titre :** POUDRE MICRONISEE PHARMACEUTIQUE OU NUTRACEUTIQUE A LIBERATION IMMEDIATE.

(57) **Abstract:** The invention concerns a micronized pharmaceutical or nutraceutical powder with immediate release having a grain size distribution of not more than 100 μm, and comprising the combination of at least an active substance, at least a wetting agent and at least a diluent.

(57) **Abrégé :** La présente invention concerne une poudre micronisée pharmaceutique ou nutraceutique à libération immédiate ayant une granulométrie d'au plus 100 μm, et comprenant la combinaison d'au moins une substance active, au moins un agent mouillant et au moins un agent diluant.

POUDRE MICRONISEE PHARMACEUTIQUE OU NUTRACEUTIQUE A LIBERATION IMMEDIATE

La présente invention concerne une poudre micronisée pharmaceutique ou nutraceutique à libération immédiate, pour application mucosale, en particulier buccale.

L'utilisation d'une poudre micronisée selon l'invention, pour préparer une composition pharmaceutique ou nutraceutique, permet une libération rapide (ou « flash ») de la substance active lorsque la composition la comprenant est administrée par voie mucosale, en particulier buccale.

Des formes galéniques permettant une libération rapide d'une substance active sont déjà connues. Il s'agit de comprimés de type « lyoc » ou à délitement rapide dans la bouche comme par exemple la technologie Zydis® (Scherer)®), ou encore des systèmes de type films présentés sous forme de « wafer », c'est-à-dire des films pour application buccale permettant une dissolution plus ou moins rapide des substances actives.

Cependant, ces deux formes galéniques présentent plusieurs inconvénients. Les comprimés souffrent d'une friabilité importante, ce qui rend délicate leur manipulation et par ailleurs leur temps de délitement est très souvent supérieur à 10 secondes. Les films sont difficiles à appliquer du fait de leur très faible épaisseur. En outre, les deux formes galéniques souffrent d'un inconvénient majeur en ce qu'elles ne permettent qu'une charge relativement faible en substance active, des excipients divers et variés étant nécessaires à leur intégrité structurelle.

Les Sociétés Demanderesses ont donc cherché à développer une forme galénique pouvant pallier aux inconvénients rencontrés par les formulations antérieures.

Elles ont ainsi réussi à mettre au point une poudre dont l'utilisation dans une composition pharmaceutique ou nutraceutique permet une libération rapide et immédiate de la substance active seule ou en association, lorsque ladite composition est administrée par voie buccale.

Au sens de la présente invention, on entend par « libération rapide et immédiate » une libération de la totalité de la ou les substances actives en moins de 30 secondes, de préférence moins de 15, et plus préférentiellement encore en moins de 10 secondes.

La poudre selon l'invention, contrairement aux comprimés et films de l'art antérieur, n'est délicate ni dans sa manipulation ni dans son application. Elle permet en outre une charge importante en substance active En effet la charge en substances actives par unité de prises peut être largement supérieure aux 20 mg imposés notamment par la technologie des films de type « WAFER » ou équivalent.

La poudre selon la présente invention présente donc de nombreux avantages par rapport aux formes galéniques connues dans l'art antérieur.

Ainsi, la présente invention concerne une poudre micronisée pharmaceutique ou nutraceutique à libération immédiate ayant une granulométrie d'au plus 100 µm, et comprenant la combinaison d'au moins une substance active, au moins un agent mouillant et au moins un agent diluant.

De préférence, la poudre micronisée à libération immédiate de l'invention comprend, par rapport au poids total de la composition, de 0,001% à 99% en poids de substance(s) active(s), de 1% à 60% en poids d'agent(s) mouillant(s) et de 0,1% à 99% d'agent(s) diluant(s). L'homme du métier adapte les proportions des différents constituants de la poudre micronisée à libération immédiate, selon des techniques conventionnelles de préparation de formulations galéniques comme par exemple celles décrites dans (i) J. Control Release, 1999, Vol. 61 : 175-183, (ii) J. Pharm., 2000, 171-277, (iii) J. Control Release, 2001, Vol. 77 : 1-6 ou encore (iv) J. Pharm. Pharmacol., 1996, Vol. 48 : 255, afin que la poudre possède les caractéristiques physiques, mécaniques et chimiques définies dans la présente description, notamment les caractéristiques de granulométrie, de cinétique de libération de la ou des substances actives ou encore d'humidité résiduelle.

Par substance active, on entend selon l'invention toute substance ayant une activité mesurable de nature thérapeutique ou nutraceutique envers l'organisme, homme ou animal, sur lequel cette substance active est appliquée ou administrée.

Par agent mouillant, on entend selon l'invention un agent accélérant la solubilisation et/ou la dissolution de la ou des substances actives et des autres excipients contenus dans la poudre micronisée. En particulier, un agent mouillant selon l'invention se caractérise en ce qu'il permet un haut indice de mouillabilité de ladite poudre micronisée, comme cela peut être visualisé par mesure de l'angle de contact (α) à l'aide d'un goniomètre, qui est faible et de

préférence compris entre 0 et 90°, préférentiellement entre 0 et 60° et plus préférentiellement entre 0 et 45°

Par agent diluant, on entend selon l'invention un agent utilisé pour compléter la composition de la poudre micronisée contenant la ou les substances actives, jusqu'à obtention d'un volume total prédéterminé contenant une quantité choisie de la ou des substance(s) active(s), le volume de la ou des substances actives elles-mêmes, selon la nature de ces substances actives, étant en général insuffisant pour la réalisation d'une poudre micronisée finale dont le volume désiré comprend la quantité adaptée de ladite ou desdites substances actives.

Selon l'invention, on a montré qu'une poudre micronisée ayant la combinaison des caractéristiques ci-dessus et possédant une granulométrie d'au plus 100 µm, du fait d'une grande surface active, permettait une excellente biodisponibilité de la ou des substances actives qu'elle contient, pour les sites ou récepteurs cellulaires cibles visés sur la muqueuse.

Par « granulométrie » d'une poudre micronisée à libération immédiate selon l'invention, on entend la taille moyenne des grains qui la constituent. La taille moyenne des grains peut être mesurée par toute technique conventionnelle connue en soi. Notamment, l'homme du métier peut avoir recours à une mesure de la granulométrie à laser du type Beckman Coulter® ou Malvern®, comme cela est décrit dans les exemples.

Le demandeur a observé que la distribution de taille des grains de la poudre micronisée à libération immédiate de l'invention suit une courbe de Gauss étroite, la valeur de granulométrie correspondant en conséquence à la taille réelle de la majorité des grains contenue dans ladite poudre.

La poudre micronisée à libération immédiate selon l'invention possède avantageusement une humidité résiduelle comprise entre 0,01% et 15%, et de préférence entre 0,1% et 5%, comme mesuré avec un analyseur d'humidité de type Sartorius® MA 30 commercialisé par la société Sartorius et utilisé selon les recommandations du fabricant, comme cela est illustré dans les exemples. La faible humidité résiduelle de la poudre micronisée à libération immédiate selon l'invention permet d'éviter, ou à tout le moins de réduire fortement, la formation d'agrégats entre les grains contenus dans ladite poudre. En effet, la formation d'agrégats est de nature à affecter la valeur de surface active de la poudre en contact avec les muqueuses, lors de son application, et en

conséquence la valeur de biodisponibilité de la ou des substances actives pour les sites ou récepteurs cibles dans les muqueuses.

On a aussi montré selon l'invention que, dans certaines limites, plus la granulométrie de la poudre micronisée est petite, plus on accroît la biodisponibilité de la ou des substances actives vis-à-vis des sites cibles visés et plus on réduit la durée nécessaire à la libération totale de la ou des substances actives vers les sites ou récepteurs cibles sur la muqueuse.

Ainsi, préférentiellement, la poudre micronisée selon l'invention possède une granulométrie d'au plus 50 µm, et de manière tout à fait préférée d'au plus 10 µm.

A l'exemple 1, on illustre une poudre micronisée à libération immédiate selon l'invention possédant une granulométrie de moins de 3 µm.

On a aussi montré selon l'invention qu'avec une poudre micronisée ayant une granulométrie inférieure à 0,01 µm, la capacité de libération immédiate de la ou des substances active était altérée, notamment du fait d'une agglomération en amas des grains de la poudre, entre eux. Ainsi, avec une poudre micronisée de granulométrie trop fine, on réduit la biodisponilité de la ou des substances actives pour les sites cibles sur les muqueuses, du fait de la rétention de la ou des substances actives au sein de la poudre, au cœur des agglomérats de grains qui se forment. En d'autres termes, contrairement à ce qui pouvait être attendu, une réduction trop grande de la granulométrie de la poudre micronisée, en deçà de 0,01 µm, a pour effet de réduire la surface active de ladite poudre en contact avec les muqueuses, par rapport à une poudre micronisée de granulométrie plus grande, par exemple de 1 µm ou 5 µm.

Selon un mode préférentiel de réalisation de la poudre micronisée à libération immédiate selon l'invention, ladite poudre présente une granulométrie comprise entre 0,01 µm et 100 µm, avantageusement entre 0,1 µm et 100 µm, préférentiellement encore entre 1 µm et 50 µm et de manière tout à fait préférée entre 1 µm et 20 µm.

La poudre micronisée à libération immédiate de l'invention possède une cinétique de dissolution dans un milieu aqueux de moins de trente secondes, et le plus souvent de moins de dix secondes, que ce soit dans des tampons ayant un pH allant de 5 à 9, ou que ce soit dans une solution aqueuse de salive artificielle.

Ainsi, selon une caractéristique avantageuse de la poudre micronisée à libération immédiate de l'invention, ladite poudre permet la libération de la totalité de la ou des substances actives en moins de 30 secondes, avantageusement en moins de 15 secondes, et de manière tout à fait préférée en moins de 10 secondes.

La poudre micronisée à libération immédiate de l'invention est spécifiquement adaptée à la libération rapide d'une substance active, ou d'une combinaison de substances actives, *in situ*, au niveau des muqueuses, en particulier des muqueuses buccales.

Selon un mode de réalisation préféré de la poudre micronisée à libération immédiate, la ou les substance(s) active(s) elle(s)-même(s) est (sont) sous forme micronisée.

Ainsi, selon un mode préférentiel de réalisation de la poudre micronisée selon l'invention, les substances actives sont micronisées avec les autres ingrédients. Ceci accroît encore la capacité de la poudre à libérer rapidement, et de manière homogène, la ou les substances actives, du fait d'une augmentation de la surface de contact de celles-ci avec la muqueuse. Par ailleurs, plusieurs systèmes de conditionnement de la poudre sont particulièrement bien adaptés tel que la pulvérisation de produits micronisés ou l'utilisation de sachets-doses ou capsules thermoformées muni d'un opercule pelable.

Les substances actives de la poudre utilisée selon l'invention peuvent être sélectionnées parmi celles classiquement utilisées dans les familles pharmaco-thérapeutiques suivantes : allergologie, anesthésie/réanimation, cancérologie et hématologie, cardiologie et angiologie, contraception et interruption de grossesse, dermatologie, endocrinologie, gastro-entérohépatologie, gynécologie et obstétrique, immunologie et médicament de transplantation, infectiologie et parasitologie, métabolisme diabète et nutrition, neurologie/psychiatrie, ophtalmologie, oto-rhino-laryngologie, pneumologie, rhumatologie, stomatologie, toxicologie, urologie/néphrologie, ainsi que parmi les antalgiques / antipyrétique et antispasmodiques, anti-inflammatoires, les produits de contraste utilisés en radiologie, les hémostatiques, et les produits de traitement du sang et dérivés.

Avantageusement, les substances actives peuvent être sélectionnées dans le groupe constitué par les substances actives passant la barrière mucosale et atteignant la circulation systémique, telles que les exemples non

limitatifs cités ci-après : l'acétate de cyprotérone, l'acétate de norethistérone, la progestérone, le 3-kéto-désogestrel, le norgestimate, le lévonorgestrel, le désogestrel, le gestodène, les estrogènes naturels tels que l'estradiol ou ses dérivés, les estrogènes synthétiques tels que l'éthinylestradiol, la Δ-4-androstènedione, la testostérone, la dihydrotestostérone ou androstanolone, la DHEA, la trinitrine, le fentanyl, la nitroglycérine, la nicotine (nicotine S(-)), la scopolamine, la clonidine, l'isosorbide dinitrate, l'alclométasone dipropionate, le phloroglucinol, la molsidomine, ainsi que leurs associations.

Elles peuvent également être sélectionnées parmi les substances actives passant la barrière mucosale et ayant une action localisée telles que : l'acétazolamide, l'acyclovir, l'adapalène, l'alclométhasone dipropionate, l'amcinonide, l'améleine, le bamethan sulfate + escine, la bétaméthasone valérate, la bétaméthasone dipropionate, le bufexamac, la caféine, le calcipotriol monohydrate, le cetrimonium bromure, le clobétasol propionate, le crilanomère, la désonide, le dexpanthénol, le diclofénac, le diflucortolone, la valérate, le difluprednate, la diphénydramine chlorhydrate, l'econazole nitrate, l'erythromicine, le flumétasone pivalate, le fluocinolone acétonide, la fluocinodine, le fluocortolone, le fluocortolone hexanoate, le fluocortolone pivalate, l'hydrocortisone, l'hydrocortisone acétate, l'ibacitabine, l'ibuprofène, l'imiquimod, le kétoconazole, le kétoprofène, la lidocaine, la métronidazole, le miconazole nitrate, le minoxidil, le niflumide acide, la penciclovir, le peroxyde benzoyle, la piroxam, la povidone iodé, la promestriène, la pyrazonibutasone, la roxithromycine, la sulfacétalmide, le triamconolone, le tazarotène, le trétinoïne et l'isotrétinoïne, le triclocarban, le vidarabine monophosphate ainsi que leurs associations.

Elles peuvent également être sélectionnées parmi les substances actives suivantes : l'agoniste β-3 adrénergique, l'hormone de croissance, l'oxybutinine, la buprenorphine, le pergolide, le nestorone, le 7α-méthyl-19-nortestérone, la mécamylamine, le salbutamol, le clenbutérol, la sélégiline, la buspirone, la kétotifen, la lidocaïne, le kétorolac, l'eptazocine, l'insuline, l'interféron α, les prostaglandines, l'acide 5 aminolévulinique, la benzodiazepine alprozolam, le diclofenac, le fenoprofen, le flubiprofen, le kétoprofen, la méthylphénidate, la miconazole, le piroxicam, la bruprenorphine, l'alprozolam, la dexmedetomidine, la prazosin (antagoniste α adrénergique), l'alprostadil, le tulobutérol (agoniste β adrénergique), thinylestradiol + norelgestromi, le kétorolac, la physostigmine, le

medindolol (agoniste α adrénergique), la rotigotine (dopamine D2 antagoniste), la thiatolserine ainsi que leurs associations.

Elles peuvent également être sélectionnées parmi les substances actives suivantes : Esomeprazole, Melagatran (en cas de thrombose), Rosuvastatine, Ezetimide, Pitavastatine (Hyperlipidemie), Mitiglinide (Diabète de type II), Cilomilast, Viozan (Asthme), Aripipazole (psychiatrie), Omapatrilat (hypertenseur),Orzel (Cancérologie), Caspofongine acétate, Voriconazole (infections), nouveaux Inhibiteurs COX tels que Etoricoxib (inflammation), Valdecoxib (Arthrites) et Parecoxib, Substance P antagoniste (Dépression), Darifenacine (urologie), Eletriptan (Migraine), Alosetron, Tegaserod, Capravirine (HIV) , Finastéride (inhibiteur de la 5-alpha réductase) ainsi que leurs associations (liste non limitative).

La poudre utilisée selon l'invention peut contenir une ou plusieurs substances actives, en association entre elles.

Pour des applications nutraceutiques, la substance active peut être choisie parmi la liste des matières premières autorisées en tant que compléments alimentaires comme par exemple dans le groupe constitué par les vitamines, les sels minéraux, la levure de bière, etc.

L'agent mouillant peut être un agent mouillant conventionnellement désigné comme tel, par exemple dans la Pharmacopée européenne ou encore dans la Pharmacopée des Etats-Unis d'Amérique (USP) en vigueurou touts autres agents mouillant de qualité pharmaceutique ou nutraceutique. Un agent mouillant contenu dans une poudre micronisée de l'invention englobe également les agents classés dans la Pharmacopée européenne ou dans la Pharmacopée des Etats-Unis d'Amérique (USP) comme agents tensioactifs. En effet, selon un aspect particulier de la poudre micronisée à libération immédiate de l'invention, on utilise aussi les agents tensioactifs comme agents mouillants.

De préférence, un agent mouillant est sélectionné dans le groupe constitué par les polyols tels que le sorbitol, ou encore la glycérine, le PEG, l'hexylène glycol, la triacétine, les huiles végétales hydrogénées telle que l'huile de ricin hydrogénée, les copolymères du polyoxy(éthylène)polyoxy(propylène) tel que le Lutrol® F68, les polyoxyéthylène alkyl éthers tel que le Cremophor®, ainsi que leurs mélanges (liste non limitative).

De préférence, l'agent diluant est sélectionné dans le groupe constitué par le carbonate ou bicarbonate de calcium, sodium, le sucrose, le mannitol, le xylitol, le sorbitol, le lactose, le maltotol, le glucose, la poudre de cellulose ou

cellulose microcristalline, l'amidon et ses dérivés, le phosphate de calcium dibasique, le phosphate de calcium tribasique, le sulfate de calcium, les dextrates, les dextrines, les excipients de dextrose, le fructose, le kaolin, le lactitol, ainsi que leurs mélanges (liste non limitative).

Préférentiellement, la poudre micronisée selon l'invention comprend aussi au moins un agent anti-statique.

On a en effet montré selon l'invention que l'ajout d'au moins un agent anti-statique permettait d'accroître de manière significative la capacité de la poudre micronisée selon l'invention à libérer rapidement la totalité de la ou des substances actives que ladite poudre contient. L'ajout d'au moins un agent anti-statique permet d'éviter, ou à tout le moins de réduire fortement, la formation d'agrégats de poudre qui sont dus à la faible granulométrie de cette dernière. Ainsi, l'ajout d'au moins un agent anti-statique permet l'obtention d'une poudre micronisée de faible granulométrie ne comprenant pas d'agrégats entre les grains, et dont les grains, bien séparés les uns des autres, permettent l'obtention d'une surface de contact maximale de la poudre avec les muqueuses, lors de son application sur ces dernières, et en conséquence une accessibilité ou biodisponibilité maximale de la ou des substances actives pour les sites ou récepteurs cibles correspondants sur les muqueuses.

De préférence, la poudre micronisée à libération immédiate de l'invention comprend, par rapport au poids total de la composition, de 0,01% à 10% d'un ou plusieurs agent(s) anti-statique(s).

De préférence, un agent anti-statique est sélectionné dans le groupe constitué de la silice colloïdale, du silicate de magnésium, du talc, du silicate de calcium et du phosphate de calcium tribasique (liste non limitative).

La poudre utilisée selon l'invention peut également comprendre un liant sélectionné dans le groupe constitué par l'acacia, l'acide alginique, la carboxyméthylcellulose sodique, la cellulose microcristalline, les dextrines, l'éthylcellulose, la gélatine, le glucose, la gomme guar, l'hydroxypropylméthylcellulose, la méthylcellulose, l'oxyde de polyéthylène, la povidone, l'amidon prégélatinisé, ainsi que leurs mélanges (liste non limitative).

La poudre utilisée selon l'invention peut également comprendre, si nécessaire, un promoteur de pénétration, préférentiellement désigné dans la présente description « promoteur d'absorption ». On entend par « promoteur d'absorption», toute molécule favorisant la diffusion d'une substance active à travers la peau ou de la muqueuse de façon réversible, et tout agent de

solubilisation ou agent mouillant favorisant le partage de la substance active entre le véhicule et la couche cornée de l'épiderme ou la muqueuse.

Dans les cas où le promoteur d'absorption est aussi un agent mouillant tel que défini ci-dessus, ledit promoteur d'absorption est ajouté à la composition de la poudre micronisée qui comprend déjà un agent mouillant.

Le promoteur d'absorption peut être sélectionné dans le groupe constitué par les esters d'acide gras aliphatiques comme le myristate d'isopropyle, les acides gras comme l'acide oléique ; les alcools ou polyols tels que l'éthanol, le propylèneglycol et le polyéthylèneglycol ; les composants des huiles essentielles et dérivés terpéniques (comme l'eugenol, le géraniol, le nérol, l'eucalyptol, le menthol) ; les tensioactifs, de préférence non ioniques, tels que le polyoxyéthylène sorbitan (ester d'acide gras), le polyoxyéthylène alkyl éther, le polyoxyéthylène dérivé de l'huile de ricin; les hydratants comme la glycérine, l'urée ; des kératolytiques comme les alpha-hydroxyacides (acide lactique, acide citrique, etc.), le 23-lauryl ether, l'aprotinin, l'azone, le chlorure de benzalkonium, le chlorure de cétylpyridinium, le bromure de cétyltriméthylammonium, les cyclodextrines, le dextran sulfate, l'acide laurique, l'acide laurique, la lysophosphatidylcholine, le menthol, le méthoxysalicylate, le méthyloleate, l'acide oléique, la phosphatidylcholine, le polyoxyethylene, le polysorbate 80, l'EDTA de sodium, le glycocholate de sodium, le glycodeoxycholate de sodium, le lauryl sulfate de sodium, le salycilate de sodium, le taurocholate de sodium, le taurodeoxycholate de sodium, les sulfoxides, les alkyl glycosides, ainsi que leur mélange (liste non limitative). Par ailleurs, afin d'améliorer la compliance du patient, on peut éventuellement ajouter à la composition un agent édulcorant et/ou un agent aromatisant

L'agent édulcorant peut être sélectionné dans le groupe constitué par l'aspartame, les dextrates, le dextrose, le fructose, le mannitol, le saccharinate de sodium ou de calcium, le sorbitol, le sucralose, le sucrose, ainsi que leurs mélanges (liste non limitative).

L'agent aromatisant peut être sélectionné dans le groupe constitué par les arômes d'origine synthétiques, semi-synthétiques ou naturels. On peut citer par exemple la menthe, la menthe poivrée, le citron, la banane, la fraise, la framboise, la mandarine, l'orange, la vanille, les fruit de la passion, le caramel, ainsi que leurs mélanges.

La composition contenant la poudre utilisée selon l'invention est administrée par voie mucosale. Elle peut être appliquée, par exemple, sur la

muqueuse buccale, la muqueuse nasale ou la muqueuse vaginale, et également en application sublinguale.

De manière générale, la poudre micronisée à libération immédiate de l'invention peut être utilisée avec ou dans tout dispositif permettant son application sur la surface d'une muqueuse.

De façon avantageuse, la composition comprenant la poudre utilisée selon l'invention, se présente sous une forme sèche conditionnée dans un pulvérisateur oudans un sachet-dose à 4 soudures ou dans un sachet-dose à 3 soudures tel que le « stick pack qui est un sachet tubulaire avec une soudure longitudinale et une soudure à chaque extrémité du tube, ou dans une capsule thermoformée muni d'un opercule pelable ou encore dans tout autre conditionnement adapté à l'administration de poudre connu de l'homme du métier. Ces conditionnements permettent la délivrance aisée d'une dose précise de matière active.

Tous les procédés connus de l'homme du métier peuvent être utilisés dans le cadre de la réalisation de la poudre utilisée selon l'invention.

On peut citer comme exemple de méthode de préparation d'une poudre : la granulation, par voie humide ou par voie sèche, suivie d'une micronisation.

Ou selon un autre mode de réalisation, la substance active est micronisée puis mélangée avec les excipients sous forme de poudre, et le mélange ainsi obtenu est granulé, par granulation par voie humide ou par voie sèche, puis micronisé.

Avantageusement, pour préparer une poudre micronisée à libération immédiate selon l'invention, on mélange (i) la ou les substances actives, (ii) le ou les agent(s) mouillant(s), (iii) le ou les agent(s) diluant(s), préférentiellement (iv) le ou les agent(s) anti-statique(s) et éventuellement aussi (v) les autres excipients, tels que le ou les agent(s) liant(s) et/ou le ou les promoteur(s) d'absorption dans un dispositif du type mélangeur-granulateur-sécheur, jusqu'à homogénéisation du mélange. Puis, une solution ou suspension de mouillage est incorporée sous agitation afin d'obtenir un granulé humide, qui est ensuite séché afin d'évaporer le solvant de granulation.

La poudre est ensuite micronisée, après calibrage.

Pour la micronisation, on utilise de préférence la méthode conventionnelle à jet d'air, par exemple en utilisant un appareil de micronisation à jet d'air du type ALPINE ou JET MILL, selon les recommandations du fabricant.

Les paramètres préférés pour une micronisation sur un appareil microniseur GALETTE Alpine 200AS sont les suivants :

- Injecteur : 7 à 8 bars ;
- Couronne : 4 à 6 Bars ; et
- Vitesse : 25 kg/h.

Dans un essai particulier réalisé par le demandeur, la poudre avant micronisation avait une taille moyenne de grains (granulométrie)d'environ 160 µm. A près micronisation, la poudre micronisée à libération immédiate obtenue possédait une granulométrie de 2,3 µm.

La substance active seule ou bien le mélange final d'ingrédients peuvent être micronisés.

L'invention est en outre illustrée, sans pour autant être limitée, la figure et les exemples suivants.

La **Figure 1** illustre le profil de distribution de taille des grains de la poudre micronisée à libération immédiate de l'invention préparée à l'Exemple 2, avant et après micronisation.

- En abscisse : Taille des particules, exprimée en µm ;
- En ordonnées : Volume, exprimé en pourcentage.

La **Figure 2** illustre le profil de distribution de taille des grains de la poudre micronisée à libération immédiate de l'invention préparée à l'Exemple 3, avant et après micronisation.

- En abscisse : Taille des particules, exprimée en µm ;
- En ordonnées : Volume, exprimé en pourcentage.

EXEMPLE 1 : POUDRES A UTILISER SELON L'INVENTION

On prépare quatre poudres présentant chacune la composition pondérale suivante :

Tableau 1

Composition	Quantité en %
Phloroglucinol	10
Sorbitol	89
Propylène glycol	1

Tableau 2

Composition	Quantité en %
Testostérone	10
Sorbitol	88
Crémophor RH40	2

Tableau 3

Composition	Quantité en %
Dihydrotestostérone	5
Xylitol	90
Glycérol	3
Tween 80	2

Tableau 4

Composition	Quantité en %
Molsidomine	10
Xylitol	83
Propylène glycol	5
Montanox 80	2

Les différents composants pulvérulents à l'exception de l'agent anti-statique sont mélangés dans un mélangeur-granulateur de type mélangeur-granulateur-sécheur sous vide ROTOLAB ZANCHETTA® ou équivalent jusqu'à homogénéisation du mélange. Ensuite, une solution ou suspension de mouillage comprenant le ou les composant(s) liquide(s) est incorporée sous agitation afin d'obtenir un granulé humide.

Ce granulé est ensuite séché dans des conditions adaptées afin d'évaporer le solvant de granulation. Ce granulé est ensuite séché et calibré

puis micronisé à l'aide d'un appareil de micronisation à jet d'air de type ALPINE ou JETMIL (ou équivalent).

EXEMPLE 2 : POUDRE A LIBERATION IMMEDIATE SELON L'INVENTION

On prépare une poudre présentant la composition pondérale suivante :

Tableau 5

Composition	Quantité en %
Apomorphine	10
Sorbitol	89,01
Propylène glycol	0,90
Silice colloïdale	0,09

Procédé de fabrication :

Les différents composants pulvérulents à l'exception de l'agent anti-statique sont mélangés dans un mélangeur-granulateur de type mélangeur-granulateur-sécheur sous vide ROTOLAB ZANCHETTA ou équivalent jusqu'à homogénéisation du mélange. Ensuite, une solution ou suspension de mouillage comprenant le ou les composant(s) liquide(s) est incorporée sous agitation afin d'obtenir un granulé humide.

Ce granulé est ensuite séché dans des conditions adaptées afin d'évaporer le solvant de granulation, calibré, puis micronisé à l'aide d'un appareil de micronisation à jet d'air de type GALETTE ALPINE 200AS ou JETMIL (ou équivalent)

Paramètre de micronisation :

Injecteur : 8Bars, Couronne : 6Bars, Vitesse : 25Kg/h.

Afin de réduire les phénomènes d'agglomération dus à la faible granulométrie de la poudre micronisée, un agent anti-statique (silice colloïdale) préalablement tamisé est ajouté par mélange progressif dans un mélangeur Turbula.

Contrôles sur granulé avant micronisation

-Granulométrie : réalisée à l'aide d'un granulomètre laser Malvern Mastersizer 2000 équipé d'un vibreur Sirocco 2000

Paramètres : Pression=2bars ; Vibration=80%

Résultat : granulométrie moyenne=157,98µm

-Aptitude à l'écoulement : selon test Pharmacopée européenne 4.2 ; 2.9.16 Ecoulement
masse échantillon=100g, Temps d'écoulement = ∞

-Volume apparent : selon test Pharmacopée Européenne 4.2 ; 2.9.15
masse échantillon=100g
Volume apparent à V0=166 mL
Volume apparent à V10= 156 mL
Volume apparent à V500= 148 mL
V10-V500= 6 mL

-Mesure du taux d'humidité relative : réalisé à l'aide d'un analyseur d'humidité MA 30 Sartorius
Paramètres : masse de l'échantillon=2g, Température=75°C, Temps de dessiccation=automatique
Résultat : Humidité relative= 1,41%

Contrôle sur poudre micronisée finale

-Granulométrie : réalisée à l'aide d'un granulomètre laser Malvern Mastersizer 2000 équipé d'un vibreur Sirocco 2000
Paramètres : Pression=3bars ; Vibration=70%
Résultat : granulométrie moyenne=2,349µm

-Aptitude à l'écoulement : selon test Pharmacopée européenne 4.2 ; 2.9.16 Ecoulement
masse échantillon=100g, Temps d'écoulement = ∞

-Volume apparent : selon test Pharmacopée européenne 4.2 ; 2.9.15
masse échantillon=50g
Volume apparent à V0=178 mL
Volume apparent à V10= 170 mL
Volume apparent à V500= 164 mL
V10-V500= 8 mL

-Mesure du taux d'humidité relative : réalisée à l'aide d'un analyseur d'humidité MA 30 Sartorius
Paramètres : masse de l'échantillon=3g environ, Température=75°C, Temps de dessiccation = automatique, nombre d'essai = 3
Résultat : Humidité relative moyenne = 1,08%

-Cinétique de dissolution in vitro
Conditions opératoires : 1g de poudre micronisée sont dissous à 37°C dans 10g de milieu, sous agitation magnétique à 500 RPM

Tableau 6

Milieu	Temps (s)
Tampon phosphate pH 4,5	4,63
Tampon phosphate pH 8	8,36
Tampon phosphate pH 7,4	5,87
Salive artificielle	2,72

Le profil de distribution de taille des grains de la poudre selon l'Exemple 2, avant et après micronisation, est illustré sur la Figure 1.

EXEMPLE 3 : POUDRE A LIBERATION IMMEDIATE SELON L'INVENTION

On prépare une poudre présentant la composition pondérale suivante :

Tableau 7

Composition	Quantité en %
Testostérone	10

Dextran	87,91
Glycérol	1,99
Silice colloïdale	0,1

Procédé de fabrication :

Les différents composants pulvérulant à l'exception de l'agent anti-statique sont mélangés dans un mélangeur-granulateur de type mélangeur-granulateur-sécheur Lit d'air fluidisé équipé d'une buse top spray ou équivalent jusqu'à homogénéisation du mélange. Ensuite, une solution ou suspension de mouillage comprenant le ou les composant(s) liquide(s) est pulvérisée à l'aide d'une buse de pulvérisation, sur le produit en mouvement afin simultanément de répartir la solution de façon homogène et de le sécher pour évaporer le solvant de granulation.

Ce granulé est calibré, puis micronisé à l'aide d'un appareil de micronisation à jet d'air de type GALETTE ALPINE 200AS ou JETMIL (ou équivalent). Les paramètres de réglage sont identiques à ceux décrits dans l'exemple I.

Afin de réduire les phénomènes d'agglomération dus à la faible granulométrie de la poudre micronisée, un agent anti-statique (silice colloïdale) préalablement tamisé est ajouté par mélange progressif dans un mélangeur Turbula.

Contrôles sur poudre micronisée finale

-Cinétique de dissolution in vitro

Conditions opératoires : 1g de poudre micronisée sont dissous à 37°C dans 10g de milieu, sous agitation magnétique à 500 RPM

Tableau 8

Milieu	Temps (s)
Tampon phosphate pH 4,5	8,9
Tampon phosphate pH 8	7,23
Tampon phosphate pH 7,4	7,74

Salive artificielle	6,78

Le profil de distribution de taille des grains de la poudre selon l'Exemple 3, avant et après micronisation, est illustré sur la Figure 2.

Exemple 4 : POUDRE A LIBERATION IMMEDIATE SELON L'INVENTION

On prépare une poudre présentant la composition pondérale suivante :

Tableau 9

Composition	Quantité en %
Dihydrotestostérone	5
Mannitol	90
Propylène glycol	3
	2

Procédé de fabrication :

Selon exemple 2.

Contrôles sur poudre micronisée finale

-Cinétique de dissolution in vitro

Conditions opératoires : 1g de poudre micronisée sont dissous à 37°C dans 10g de milieu, sous agitation magnétique à 500 RPM

Tableau 10

Milieu	Temps (s)
Tampon phosphate pH 4,5	6,28
Tampon phosphate pH 8	7,71
Tampon phosphate pH 7,4	6,14
Salive artificielle	4,97

REVENDICATIONS

1. Poudre micronisée pharmaceutique ou nutraceutique à libération immédiate ayant une granulométrie d'au plus 100 µm, et comprenant la combinaison d'au moins une substance active, au moins un agent mouillant et au moins un agent diluant.

2. Poudre selon la revendication 1, caractérisée en ce qu'elle possède une granulométrie d'au plus 50 µm.

3. Poudre selon la revendication 1, caractérisée en ce qu'elle possède une granulométrie d'au plus 10 µm.

4. Poudre selon l'une des revendications 1 à 3, caractérisée en ce qu'elle permet la dissolution de la totalité de la ou des substances actives en moins de 30 secondes, lorsqu'elle est administrée par voie mucosale.

5. Poudre selon l'une des revendications 1 à 4, caractérisée en ce que la substance active est sous forme micronisée.

6. Poudre selon l'une quelconque des revendications 1 à 5, caractérisée en ce que la substance active est sélectionnée dans le groupe constitué par l'acétate de cyprotérone, l'acétate de norethistérone, la progestérone, le 3-kéto-désogestrel, le norgestimate, le lévonorgestrel, le désogestrel, le gestodène, les estrogènes naturels tels que l'estradiol ou ses dérivés, les estrogènes synthétiques tels que l'éthinylestradiol, la Δ-4-androstènedione, la testostérone, la dihydrotestostérone ou androstanolone, la DHEA, la trinitrine, le fentanyl, la nitroglycérine, la nicotine (nicotine S(-)), la scopolamine, la clonidine, l'isosorbide dinitrate, l'alclométasone dipropionate, le phloroglucinol, la molsidomine, l'acétazolamide, l'acyclovir, l'adapalène, l'alclométhasone dipropionate, l'amcinonide, l'améleine, le bamethan sulfate + escine, la bétaméthasone valérate, la bétaméthasone dipropionate, le bufexamac, la caféine, le calcipotriol monohydrate, le cetrimonium bromure, le clobétasol propionate, le crilanomère, la désonide, le dexpanthénol, le diclofénac, le diflucortolone, la valérate, le difluprednate, la diphénydramine chlorhydrate, l'econazole nitrate, l'erythromicine, le flumétasone pivalate, le fluocinolone acétonide, la fluocinodine, le fluocortolone, le fluocortolone hexanoate, le fluocortolone pivalate, l'hydrocortisone, l'hydrocortisone acétate, l'ibacitabine, l'ibuprofène, l'imiquimod, le kétoconazole, le kétoprofène, la lidocaine, la métronidazole, le miconazole nitrate, le minoxidil, le niflumide

acide, la penciclovir, le peroxyde benzoyle, la piroxam, la povidone iodé, la promestriène, la pyrazonibutasone, la roxithromycine, la sulfacétalmide, le triamconolone, le tazarotène, le trétinoïne et l'isotrétinoïne, le triclocarban, le vidarabine monophosphate, l'agoniste β-3 adrénergique, l'hormone de croissance, l'oxybutinine, la buprenorphine, le pergolide, le nestorone, le 7α-méthyl-19-nortestérone, la mécamylamine, le salbutamol, le clenbutérol, la sélégiline, la buspirone, la kétotifen, la lidocaïne, le kétorolac, l'eptazocine, l'insuline, l'interféron α, les prostaglandines, l'acide 5 aminolévulinique, la benzodiazepine alprozolam, le diclofenac, le fenoprofen, le flubiprofen, le kétoprofen, la méthylphénidate, la miconazole, le piroxicam, la bruprenorphine, l'alprozolam, la dexmedetomidine, la prazosin (antagoniste α adrénergique), l'alprostadil, le tulobutérol (agoniste β adrénergique), thinylestradiol + norelgestromi, le kétorolac, la physostigmine, le medindolol (agoniste α adrénergique), la rotigotine (dopamine D2 antagoniste), la thiatolserine, Esomeprazole, Melagatran (en cas de thrombose), Rosuvastatine, Ezetimide, Pitavastatine (Hyperlipidemie), Mitiglinide (Diabète de type II), Cilomilast, Viozan (Asthme), Aripipazole (psychiatrie), Omapatrilat (hypertenseur),Orzel (Cancérologie), Caspofongine acétate, Voriconazole (infections), nouveaux Inhibiteurs COX tels que Etoricoxib (inflammation), Valdecoxib (Arthrites) et Parecoxib, Substance P antagoniste (Dépression), Darifenacine (urologie), Eletriptan (Migraine), Alosetron, Tegaserod, Capravirine (HIV) , Finastéride (inhibiteur de la 5-alpha réductase), ainsi que leurs associations.

7. Poudre selon l'une quelconque des revendications 1 à 6, caractérisée en ce que la (les) substance(s) active(s) est (sont) sélectionnée(s) dans le groupe constitué par les vitamines, les sels minéraux, la levure de bière.

8. Poudre selon l'une quelconque des revendications 1 à 7, caractérisée en ce que l'agent mouillant est sélectionné parmi les polyols tels que le sorbitol, ou encore la glycérine, le PEG, l'hexylène glycol, la triacétine, les huiles végétales hydrogénées telle que l'huile de ricin hydrogénée, les copolymères du polyoxy(éthylène)polyoxy(propylène) tel que le Lutrol® F68, les polyoxyéthylène alkyl éthers tel que le Cremophor®, ainsi que leurs mélanges.

9. Utilisation d'une poudre selon l'une quelconque des revendications 1 à 8, caractérisée en ce que l'agent diluant est sélectionné dans le groupe constitué par le carbonate ou bicarbonate de calcium, sodium, le sucrose, le mannitol, le xylitol, le sorbitol, le lactose, le maltotol, le glucose, la

poudre de cellulose ou cellulose microcristalline, l'amidon et ses dérivés, le phosphate de calcium dibasique, le phosphate de calcium tribasique, le sulfate de calcium, les dextrates, les dextrines, les excipients de dextrose, le fructose, le kaolin, le lactitol, ainsi que leurs mélanges.

10. Poudre selon l'une des revendications 1 à 9, caractérisée en ce qu'elle comprend en outre un agent anti-statique.

11. Poudre selon la revendication 10, caractérisée en ce que l'agent anti-statique est sélectionné dans le groupe constitué de la silice colloïdale, le silicate de magnésium, le talc, le silicate de calcium et le phosphate de calcium tribasique, ainsi que leur mélanges.

12. Poudre selon l'une quelconque des revendications 1 à 11, caractérisée en ce qu'elle comprend en outre un agent liant pouvant être sélectionné dans le groupe constitué par l'acacia, l'acide alginique, la carboxyméthylcellulose sodique, la cellulose microcristalline, les dextrines, l'éthylcellulose, la gélatine, le glucose, la gomme guar, l'hydroxypropylméthylcellulose, la méthylcellulose, l'oxyde de polyéthylène, la povidone, l'amidon prégélatinisé, ainsi que leurs mélanges.

13. Poudre selon l'une quelconque des revendications 1 à 12, caractérisée en ce qu'elle comprend en outre un promoteur d'absorption sélectionné dans le groupe constitué par les esters d'acide gras aliphatiques comme le myristate d'isopropyle, les acides gras comme l'acide oléique ; les alcools ou polyols tels que l'éthanol, le propylèneglycol et le polyéthylèneglycol ; les composants des huiles essentielles et dérivés terpéniques (comme l'eugenol, le géraniol, le nérol, l'eucalyptol, le menthol) ; les tensioactifs, de préférence non ioniques, tels que le polyoxyéthylène sorbitan (ester d'acide gras), le polyoxyéthylène alkyl éther, le polyoxyéthylène dérivé de l'huile de ricin; les hydratants comme la glycérine, l'urée ; des kératolytiques comme les alpha-hydroxyacides (acide lactique, acide citrique, etc.), le 23-lauryl ether, l'aprotinin, l'azone, le chlorure de benzalkonium, le chlorure de cétylpyridinium, le bromure de cétyltriméthylammonium, les cyclodextrines, le dextran sulfate, l'acide laurique, l'acide laurique, la lysophosphatidylcholine, le menthol, le méthoxysalicylate, le méthyloleate, l'acide oléique, la phosphatidylcholine, le polyoxyethylene, le polysorbate 80, l'EDTA de sodium, le glycocholate de sodium, le glycodeoxycholate de sodium, le lauryl sulfate de sodium, le salycilate de sodium, le taurocholate de sodium, le taurodeoxycholate de sodium, les sulfoxides, les alkyl glycosides, ainsi que leur mélange

14. Poudre selon l'une quelconque des revendications 1 à 13, caractérisée en ce qu'elle comprend en outre un agent édulcorant et/ou un agent aromatisant.

15. Poudre selon la revendication 14, caractérisée en ce que l'agent édulcorant est sélectionné dans le groupe constitué par l'aspartame, les dextrates, le dextrose, le fructose, le mannitol, le saccharinate de sodium ou de calcium, le sorbitol, le sucralose, le sucrose, ainsi que leurs mélanges.

16. Poudre selon la revendication 14, caractérisée en ce que l'agent aromatisant est sélectionné dans le groupe constitué par par les arômes d'origine synthétiques, semi-synthétiques ou naturels. On peut citer par exemple la menthe, la menthe poivrée, le citron, la banane, la fraise, la framboise, la mandarine, l'orange, la vanille, les fruit de la passion, le caramel, ainsi que leurs mélanges.

17. Poudre selon l'une quelconque des revendications 1 à 16, caractérisée en ce qu'elle se présente sous une forme adaptée à son application sur la muqueuse buccale, la muqueuse nasale ou la muqueuse vaginale.

18. Poudre selon l'une des revendications 1 à 14, caractérisée en ce qu'elle se présente sous une forme adaptée à son application sur la muqueuse buccale par voie sublinguale.

19. Poudre selon l'une quelconque des revendications 1 à 18, caractérisée en ce qu'elle se présente sous une forme pulvérisable.

20. Poudre selon l'une quelconque des revendications 1 à 18, caractérisée en ce qu'elle se présente conditionnée dans un sachet-dose.

21. Poudre selon l'une quelconque des revendications 1 à 18, caractérisée en ce qu'elle se présente conditionnée dans une capsule thermoformée muni d'un opercule pelable.

22. Poudre selon l'une quelconque des revendications 1 à 18, caractérisée en ce qu'elle se présente dans un conditionnement adapté à l'administration de poudre connu de l'homme du métier.

23. Utilisation d'une poudre selon l'une des revendications 1 à 20, pour la fabrication d'une composition pharmaceutique ou nutraceutique à libération immédiate.

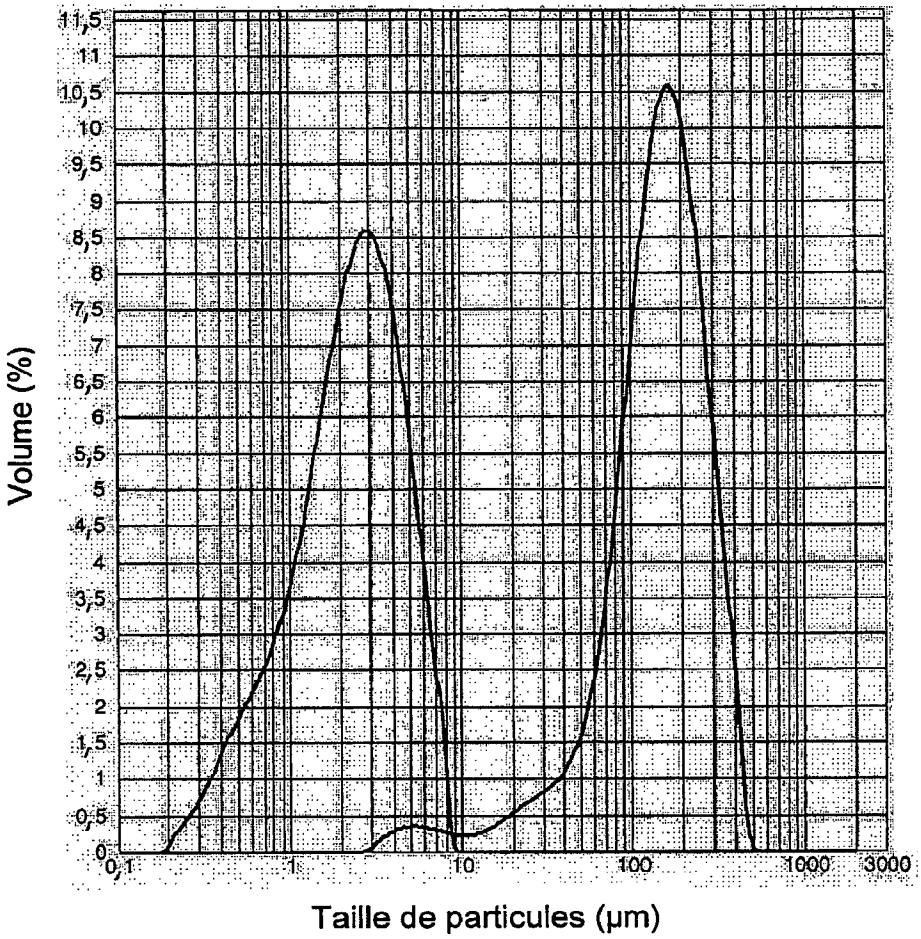
Volume (%)
11,5
11
10,5
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
0,1
1
10
100
1000
3000
Taille de particules (µm)

FIGURE 1

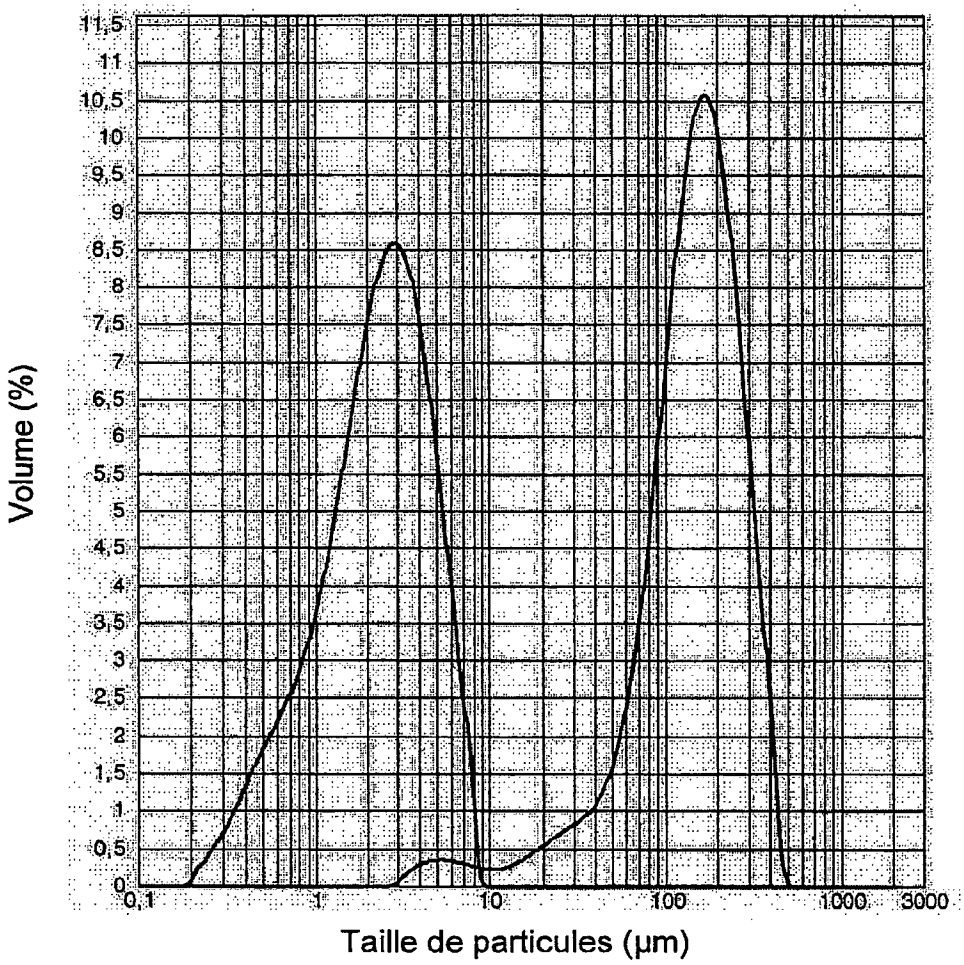
Volume (%)
11,5
11
10,5
10
9,5
9
8,5
8
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
0,1
1
10
100
1000
3000
Taille de particules (µm)

FIGURE 2

INTERNATIONAL SEARCH REPORT

Interna I Application No
PCT/FR 02/04575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K47/10 A61K47/26

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 073 374 A (J.A. MCCARTY) 17 December 1991 (1991-12-17) claims column 2, line 13 - line 48 column 1, line 23 - line 34 ---	1,6,8,9, 12,13, 17,18,23
X	US 5 157 030 A (A. GALAT) 20 October 1992 (1992-10-20) claims examples --- -/--	1,4,5,8, 9,12,13, 17,19, 22,23

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 April 2003	28/04/2003

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

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 24019 A (ORBON) 20 May 1999 (1999-05-20) claims page 4, line 4 - line 10 example 3	1,6,8,9, 13,22,23
X	WO 99 51239 A (DU PONT) 14 October 1999 (1999-10-14) claims 1-5,15-17 page 5, line 3 -page 6, line 14 page 6, line 36 -page 7, line 15 page 9, line 31 -page 10, line 25 examples page 11, line 5 - line 9 page 2, line 31 - line 33	1,4, 8-13,19, 21-23
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A	US 5 068 467 A (Y. KUNIMI ET AL.) 26 November 1991 (1991-11-26) claims	1-23
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A	WO 01 03672 A (PROGRAPHARM) 18 January 2001 (2001-01-18) claims examples	1-23

INTERNATIONAL SEARCH REPORT

nation on patent family members

Interna | Application No
PCT/FR 02/04575

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Interna | Application No
PCT/FR 02/04575

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RAPPORT DE RECHERCHE INTERNATIONALE

Demande internationale No
PCT/FR 02/04575

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 7 A61K9/00 A61K47/10 A61K47/26

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 7 A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si réalisable, termes de recherche utilisés)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	US 5 073 374 A (J.A. MCCARTY) 17 décembre 1991 (1991-12-17) revendications colonne 2, ligne 13 - ligne 48 colonne 1, ligne 23 - ligne 34 --- US 5 157 030 A (A. GALAT) 20 octobre 1992 (1992-10-20) revendications exemples --- -/--	1,6,8,9, 12,13, 17,18,23 1,4,5,8, 9,12,13, 17,19, 22,23

[X] Voir la suite du cadre C pour la fin de la liste des documents

[X] Les documents de familles de brevets sont indiqués en annexe

° Catégories spéciales de documents cités:

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"X" document particulièrement pertinent; l'inven tion revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

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"&" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
16 avril 2003	28/04/2003

Nom et adresse postale de l'administration chargée de la recherche internationale	Fonctionnaire autorisé
Office Européen des Brevets, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

Formulaire PCT/ISA/210 (deuxième feuille) (juillet 1992)

C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec,le cas échéant, l'indicationdes passages pertinents	no. des revendications visées
X	WO 99 24019 A (ORBON) 20 mai 1999 (1999-05-20) revendications page 4, ligne 4 - ligne 10 exemple 3	1,6,8,9, 13,22,23
X	WO 99 51239 A (DU PONT) 14 octobre 1999 (1999-10-14) revendications 1-5,15-17 page 5, ligne 3 -page 6, ligne 14 page 6, ligne 36 -page 7, ligne 15 page 9, ligne 31 -page 10, ligne 25 exemples page 11, ligne 5 - ligne 9 page 2, ligne 31 - ligne 33	1,4, 8-13,19, 21-23
A	US 5 320 848 A (R.P. GEYER ET AL.) 14 juin 1994 (1994-06-14) revendications colonne 4, ligne 34 - ligne 35 exemples colonne 5, ligne 3 - ligne 68	1-23
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A	US 5 068 467 A (Y. KUNIMI ET AL.) 26 novembre 1991 (1991-11-26) revendications	1-23
A	EP 0 266 113 A (AMERICAN HOME PRODUCTS) 4 mai 1988 (1988-05-04) revendications exemples	1-23
A	WO 01 03672 A (PROGRAPHARM) 18 janvier 2001 (2001-01-18) revendications exemples	1-23

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs au nbres de familles de brevets

Demande internationale No
PCT/FR 02/04575

Document brevet cité au rapport de recherche		Date de publication	Membre(s) de la famille de brevet(s)		Date de publication
US 5073374	A	17-12-1991	AU	631584 B2	03-12-1992
			AU	4665489 A	26-06-1990
			CA	2004033 A1	31-05-1990
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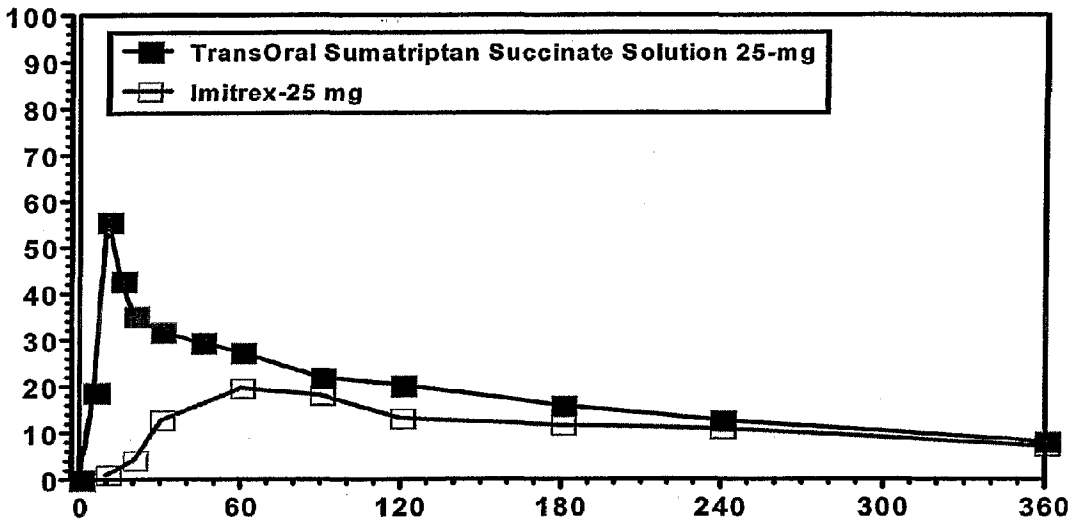
(54) Title: COMPOSITIONS FOR DELIVERING 5-HT AGONISTS ACROSS THE ORAL MUCOSA AND METHODS OF USE THEREOF



(57) Abstract: The present invention provides novel compositions for the delivery of a 5-hydroxytryptamine (5-HT) agonist across the oral mucosa. In particular, the buffer system in the compositions of the present invention raises the pH of saliva to a pH greater than about 9.9, thereby facilitating the substantially complete conversion of the 5-HT agonist from its ionized to its un-ionized form. As a result, the dose of 5-HT agonist is rapidly and efficiently absorbed by the oral mucosa. Furthermore, delivery of the 5-HT agonist across the oral mucosa advantageously bypasses hepatic first pass metabolism of the drug and avoids enzymatic degradation of the drug within the gastrointestinal tract. Methods for using the compositions of the present invention for treating migraines are also provided.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

COMPOSITIONS FOR DELIVERING 5-HT AGONISTS ACROSS THE ORAL MUCOSA AND METHODS OF USE THEREOF

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to each of USSN 10/646,659, filed August 21, 2003 and USSN 60/598,672 filed August 3, 2004 (Atty Docket No. 022205-000310US), the disclosures of each being incorporated herein by reference.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] While there are various types of dosage forms, solid dosage forms for oral administration are perhaps among the most preferred by patients, and among the most prevalently used. These dosage forms are typically medicaments formulated as tablets, capsules, or liquids, which are swallowed. Oral administration, however, has several disadvantages, such as drug losses during hepatic first pass metabolism, during enzymatic degradation within the GI tract, and during absorption. These drug losses not only increase the variability in drug response, but also often require that the medicament be given in greater initial doses. In addition, because the drug has to pass through the gastrointestinal system in order to enter the blood stream, the time to reach a therapeutic effect may be quite long, typically around forty-five minutes or longer.

[0005] Accordingly, other routes of drug administration have been investigated, including those involving transport across the mucous membranes. Of the various mucous membranes (*e.g.*, oral, rectal, vaginal, ocular, nasal, etc.), drug delivery via the mucous membranes in the

oral cavity seems to be the most easily tolerated by patients. In addition to avoiding the problems with traditional oral administration, drug delivery via the mucous membranes of the oral cavity has certain other advantages, due to the properties of the oral mucosa itself. For example, the mucous membranes of the oral cavity are highly vascularized and well supplied with lymphatic drainage sites.

[0006] In general, the mucous membranes of the oral cavity can be divided into five main regions: the floor of the mouth (sublingual), the cheeks (buccal), the gums (gingival), the roof of the mouth (palatal), and the lining of the lips. These regions differ from each other with respect to their anatomy, drug permeability, and physiological response to drugs. For example, in terms of permeability, sublingual is more permeable than buccal, which is more permeable than palatal. This permeability is generally based on the relative thickness and degree of keratinization of these membranes, with the sublingual mucosa being relatively thin and non-keratinized, the buccal mucosa being thicker and non-keratinized, and the palatal mucosa being intermediate in thickness, but keratinized.

[0007] In addition to the differences in permeability of the various mucous membranes, the extent of drug delivery is also affected by the properties of the drug to be delivered. The ability of a molecule to pass through any mucous membrane is dependent upon its size, its lipid solubility, and the extent to which it is ionized, among other factors.

[0008] The extent to which a drug is ionized has further been investigated with respect to drug delivery across the mucous membranes. Ionization is dependant on the dissociation constant, or pKa of the molecule, and the pH of the molecule's surrounding environment. In its un-ionized form, a drug is sufficiently lipophilic to traverse a membrane via passive diffusion. In fact, according to the pH partition hypothesis, only un-ionized, non-polar drugs will penetrate a lipid membrane.

[0009] At equilibrium, the concentrations of the un-ionized form of the drug are equal on both sides of the membrane. As the concentration gradient drives passive diffusion, an increase in the percentage of the un-ionized form of a drug correspondingly increases the transmucosal absorption of the drug. Maximum absorption across the membrane is thought to occur when a drug is 100% in its un-ionized form. Similarly, absorption across the membrane decreases as the extent of ionization increases. Therefore, one may influence the extent of drug absorption across the mucous membranes of the oral cavity by altering the salivary pH.

[0010] Some of the known transmucosal dosage forms include the use of a single buffering agent in order to change the pH of the saliva and tissues surrounding the buccal mucosa. However, these single buffering agents typically react with an acid or a base to create a final pH that is dependent upon the initial pH of the saliva of the user. A buffering agent used to attain a final pH that is dependent upon the initial pH of the user results in great variability. The extent of ionization, and hence the extent of absorption across the mucous membranes cannot be predicted with any sort of accuracy. This may pose significant problems when calculating precise doses, minimizing variability in patient response, and proving consistency in drug loading to the regulatory authorities. In addition, a single buffering agent is typically not capable of sustaining a given pH over a period of time for optimal absorption. While others in the art have disclosed the use of more than one buffering agent, these aforementioned problems are not easily cured by the nonchalant addition of an extra buffering agent, which may be unsafe and cause irreversible damage to the mucous membranes of the oral cavity. As such, a buffering system capable of achieving and sustaining a final pH independent of the initial pH in order to increase transmucosal absorption has not heretofore been demonstrated.

[0011] Similarly, a buffer system that facilitates substantially complete conversion of the ionized form of a drug to the un-ionized form in the shortest period of time, which is critical for producing rapid delivery of practically an entire drug dose across the oral mucosa, has not heretofore been demonstrated. Previous dosage forms resulted in great variability in drug delivery, due to the variability in the rates in which a drug was released from its carrier. That is, the rates of drug release in previously described chewing gums or lozenges are largely dependent upon the rate of chewing or sucking of the user. The variability in these rates from user to user further exacerbates the ability to predict the final amount of drug that will enter systemic circulation. In addition, the rate of drug release from chewing gums is further dependent upon the ability of the drug to be released from the gum base. Often times, the gum base strongly adheres to the drug, making portions of the drug unavailable for absorption.

[0012] Accordingly, there is a need in the art for compositions for delivering therapeutic agents across the oral mucosa having buffer systems that facilitate absorption of the agents in a safe and stable manner. Similarly, there is a need in the art for compositions for delivering therapeutic agents across the oral mucosa having a buffer system that produces a final pH, independent of the initial pH, and sustains that final pH for a given period of time. In

addition, there is a need in the art for compositions capable of rapidly facilitating substantially complete conversion of a therapeutic agent from its ionized to its un-ionized form. The present invention satisfies these and other needs.

BRIEF SUMMARY OF THE INVENTION

[0013] The present invention provides novel compositions for the delivery of a 5-hydroxytryptamine (5-HT) agonist across the oral mucosa. In particular, the buffer system in the compositions of the present invention raises the pH of saliva to a pH greater than about 9.9, thereby facilitating the substantially complete conversion of the 5-HT agonist from its ionized to its un-ionized form. As a result, the dose of 5-HT agonist is rapidly and efficiently absorbed by the oral mucosa. Furthermore, delivery of the 5-HT agonist across the oral mucosa advantageously bypasses hepatic first pass metabolism of the drug and avoids enzymatic degradation of the drug within the gastrointestinal tract. Methods for using the compositions of the present invention for treating migraines are also provided.

[0014] As such, in one aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a metal oxide,

wherein the ternary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0015] In another aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a citrate, phosphate, or borate salt,

wherein the ternary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0016] In yet another aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a buffer system comprising a carbonate salt or a bicarbonate salt and two or more buffering agents selected from the group consisting of a metal oxide, a citrate salt, a phosphate salt, and a borate salt,

wherein the buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0017] In still yet another aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt or a bicarbonate salt and a metal oxide,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0018] In a further aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt or a bicarbonate salt and a citrate, phosphate, or borate salt,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0019] In another aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a metal oxide and a citrate, phosphate, or borate salt,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0020] In yet another aspect, the present invention provides a method for treating a migraine in a subject in need thereof, the method comprising:

administering to the subject a composition comprising a therapeutically effective amount of a 5-HT agonist or a pharmaceutically acceptable salt thereof, a carrier, and a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a metal oxide, wherein the ternary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0021] Other objects, features, and advantages of the present invention will be apparent to one of skill in the art from the following detailed description and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] Figure 1 shows the mean plasma concentration over time for Formulation A (25 mg buccal sumatriptan succinate solution) and Formulation B (25 mg Imitrex® oral tablet).

[0023] Figure 2 shows the pH stability of a 9 mg and a 12.5 mg sublingual sumatriptan composition of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0024] As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0025] The term "migraine" refers to an intense, throbbing, typically unilateral headache characterized by sharp pain and often accompanied by symptoms such as nausea, vomiting, sensitivity to light and/or sound, stuffy or runny nose, watery eyes, dizziness, mood changes, allodynia, and visual disturbances. Migraines are typically recurring headaches, and most migraine sufferers (*i.e.,* subjects) experience at least one migraine attack a month. Migraines can happen at any time and, if left untreated, can last from about 4 hours to about 3 days. One skilled in the art will appreciate that migraine symptoms can not only vary between subjects, but can also vary between migraine attacks in a given subject. The pain from a migraine is moderate to severe in intensity and can affect one of both sides of the head as well as other areas such as the back of the neck, the face, the eyes, and the sinuses. Types of migraine suitable for treatment with the compositions of the present invention include,

without limitation, migraine without aura and migraine with aura. The term "migraine without aura" refers to the most common type of migraine and includes an intense, throbbing headache that is typically accompanied by sensitivity to light and/or sound. The term "migraine with aura" refers to a type of migraine that is preceded by aura.

[0026] As used herein, the term "aura" refers to the visual disturbances that some migraine sufferers have before a migraine attack. Aura typically develops gradually immediately preceding a migraine and lasts less than about an hour. Generally, about 3 out of every 10 subjects who suffer from migraines experience aura before a migraine attack. Aura is accompanied by symptoms including, without limitation, visual changes such as tunnel vision, blind spots, blurred vision, seeing flashing lights, seeing jagged lines, seeing spots, and difficulty in focusing; sensory or motor changes such as numbness or tingling of the lips, face, or hands on one or both sides and weakness in the arms and/or legs on one or both sides; and speech or language changes such as the inability to understand words, loss of speech, and the inability to speak normally.

[0027] The terms "therapeutic agent" and "drug" are used interchangeably herein to refer to a substance having a pharmaceutical, pharmacological, psychosomatic, or therapeutic effect. Preferably, the therapeutic agent or drug is a 5-hydroxytryptamine (5-HT) agonist. Suitable 5-HT agonists for use in the present invention include, without limitation, sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, F 11356, pharmaceutically acceptable salts thereof, and combinations thereof. In a particularly preferred embodiment, the 5-HT agonist is sumatriptan, in all suitable forms. In other embodiments of the present invention, the therapeutic agent or drug is a combination of a 5-HT agonist and a 5-HT antagonist. Suitable 5-HT antagonists for use in the present invention include, without limitation, ondansetron, palonosetron, tropisetron, lerisetron, alosetron, granisetron, dolasetron, bernesetron, ramosetron, azaseteron, itasetron, zacopride, cilasetron, and any other 5-HT antagonist containing an imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, or pyrrolidine group. In still other embodiments of the present invention, the therapeutic agent or drug is a combination of a 5-HT agonist and a non-steroidal anti-inflammatory drug (NSAID). Suitable NSAIDs for use in the present invention include, without limitation, traditional NSAIDs such as aspirin (*i.e.,* acetylsalicylic acid), ibuprofen, flurbiprofen, acetaminophen, diclofenac, diflunisal, etodolac, indomethacin, ketoprofen, ketorolac, naproxen, nabumetone, oxaprozin, piroxicam, sulindac, and tolmetin; selective

cyclooxygenase inhibitors such as celecoxib, rofecoxib, and valdecoxib; and combinations thereof.

[0028] The term "therapeutically effective amount" refers to the amount of a 5-HT agonist that is capable of achieving a therapeutic effect in a subject in need thereof. For example, a therapeutically effective amount of a 5-HT agonist can be the amount that is capable of preventing or relieving one or more symptoms associated with a migraine or a cluster headache.

[0029] The term "bioavailability" refers to the rate and/or extent to which a drug is absorbed or becomes available to the treatment site in the body.

[0030] As used herein, the phrase "substantially complete conversion of the 5-HT agonist from its ionized to its un-ionized form" refers to greater than about 50% conversion of the 5-HT agonist from its ionized form into its un-ionized form. For example, the buffer system may favor at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% conversion of the 5-HT agonist from its ionized form into its un-ionized form. In some embodiments, the conversion occurs within about 10 minutes following administration.

[0031] The term "administering" refers to administration of the compositions of the present invention to the mucous membranes of the oral cavity (*i.e.,* oral mucosa). Examples of suitable sites of administration within the oral mucosa include, without limitation, the mucous membranes of the floor of the mouth (sublingual mucosa), the cheeks (buccal mucosa), the gums (gingival mucosa), the roof of the mouth (palatal mucosa), the lining of the lips, and combinations thereof. Preferably, the compositions of the present invention are administered to the sublingual mucosa, buccal mucosa, or a combination thereof.

II. General

[0032] The present invention provides novel compositions for the delivery of a 5-HT agonist across the oral mucosa. In particular, the buffer system in the compositions of the present invention raises the pH of saliva to a pH greater than about 9.9, thereby facilitating the substantially complete conversion of the 5-HT agonist from its ionized to its un-ionized form. Furthermore, delivery of the 5-HT agonist across the oral mucosa advantageously bypasses hepatic first pass metabolism of the drug and avoids enzymatic degradation of the drug within the gastrointestinal tract. As a result, the 5-HT agonist reaches the systemic circulation in a substantially shorter period of time and at a substantially higher concentration

than with traditional oral (*e.g.*, tablet) administration. Methods for using the compositions of the present invention for treating migraines are also provided.

[0033] The present invention is based upon the surprising discovery that the addition of an oxide component such as magnesium oxide to the buffer system is extremely beneficial for (a) raising the pH of saliva to a pH of about 9.9 or more, irrespective of starting pH; (b) reducing the corrosivity of the carbonate component present in the buffer system; (c) serving as a secondary binding agent thereby eliminating the need for stearic acid; and (d) lowering the amount of the carbonate component needed to produce the desired pH. Without intending to be bound by any particular theory, it is believed that the oxide component (*e.g.*, magnesium oxide and aluminum oxide) acts as a cytoprotective agent, protecting cells against the high pH of carbonate and bicarbonate components present in the buffered compositions.

III. Description of the Embodiments

[0034] The present invention provides, in one aspect, a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a metal oxide,

wherein the ternary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0035] In one embodiment, the ternary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11, *e.g.*, about 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, irrespective of the starting pH of saliva. In another embodiment, the 5-HT agonist is selected from the group consisting of sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, and combinations thereof. In some embodiments, sumatriptan is the preferred 5-HT agonist. In certain instances, the composition further comprises a 5-HT antagonist. In certain other instances, the composition further comprises a non-steroidal anti-inflammatory drug (NSAID). In another embodiment, the carbonate salt is selected from the group consisting of sodium carbonate, potassium carbonate, calcium carbonate, ammonium carbonate, and magnesium carbonate. In yet another embodiment, the bicarbonate salt is selected from the group consisting of sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate, and magnesium bicarbonate. In

still yet another embodiment, the metal oxide is amorphous magnesium oxide or aluminum oxide. In a preferred embodiment, the ternary buffer system comprises sodium carbonate, sodium bicarbonate, and amorphous magnesium oxide. In another preferred embodiment, the sodium bicarbonate is dessicant-coated sodium bicarbonate.

[0036] In another embodiment, the compositions of the present invention are in a dosage form selected from the group consisting of a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet. Preferably, the composition is a lozenge or a dissolving tablet. A description of lozenge, chewing gum, and quick-dissolving tablet compositions containing a 5-HT agonist is provided in the Examples below.

[0037] In a preferred embodiment, the 5-HT agonist is delivered across an oral mucosa selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof. Preferably, the composition is administered sublingually so that the 5-HT agonist is delivered across the sublingual mucosa.

[0038] In another embodiment, the carrier is typically a solid, semi-solid, or liquid such as a binder, a gum base, or combinations thereof. Suitable binders for use in the compositions of the present invention include, without limitation, sugar alcohols such as mannitol, sorbitol, and xylitol; sugars such as lactose, dextrose, sucrose, glucose, and powdered sugar; other substances such as inositol, molasses, maltodextrin, starch, cellulose, microcrystalline cellulose, polyvinylpyrrolidone, acacia gum, guar gum, tragacanth gum, alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, Veegum®, larch arabogalactan, gelatin, methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, polyacrylic acid (*e.g.,* Carbopol), calcium silicate, calcium phosphate, dicalcium phosphate, calcium sulfate, kaolin, sodium chloride, polyethylene glycol; and combinations thereof. Suitable gum bases for use in the compositions of the present invention include, for example, materials selected from among the many water-insoluble and saliva-insoluble gum base materials known in the art. In certain instances, the gum base comprises at least one hydrophobic polymer and at least one hydrophilic polymer. Non-limiting examples of suitable hydrophobic and hydrophilic polymers for gum bases include both natural and synthetic polymers such as elastomers, rubbers, and combinations thereof. Examples of suitable natural polymers include, without limitation, substances of plant origin such as chicle, jelutong, gutta percha, crown gum, and combinations thereof.

Examples of suitable synthetic polymers include elastomers such as butadiene-styrene copolymers, isobutylene and isoprene copolymers (*e.g.*, "butyl rubber"), polyethylene, polyisobutylene, polyvinylester (*e.g.*, polyvinyl acetate and polyvinyl acetate phthalate), and combinations thereof. In other instances, the gum base comprises a mixture of butyl rubber (*i.e.*, isobutylene and isoprene copolymer), polyisobutylene, and optionally, polyvinylacetate (*e.g.*, having a molecular weight of approximately 12,000).

[0039] In yet another embodiment, the compositions of the present invention can further comprise a sweetening agent, a flavoring agent, a protecting agent, a plasticizer, a wax, an elastomeric solvent, a filler material, a preservative, or combinations thereof. In still yet another embodiment, the compositions of the present invention can further comprise a lubricating agent, a wetting agent, an emulsifying agent, a solubilizing agent, a suspending agent, a coloring agent, a disintegrating agent, or combinations thereof. In a preferred embodiment, the average particle size of the drug in the compositions described herein is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In another preferred embodiment, the average particle size of the drug in the compositions described herein is less than or equal to the average particle size of the carrier ingredients (*e.g.*, gum base, binders, *etc.*).

[0040] In preferred embodiments of the present invention, the 5-HT agonist is sumatriptan and the ternary buffer system comprises sodium carbonate, sodium bicarbonate, and amorphous magnesium oxide. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration. As a result, upon sublingual administration, sumatriptan is delivered across the sublingual mucosa. Preferably, the sodium bicarbonate is dessicant-coated sodium bicarbonate. In certain instances, a weight percent of amorphous magnesium oxide greater than or equal to the combined or individual weight percent of sodium carbonate and sodium bicarbonate is preferred. In certain other instances, a weight percent of amorphous magnesium oxide less than the combined or individual weight percent of sodium carbonate and sodium bicarbonate is used, *e.g.*, from about 0.1% to about 10%.

[0041] In certain instances, the composition comprises from about 2.5 to about 4.5 weight percent sumatriptan; from about 4.0 to about 7.0 weight percent sodium carbonate; from about 8.0 to about 12.0 weight percent dessicant-coated sodium bicarbonate; and from about 20 to about 30 weight percent amorphous magnesium oxide. In a preferred embodiment, the

composition comprises about 3.5 weight percent sumatriptan; about 5.5 weight percent sodium carbonate; about 9.0 weight percent dessicant-coated sodium bicarbonate; and about 25 weight percent amorphous magnesium oxide.

[0042] In another aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a citrate, phosphate, or borate salt,

wherein the ternary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0043] In one embodiment, the ternary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11, irrespective of the starting pH of saliva. Suitable 5-HT agonists for use in the present invention are described above. Suitable carbonate salts and bicarbonate salts for use in the ternary buffer systems of the present invention are also described above. In certain instances, the composition further comprises a 5-HT antagonist. In certain other instances, the composition further comprises an NSAID.

[0044] Suitable citrate, phosphate, and borate salts include, without limitation, any salt of citric acid, phosphoric acid, or boric acid known in the art. For example, in some embodiments, the citrate salt is selected from the group consisting of sodium citrate, potassium citrate, calcium citrate, magnesium citrate, and ammonium citrate. In other embodiments, the phosphate salt is selected from the group consisting of monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, dibasic potassium phosphate, monobasic calcium phosphate, dibasic calcium phosphate, monobasic magnesium phosphate, dibasic magnesium phosphate, monobasic ammonium phosphate, and dibasic ammonium phosphate. In yet other embodiments, the borate salt is selected from the group consisting of sodium borate, potassium borate, calcium borate, magnesium borate, and ammonium borate. In certain instances, the ternary buffer system comprises a carbonate salt, a bicarbonate salt, and a citrate salt. In certain other instances, the ternary buffer system comprises a carbonate salt, a bicarbonate salt, and a phosphate salt. In further instances, the ternary buffer system comprises a carbonate salt, a bicarbonate salt, and a borate salt.

[0045] In another embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the 5-HT agonist is delivered across an oral mucosa as described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above.

[0046] In still yet another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (*e.g.*, gum base, binders, *etc.*).

[0047] In preferred embodiments of the present invention, the 5-HT agonist is sumatriptan and the ternary buffer system comprises sodium carbonate, sodium bicarbonate, and a citrate, phosphate, or borate salt. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration.

[0048] In yet another aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a buffer system comprising a carbonate salt or a bicarbonate salt and two or more buffering agents selected from the group consisting of a metal oxide, a citrate salt, a phosphate salt, and a borate salt,

wherein the buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0049] In one embodiment, the buffer system raises the pH of saliva to a pH of from about 9.9 to about 11, irrespective of the starting pH of saliva. Suitable 5-HT agonists for use in the present invention are described above. Suitable carbonate salts and bicarbonate salts for use in the buffer systems of the present invention are also described above. In certain instances, the composition further comprises a 5-HT antagonist. In certain other instances, the composition further comprises an NSAID.

[0050] In another embodiment, the metal oxide is magnesium oxide or aluminum oxide. Preferably, the magnesium oxide is amorphous magnesium oxide. Suitable citrate, phosphate, and borate salts include, without limitation, any salt of citric acid, phosphoric

acid, or boric acid known in the art such as those described above. In certain instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a metal oxide, and a citrate, phosphate, or borate salt. In certain other instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a citrate salt, and a phosphate salt. In certain instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a citrate salt, and a borate salt. In certain other instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a phosphate salt, and a borate salt.

[0051] In yet another embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the 5-HT agonist is delivered across an oral mucosa as described above. In still yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above.

[0052] In a further embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (*e.g.*, gum base, binders, *etc.*).

[0053] In preferred embodiments of the present invention, the 5-HT agonist is sumatriptan and the buffer system comprises sodium carbonate or sodium bicarbonate and two or more buffering agents selected from the group consisting of a metal oxide, a citrate salt, a phosphate salt, and a borate salt. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration.

[0054] In still yet another aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt or a bicarbonate salt and a metal oxide,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0055] In one embodiment, the binary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11, irrespective of the starting pH of saliva. Suitable 5-HT agonists for use

in the present invention are described above. Suitable carbonate salts, bicarbonate salts, and metal oxides for use in the binary buffer systems of the present invention are also described above. In certain instances, the composition further comprises a 5-HT antagonist. In certain other instances, the composition further comprises an NSAID.

[0056] In another embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the 5-HT agonist is delivered across an oral mucosa as described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above.

[0057] In still yet another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (*e.g.*, gum base, binders, *etc.*).

[0058] In preferred embodiments of the present invention, the 5-HT agonist is sumatriptan and the binary buffer system comprises sodium carbonate or sodium bicarbonate and amorphous magnesium oxide. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration. In certain instances, a weight percent of amorphous magnesium oxide greater than or equal to the weight percent of sodium carbonate or sodium bicarbonate is preferred. In certain other instances, a weight percent of amorphous magnesium oxide less than the weight percent of sodium carbonate or sodium bicarbonate is used, *e.g.*, from about 0.1% to about 10%.

[0059] In a further aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt or a bicarbonate salt and a citrate, phosphate, or borate salt,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0060] In one embodiment, the binary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11, irrespective of the starting pH of saliva. Suitable 5-HT agonists for use

in the present invention are described above. Suitable carbonate salts, bicarbonate salts, and citrate, phosphate, and borate salts for use in the binary buffer systems of the present invention are also described above. In certain instances, the composition further comprises a 5-HT antagonist. In certain other instances, the composition further comprises an NSAID.

[0061] In another embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the 5-HT agonist is delivered across an oral mucosa as described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above.

[0062] In still yet another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (*e.g.*, gum base, binders, *etc.*).

[0063] In preferred embodiments of the present invention, the 5-HT agonist is sumatriptan and the binary buffer system comprises sodium carbonate or sodium bicarbonate and a citrate, phosphate, or borate salt. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration.

[0064] In another aspect, the present invention provides a composition for delivery of a 5-HT agonist across the oral mucosa, the composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a metal oxide and a citrate, phosphate, or borate salt,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0065] In one embodiment, the binary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11, irrespective of the starting pH of saliva. Suitable 5-HT agonists for use in the present invention are described above. Suitable metal oxides and citrate, phosphate, and borate salts for use in the binary buffer systems of the present invention are also described above. In certain instances, the composition further comprises a 5-HT antagonist. In certain other instances, the composition further comprises an NSAID.

[0066] In another embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the 5-HT agonist is delivered across an oral mucosa as described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above.

[0067] In still yet another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (*e.g.,* gum base, binders, *etc.*).

[0068] In preferred embodiments of the present invention, the 5-HT agonist is sumatriptan and the binary buffer system comprises amorphous magnesium oxide and a citrate, phosphate, or borate salt. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration.

[0069] In yet another aspect, the present invention provides a method for treating a migraine in a subject in need thereof, the method comprising:

administering to the subject a composition comprising a therapeutically effective amount of a 5-HT agonist or a pharmaceutically acceptable salt thereof, a carrier, and a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a metal oxide, wherein the ternary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

[0070] In a preferred embodiment, the composition delivers the 5-HT agonist across the oral mucosa such as, for example, the sublingual mucosa, the buccal mucosa, or a combination thereof. Preferably, the composition is administered sublingually so that the 5-HT agonist is delivered across the sublingual mucosa. Suitable migraines that can be treated with the compositions of the present invention include, without limitation, a migraine without aura and a migraine with aura.

[0071] In one embodiment, the ternary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11, irrespective of the starting pH of saliva. Suitable 5-HT agonists for use in the present invention are described above. Suitable carbonate salts, bicarbonate salts, and metal oxides for use in the ternary buffer systems of the present invention are also

described above. In certain instances, the composition further comprises a 5-HT antagonist. In certain other instances, the composition further comprises an NSAID.

[0072] In addition to a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a metal oxide, other buffer systems are suitable for use in the compositions of the present invention. For example, in an alternative embodiment, the ternary buffer system comprises a carbonate salt, a bicarbonate salt, and a citrate, phosphate, or borate salt. In another alternative embodiment, the buffer system comprises a carbonate salt or a bicarbonate salt and two or more buffering agents selected from the group consisting of a metal oxide, a citrate salt, a phosphate salt, and a borate salt. In yet another alternative embodiment, the buffer system is a binary buffer system comprising a carbonate salt or a bicarbonate salt and a metal oxide. In still yet another alternative embodiment, the buffer system is a binary buffer system comprising a carbonate salt or a bicarbonate salt and a citrate, phosphate, or borate salt. In a further alternative embodiment, the buffer system is a binary buffer system comprising a metal oxide and a citrate, phosphate, or borate salt. In still yet another alternative embodiment, the buffer system is a binary buffer system comprising a carbonate salt and a bicarbonate salt, preferably sodium carbonate and sodium bicarbonate.

[0073] In another embodiment, the compositions of the present invention are in any of the dosage forms described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above.

[0074] In still yet another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (*e.g.,* gum base, binders, *etc.*).

[0075] In preferred embodiments of the present invention, the 5-HT agonist is sumatriptan and the ternary buffer system comprises sodium carbonate, sodium bicarbonate, and amorphous magnesium oxide. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration. In certain instances, a weight percent of amorphous magnesium oxide greater than or equal to the combined or individual weight percent of sodium carbonate and sodium bicarbonate is preferred. In certain other instances, a weight percent of amorphous magnesium oxide less than the

combined or individual weight percent of sodium carbonate and sodium bicarbonate is used, *e.g.*, from about 0.1% to about 10%.

A. 5-HT Agonists

[0076] The 5-hydroxytryptamine (5-HT) agonists of the present invention are preferably selected from sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, F 11356, pharmaceutically acceptable salts thereof, and combinations thereof. More preferably, the 5-HT agonist is sumatriptan, in all suitable forms. The 5-HT agonists described herein are basic compounds with selective or non-selective vasoactivity on blood vessels.

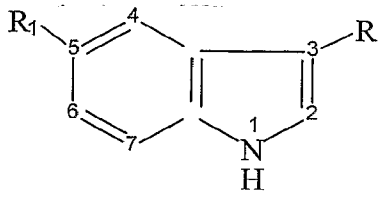
[0077] In general, the 5-HT agonists of the present invention have an ionized form and an un-ionized form. In certain instances, the 5-HT agonist is initially present at least partly in an ionized form. In certain other instances, the 5-HT agonist is initially present in an un-ionized form. As described in more detail below, the buffer system of the compositions described herein helps to convert substantially all of the 5-HT agonist from its ionized form to its un-ionized form. Alternatively, the buffer system helps ensure that the 5-HT agonist, initially in an un-ionized form, remains in an un-ionized form.

[0078] As used herein, the term "5-HT agonist" includes all pharmaceutically acceptable forms of the 5-HT agonist being described. For example, the 5-HT agonist can be in a racemic or isomeric mixture, a solid complex bound to an ion exchange resin, or the like. In addition, the 5-HT agonist can be in a solvated form. The term "5-HT agonist" is also intended to include all pharmaceutically acceptable salts, derivatives, and analogs of the 5-HT agonist being described, as well as combinations thereof. For example, the pharmaceutically acceptable salts of the 5-HT agonist include, without limitation, the succinate, tartarate, bitartarate, dihydrochloride, salicylate, hemisuccinate, citrate, maleate, hydrochloride, carbamate, sulfate, nitrate, and benzoate salt forms thereof, as well as combinations thereof and the like.

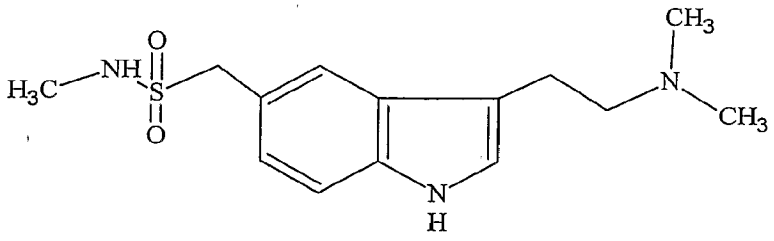
[0079] Conversion of the ionized form to the un-ionized form for the 5-HT agonist is related to pH according to the formula: $pH = pKa + Log_{10}$ (un-ionized concentration/ionized concentration). When the pH is the same as the pKa, equimolar concentrations of the un-ionized form and ionized form exist. For basic compounds such as the 5-HT agonists described herein, when the pH is one unit higher than the pKa, the ratio of the un-ionized form to the ionized form is 91:9. Similarly, when the pH is two units higher than the pKa, the

ratio of un-ionized form to the ionized form is 100:1. As noted above, the un-ionized form is lipophilic and, therefore, more capable of passing through mucous membranes such as the oral mucosa than the ionized form, which is lipophobic in nature. Accordingly, increasing the pH of the saliva favors conversion of the ionized form into the un-ionized form for basic compounds such as the 5-HT agonists described herein, and the final pH can be determined by making use of the above formula.

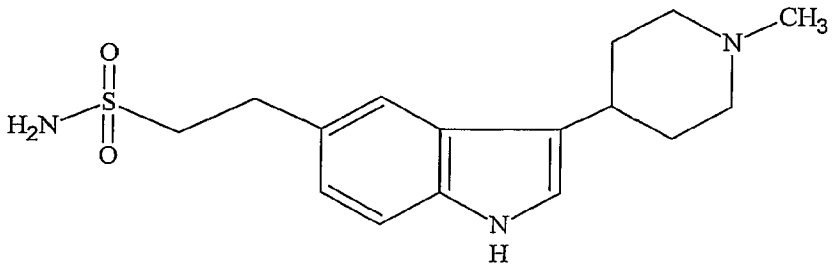
[0080] The 5-HT agonists of the present invention are indole derivatives useful in the treatment of conditions such as migraines, having the following basic indole nucleus:



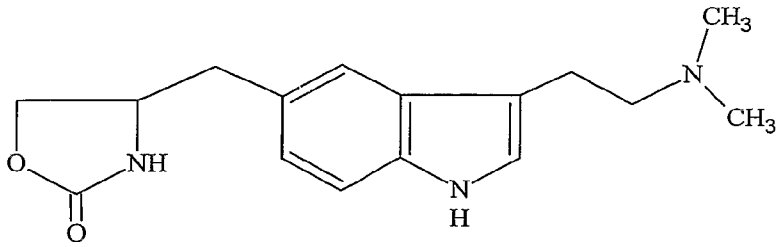
wherein R is typically an alkyl, alkenyl, cycloalkyl, or cycloalkenyl group and R_1 is typically a sulfonamide, an oxazolidinone, a triazole, or a sulfonyl group, any of which may be optionally substituted. More particularly, the 5-HT agonists of the present invention are preferably selected from the group consisting of sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, and F 11356, having the following structures:



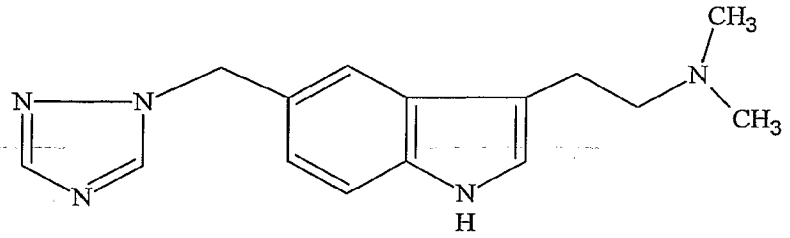
Sumatriptan



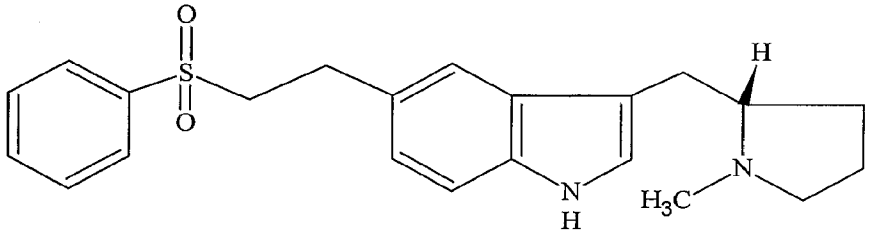
Naratriptan



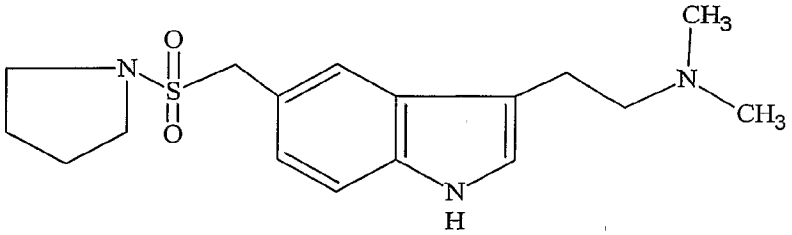
Zolmitriptan



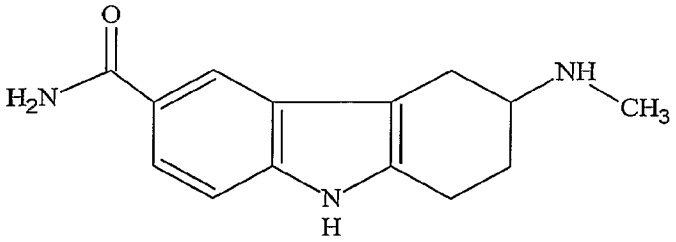
Rizatriptan



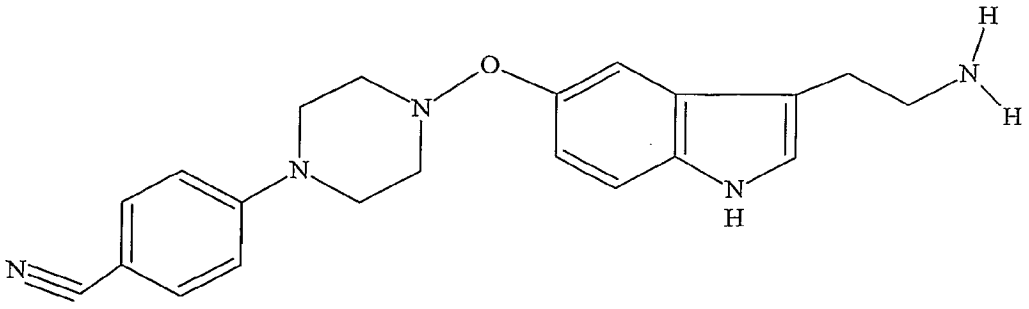
Eletriptan



Almotriptan



Frovatriptan

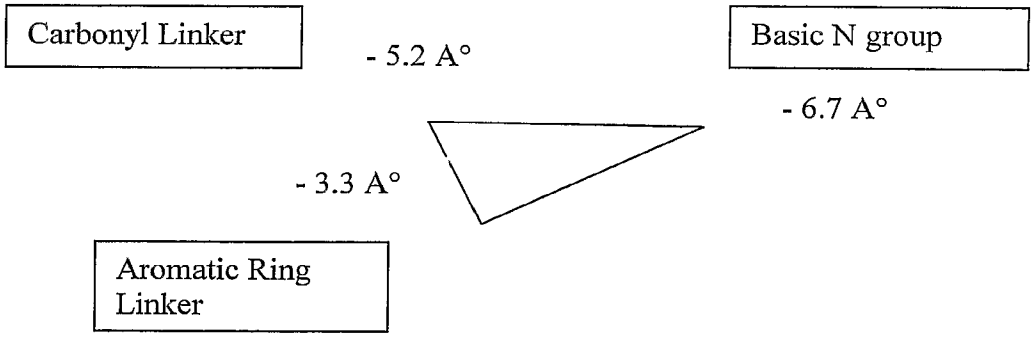


F 11356

[0081] For the above-described 5-HT agonists, the primary, secondary, or tertiary amines typically control the extent of ionization of the compound.

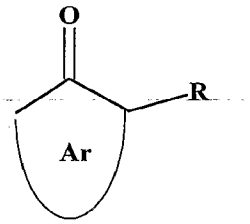
[0082] The 5-HT agonists of the present invention bind with high affinity to one or more 5-HT_1 receptor subtypes. Without being bound to any particular theory, the therapeutic activity of the 5-HT agonists of the present invention in treating migraines is attributed to one or more of the following mechanisms: (1) activation of 5-HT_1 receptors located on intracranial blood vessels (*e.g.*, arteriovenous anastomoses) by 5-HT agonists to stimulate vasoconstriction; and (2) activation of 5-HT_1 receptors located on sensory nerve endings in the trigeminal system to inhibit pro-inflammatory neuropeptide (*e.g.*, vasoactive intestinal peptide, substance P, calcitonin gene-related peptide) release.

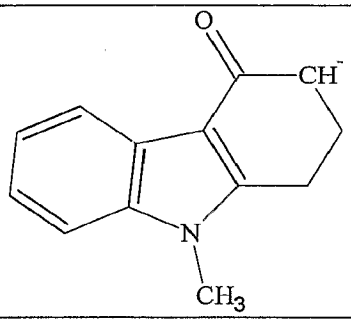
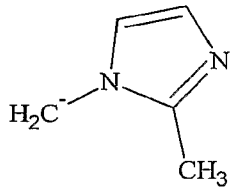
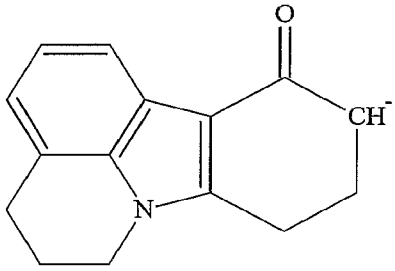
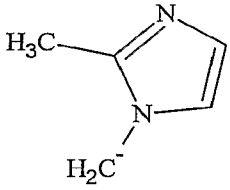
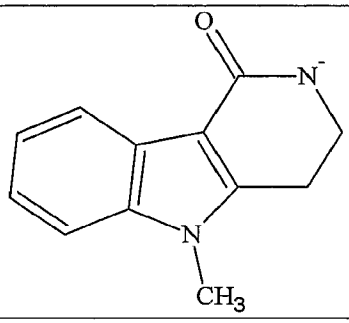
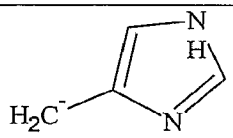
[0083] In other embodiments of the present invention, a 5-HT antagonist and/or a non-steroidal anti-inflammatory drug (NSAID) is delivered in combination with a 5-HT agonist. 5-HT antagonists typically consist of three main components: (1) an aromatic structure; (2) a carbonyl-containing linking moiety; and (3) an out-of-plane basic nitrogen containing heterocyclic group. These groups have the specific spatial arrangement shown below:



[0084] Suitable 5-HT antagonists for use in the present invention include, without limitation, 5-HT antagonists wherein the carbonyl linker is incorporated within the fused ring of the aromatic group (*see,* Table 1) and 5-HT antagonists wherein the carbonyl linker is directly attached (*i.e.,* as a spacer unit) to the aromatic ring and the basic nitrogen group (*see,* Table 2).

Table 1. 5-HT antagonists wherein the carbonyl linker is incorporated within the fused aromatic ring.



5-HT Antagonist	Ar	R
Ondansetron		
Cilasetron		
Alosetron		

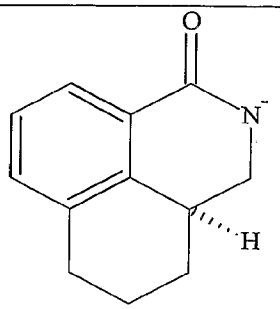
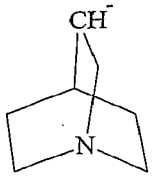
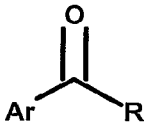
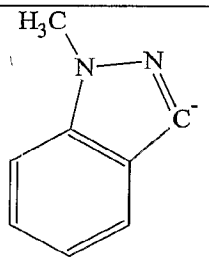
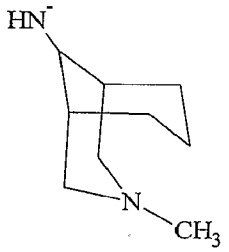
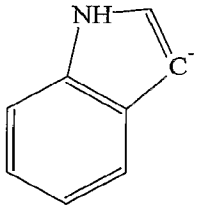
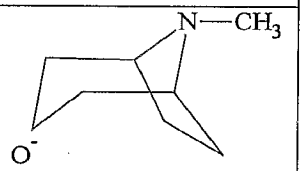
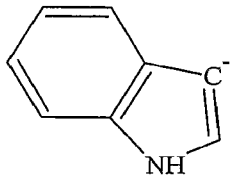
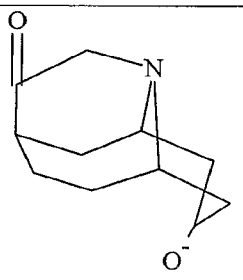
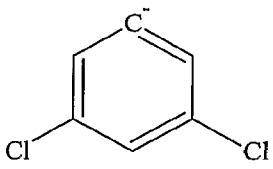
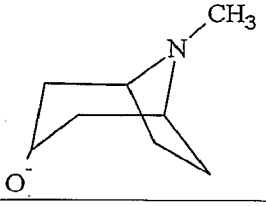
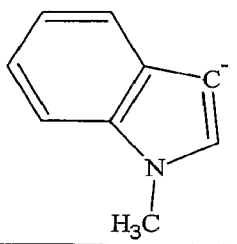
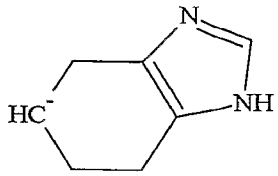
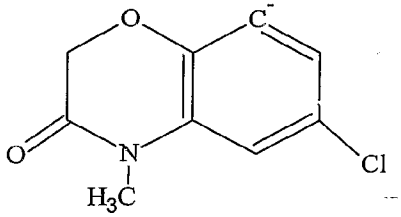
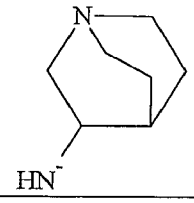
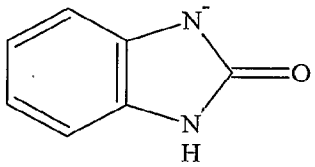
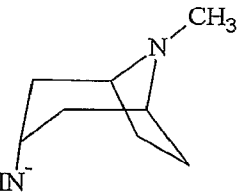
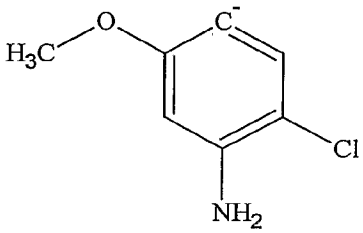
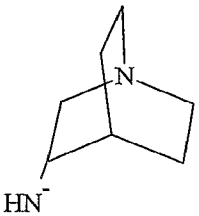
5-HT Antagonist	Ar	R
Palonosetron		

Table 2. 5-HT antagonists wherein the carbonyl linker is attached to the aromatic ring and the basic nitrogen group as a spacer.



5-HT Antagonist	Ar	R
Granisetron		
Tropisetron		
Dolasetron		
Bernesetron		

5-HT Antagonist	Ar	R
Ramosetron		
Azasetron		
Itasetron		
Zacopride		

[0085] As shown in Tables 1 and 2, the constant feature among the 5-HT antagonists is the basic nitrogen group. The basic nitrogen group can be classified generally as an imidazole group or as a nitrogen-containing heterobicyclic derivative.

[0086] Using the above formula, the overall lipophilicity and ionization of the 5-HT antagonists can be controlled and modulated by regulating the pH of the medium containing the 5-HT antagonist relative to the pKa of the basic nitrogen group. For example, 5-HT antagonists that contain nitrogen in an imidazole group have a pKa in the region of about 7.4, and can thus be substantially converted to their un-ionized, lipophilic form at a pH greater than about 8.4. Similarly, 5-HT antagonists that contain nitrogen in a bicyclic ring have a pKa of about 8.8, and can thus be substantially converted to their un-ionized, lipophilic form at a pH greater than about 9.8. Specific examples of suitable 5-HT antagonists for use in the present invention include, without limitation, ondansetron, palonosetron, tropisetron, lerisetron, alosetron, granisetron, dolasetron, bernesetron, ramosetron, azaseteron, itasetron,

zacopride, cilasetron, and any other 5-HT antagonist containing an imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, or pyrrolidine group.

[0087] Suitable NSAIDs for use in the present invention include, without limitation, traditional NSAIDs such as aspirin (*i.e.*, acetylsalicylic acid), ibuprofen, flurbiprofen, acetaminophen, diclofenac, diflunisal, etodolac, indomethacin, ketoprofen, ketorolac, naproxen, nabumetone, oxaprozin, piroxicam, sulindac, and tolmetin; selective cyclooxygenase inhibitors such as celecoxib, rofecoxib, and valdecoxib; and combinations thereof.

B. Buffer Systems

[0088] Although a binary composition of sodium carbonate and sodium bicarbonate can generally raise the pH of saliva to a level of about 8.0-9.8, the carbonate component must be present in an amount substantially higher than the bicarbonate component when a pH of about 9.0-9.8 is desired. However, with higher levels of carbonate, a corrosive effect on the oral mucosa and other oral tissues generally develops. As such, binary compositions containing only sodium carbonate and sodium bicarbonate have reduced utility for delivering the therapeutic agents of the present invention across the oral mucosa.

[0089] The present invention overcomes such limitations by providing, in one embodiment, ternary buffer systems comprising a carbonate salt, a bicarbonate salt, and an oxide component such as, for example, magnesium oxide or aluminum oxide. Although basic buffering agents are typically used in the buffer systems of the present invention, one skilled in the art will appreciate that acidic agents can also be used to adjust the pH of the buffer system as long as the buffer system as a whole raises the pH of saliva to a pH greater than about 9.9 (*e.g.*, about 9.9-11).

[0090] The concentration of each buffer system component is tailored such that the final salivary pH is achieved and sustained for a period of time, *e.g.*, for at least about 2 minutes, at least about 5 minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes. This typically involves a sensory and safety procedure involving adjusting the amounts of each buffer system component and measuring the final pH over time. In this way, selection of an appropriate weight ratio for each buffer system component can be easily determined in just a few trials. For example, the weight ratio of carbonate salt to bicarbonate salt for a ternary buffer system can be from about 1:10 to about 10:1, preferably from about

1:5 to about 5:1, more preferably from about 1:3 to about 3:1, and still more preferably from about 1:2 to about 2:1.

[0091] The carbonate salt is generally selected from sodium carbonate, potassium carbonate, calcium carbonate, ammonium carbonate, and magnesium carbonate. Preferably, the carbonate salt is sodium carbonate or potassium carbonate. Most preferably, the carbonate salt is sodium carbonate. Similarly, the bicarbonate salt is generally selected from sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate, and magnesium bicarbonate. Preferably, the bicarbonate salt is sodium bicarbonate or potassium bicarbonate. Most preferably, the bicarbonate salt is sodium bicarbonate. In some embodiments, a dessicant-coated sodium bicarbonate is preferred. The amount of carbonate salt and bicarbonate salt used in the ternary buffer system is an amount that is sufficient, when used with the metal oxide, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, *e.g.,* about 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, irrespective of the starting pH.

[0092] In certain instances, the amount of bicarbonate salt in the ternary buffer system is greater than or equal to the amount of carbonate salt. For example, the weight ratio of bicarbonate salt to carbonate salt can be from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 3:1. In a particularly preferred embodiment, the weight ratio of bicarbonate salt to carbonate salt is from about 1.5:1 to about 2:1. In certain other instances, the amount of bicarbonate salt in the ternary buffer system is less than the amount of carbonate salt.

[0093] Quite surprisingly, the addition of an oxide component such as magnesium oxide as a third component of the ternary buffer system has now been found to be extremely beneficial for (a) raising the pH of saliva to a pH of about 9.9 or more, irrespective of starting pH; (b) reducing the corrosivity of the carbonate component; (c) serving as a secondary binding agent thereby eliminating the need for stearic acid; and (d) lowering the amount of the carbonate component needed to produce the desired pH. Without intending to be bound by any particular theory, it is believed that the oxide component (*e.g.,* magnesium oxide and aluminum oxide) acts as a cytoprotective agent, protecting cells against the high pH of carbonate and bicarbonate in the buffered compositions.

[0094] The amount of the oxide component used in the ternary buffer systems of the present compositions is an amount that is sufficient, when used with the remaining

components, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, irrespective of the starting pH. In some embodiments, amorphous magnesium oxide is preferred. In certain instances, the weight percent of the oxide component is greater than or equal to the combined weight percent of the carbonate salt and the bicarbonate salt. For example, the weight ratio of the oxide component to the carbonate salt and the bicarbonate salt can be from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 3:1, and most preferably from about 1.5:1 to about 2:1. In certain other instances, the weight percent of the oxide component is greater than or equal to the weight percent of either the carbonate salt or the bicarbonate salt. In still other instances, the weight percent of the oxide component is less than the combined or individual weight percent of the carbonate salt and the bicarbonate salt, yet sufficient to provide an optimum pH of saliva as described above as well as good mouth feel properties.

[0095] In view of the above, the buffer systems of the present invention, in some of the most preferred embodiments, are ternary buffer systems containing sodium carbonate, sodium bicarbonate, and amorphous magnesium oxide.

[0096] Alternatively, in another embodiment, the buffer systems of the present invention are ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a third buffering agent such as a citrate, phosphate, or borate salt. The concentration of each buffer system component is tailored such that the final salivary pH is achieved and sustained for a period of time, *e.g.,* for at least about 2 minutes, at least about 5 minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes.

[0097] Suitable carbonate salts and bicarbonate salts are described above. The amount of carbonate salt and bicarbonate salt used in the ternary buffer system is an amount that is sufficient, when used with the third buffering agent, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, irrespective of the starting pH.

[0098] The third buffering agent is generally selected from a citrate salt such as sodium citrate, potassium citrate, calcium citrate, magnesium citrate, and ammonium citrate; a phosphate salt such as monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, dibasic potassium phosphate, monobasic calcium phosphate, dibasic calcium phosphate, monobasic magnesium phosphate, dibasic magnesium phosphate,

monobasic ammonium phosphate, and dibasic ammonium phosphate; a borate salt such as sodium borate, potassium borate, calcium borate, magnesium borate, and ammonium borate; an ascorbate salt such as potassium ascorbate or sodium ascorbate; an acetate salt such as potassium acetate or sodium acetate; and alkaline starch. However, one skilled in the art will appreciate that essentially any salt of citric acid, phosphoric acid, boric acid, ascorbic acid, or acetic acid is suitable for use in the buffer systems of the present invention. The amount of the third buffering agent used in the ternary buffer system is an amount that is sufficient, when used with the remaining components, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, irrespective of the starting pH.

[0099] In certain instances, the amount of the carbonate salt or bicarbonate salt in the ternary buffer system is greater than or equal to the amount of the third buffering agent. For example, the weight ratio of the carbonate salt or bicarbonate salt to the third buffering agent can be from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 3:1. In certain other instances, the amount of the carbonate salt or bicarbonate salt in the ternary buffer system is less than or equal to the amount of the third buffering agent. For example, the weight ratio of the carbonate salt or bicarbonate salt to the third buffering agent can be from about 1:1 to about 1:10, preferably from about 1:1 to about 1:5, and more preferably from about 1:1 to about 1:3.

[0100] Alternatively, in yet another embodiment, the buffer systems of the present invention are buffer systems comprising a carbonate salt or a bicarbonate salt and two or more buffering agents selected from the group consisting of a metal oxide, a citrate salt, a phosphate salt, and a borate salt. The concentration of each buffer system component is tailored such that the final salivary pH is achieved and sustained for a period of time, *e.g.,* for at least about 2 minutes, at least about 5 minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes.

[0101] Suitable carbonate salts and bicarbonate salts are described above. The amount of carbonate salt or bicarbonate salt used in the buffer system is an amount that is sufficient, when used with the remaining components, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, irrespective of the starting pH.

[0102] The two or more buffering agents are generally selected from a metal oxide, a citrate salt, a phosphate salt, a borate salt, an ascorbate salt, an acetate salt, and alkaline starch. Suitable metal oxides include, without limitation, magnesium oxide and aluminum oxide. Suitable citrate, phosphate, borate, ascorbate, and acetate salts include, without limitation, essentially any salt of citric acid, phosphoric acid, boric acid, ascorbic acid, or acetic acid known in the art such as those described above. The amount of the additional buffering agents used in the buffer system is an amount that is sufficient, when used with the carbonate salt or bicarbonate salt, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, irrespective of the starting pH.

[0103] In certain instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a metal oxide, and a citrate, phosphate, or borate salt. Preferably, the metal oxide is amorphous magnesium oxide. In certain other instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a citrate salt, and a phosphate salt. In certain instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a citrate salt, and a borate salt. In certain other instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a phosphate salt, and a borate salt.

[0104] In certain instances, the amount of the carbonate salt or bicarbonate salt in the buffer system is greater than or equal to the amount of the metal oxide or the citrate, phosphate, or borate salt. For example, the weight ratio of the carbonate salt or bicarbonate salt to the metal oxide or the citrate, phosphate, or borate salt can be from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 3:1. In certain other instances, the amount of the carbonate salt or bicarbonate salt in the buffer system is less than or equal to the amount of the metal oxide or the citrate, phosphate, or borate salt. For example, the weight ratio of the carbonate salt or bicarbonate salt to the metal oxide or the citrate, phosphate, or borate salt can be from about 1:1 to about 1:10, preferably from about 1:1 to about 1:5, and more preferably from about 1:1 to about 1:3.

[0105] Alternatively, in still yet another embodiment, the buffer systems of the present invention are binary buffer systems comprising a carbonate salt or a bicarbonate salt and a metal oxide. The concentration of each buffer system component is tailored such that the final salivary pH is achieved and sustained for a period of time, *e.g.*, for at least about 2 minutes, at least about 5 minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes.

[0106] Suitable carbonate salts, bicarbonate salts, and metal oxides are described above. The amount of carbonate salt or bicarbonate salt used in the binary buffer system is an amount that is sufficient, when used with the oxide component, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, irrespective of the starting pH. In certain instances, the amount of the oxide component in the binary buffer system is greater than or equal to the amount of either the carbonate salt or bicarbonate salt. For example, the weight ratio of the oxide component to the carbonate salt or bicarbonate salt can be from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 3:1. In certain other instances, the amount of the oxide component in the binary buffer system is less than the amount of either the carbonate salt or bicarbonate salt.

[0107] Alternatively, in a further embodiment, the buffer systems of the present invention are binary buffer systems comprising a carbonate salt or a bicarbonate salt and a second buffering agent such as a citrate, phosphate, or borate salt. The concentration of each buffer system component is tailored such that the final salivary pH is achieved and sustained for a period of time, *e.g.,* for at least about 2 minutes, at least about 5 minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes.

[0108] Suitable carbonate salts and bicarbonate salts are described above. The amount of carbonate salt or bicarbonate salt used in the binary buffer system is an amount that is sufficient, when used with the second buffering agent, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, irrespective of the starting pH. In certain instances, the amount of the second buffering agent in the binary buffer system is greater than or equal to the amount of either the carbonate salt or bicarbonate salt. For example, the weight ratio of the second buffering agent to the carbonate salt or bicarbonate salt can be from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 3:1. In certain other instances, the amount of the second buffering agent in the binary buffer system is less than or equal to the amount of either the carbonate salt or bicarbonate salt. For example, the weight ratio of the second buffering agent to the carbonate salt or bicarbonate salt can be from about 1:1 to about 1:10, preferably from about 1:1 to about 1:5, and more preferably from about 1:1 to about 1:3.

[0109] The second buffering agent is generally selected from a citrate salt, a phosphate salt, a borate salt, an ascorbate salt, an acetate salt, and alkaline starch as described above. The amount of the second buffering agent used in the binary buffer system is an amount that is sufficient, when used with the carbonate salt or bicarbonate salt, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, irrespective of the starting pH.

[0110] Alternatively, in another embodiment, the buffer systems of the present invention are binary buffer systems comprising a metal oxide and a citrate, phosphate, or borate salt. The concentration of each buffer system component is tailored such that the final salivary pH is achieved and sustained for a period of time, *e.g.,* for at least about 2 minutes, at least about 5 minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes.

[0111] The metal oxide is typically magnesium oxide or aluminum oxide. Preferably, the magnesium oxide is amorphous magnesium oxide. Suitable citrate, phosphate, and borate salts include, without limitation, essentially any salt of citric acid, phosphoric acid, or boric acid known in the art such as those described above. The amount of the metal oxide used in the binary buffer system is an amount that is sufficient, when used with the citrate, phosphate, or borate salt, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, irrespective of the starting pH. Similarly, the amount of the citrate, phosphate, or borate salt used in the binary buffer system is an amount that is sufficient, when used with the metal oxide, to raise salivary pH to a pH of about 9.5, preferably about 9.9 or more, and more preferably from about 9.9 to about 11, irrespective of the starting pH.

[0112] In certain instances, the amount of the metal oxide in the binary buffer system is greater than or equal to the amount of the citrate, phosphate, or borate salt. For example, the weight ratio of the metal oxide to the citrate, phosphate, or borate salt can be from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 3:1. In certain other instances, the amount of the metal oxide in the binary buffer system is less than or equal to the amount of the citrate, phosphate, or borate salt. For example, the weight ratio of the metal oxide to the citrate, phosphate, or borate salt can be from about 1:1 to about 1:10, preferably from about 1:1 to about 1:5, and more preferably from about 1:1 to about 1:3.

[0113] While the foregoing discussion has focused on the ability of the buffer system to alter salivary pH to favor substantial conversion to the un-ionized form of a therapeutic agent, the buffer system may also have subsidiary beneficial effects on the extent of absorption across the oral mucosa. For example, the buffer system can create a final salivary pH that in turn affects the molecular configuration of the therapeutic agent in a way in which absorption across the oral mucosa is increased. It is to be understood that these subsidiary beneficial effects of the buffer system are still further advantages of the present invention and are within the general scope of the buffer system and compositions herein described.

C. Dosage Forms

[0114] The compositions of the present invention may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets (*e.g.*, chewable, slow-dissolving, quick-dissolving), pills, capsules, lozenges, candies, gums, powders, solutions, suspensions, emulsions, aerosols, or the like. Preferably, the dosage form is a chewing gum, quick-dissolving tablet, candy, or lozenge.

[0115] While each subject or patient possesses unique factors that may affect the rate and extent of absorption of the therapeutic agents described herein, dosage forms such as chewing gums, quick-dissolving tablets, or lozenges offer advantages over the traditional dosage forms for oral administration. For example, each of these dosage forms avoids hepatic first pass metabolism, degradation within the gastrointestinal tract, and drug loss during absorption. Consequently, the amount of therapeutic agent required per dose is less than that which would be required if formulated, for example, in a pill or tablet for oral administration. Similarly, with each of these dosage forms, the bioavailability of the therapeutic agent is increased, thereby reducing the time to onset of therapeutic activity.

[0116] As used herein, the term "dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of therapeutic agent calculated to produce the desired onset, tolerability, and therapeutic effects, in association with one or more suitable pharmaceutical excipients such as carriers. Methods for preparing such dosage forms are known or will be apparent to those skilled in the art. For example, in some embodiments, a chewing gum dosage form of the present invention can be prepared according to the procedures set forth in U.S. Pat. No. 4,405,647. In other embodiments, a tablet, lozenge, or candy dosage form of the present invention can be prepared according to the procedures set forth in, for example, *Remington:*

The Science and Practice of Pharmacy, 20th Ed., Lippincott, Williams & Wilkins (2003); *Pharmaceutical Dosage Forms, Volume 1: Tablets*, 2nd Ed., Marcel Dekker, Inc., New York, N.Y. (1989); and similar publications. The dosage form to be administered will, in any event, contain a quantity of the therapeutic agent in a therapeutically effective amount for relief of the condition being treated when administered in accordance with the teachings of this invention.

[0117] As used herein, the term "carrier" refers to a typically inert substance used as a diluent or vehicle for a drug such as a therapeutic agent. The term also encompasses a typically inert substance that imparts cohesive qualities to the composition. Suitable carriers for use in the compositions of the present invention include, without limitation, a solid, semi-solid, or liquid such as a binder or a gum base. Non-limiting examples of binders include mannitol, sorbitol, xylitol, maltodextrin, lactose, dextrose, sucrose, glucose, inositol, powdered sugar, molasses, starch, cellulose, microcrystalline cellulose, polyvinylpyrrolidone, acacia gum, guar gum, tragacanth gum, alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, Veegum®, larch arabogalactan, gelatin, methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, polyacrylic acid (*e.g.*, Carbopol), calcium silicate, calcium phosphate, dicalcium phosphate, calcium sulfate, kaolin, sodium chloride, polyethylene glycol, and combinations thereof. These binders can be pre-processed to improve their flowability and taste by methods known in the art such as freeze drying (*see, e.g.*, Fundamentals of Freeze-Drying, *Pharm. Biotechnol.*, 14:281-360 (2002); Lyophililization of Unit Dose Pharmaceutical Dosage Forms, *Drug. Dev. Ind. Pharm.*, 29:595–602 (2003)); solid-solution preparation (*see, e.g.*, U.S. Pat. No. 6,264,987); and lubricant dusting and wet-granulation preparation with a suitable lubricating agent (*see, e.g.*, *Remington: The Science and Practice of Pharmacy*, *supra*). For example, Mannogem® and Sorbogem®, sold by SPI Pharma Group (New Castle, DE), are freeze-dried processed forms of mannitol and sorbitol, respectively. Typically, the compositions of the present invention comprise from about 25% to about 90% by weight of the binder, and preferably from about 50% to about 80%. However, one skilled in the art will appreciate that the compositions of the present invention can be made without any binders, *e.g.*, to produce a highly friable dosage form.

[0118] Non-limiting examples of gum bases include materials selected from among the many water-insoluble and saliva-insoluble gum base materials known in the art. For example, in some instances, the gum base comprises at least one hydrophobic polymer and at

least one hydrophilic polymer. Non-limiting examples of suitable hydrophobic and hydrophilic polymers for gum bases include both natural and synthetic polymers such as elastomers, rubbers, and combinations thereof. Examples of suitable natural polymers include, without limitation, substances of plant origin such as chicle, jelutong, gutta percha, crown gum, and combinations thereof. Examples of suitable synthetic polymers include elastomers such as butadiene-styrene copolymers, isobutylene and isoprene copolymers (*e.g.*, "butyl rubber"), polyethylene, polyisobutylene, polyvinylester (*e.g.*, polyvinyl acetate and polyvinyl acetate phthalate), and combinations thereof. In other instances, the gum base comprises a mixture of butyl rubber (*i.e.*, isobutylene and isoprene copolymer), polyisobutylene, and optionally, polyvinylacetate (*e.g.*, having a molecular weight of approximately 12,000). Typically, the gum base comprises from about 25% to about 75% by weight of these polymers, and preferably from about 30% to about 60%.

[0119] The compositions of the present invention can additionally include lubricating agents; wetting agents; emulsifying agents; solubilizing agents; suspending agents; preserving agents such as methyl-, ethyl-, and propyl-hydroxy-benzoates, butylated hydroxytoluene, and butylated hydroxyanisole; sweetening agents; flavoring agents; coloring agents; and disintegrating agents (*i.e.*, dissolving agents) such as crospovidone as well as croscarmellose sodium and other cross-linked cellulose polymers.

[0120] Lubricating agents can be used to prevent adhesion of the dosage form to the surface of the dies and punches, and to reduce inter-particle friction. Lubricating agents may also facilitate ejection of the dosage form from the die cavity and improve the rate of granulation flow during processing. Examples of suitable lubricating agents include, without limitation, magnesium stearate, calcium stearate, zinc stearate, stearic acid, simethicone, silicon dioxide, talc, hydrogenated vegetable oil, polyethylene glycol, mineral oil, and combinations thereof. The compositions of the present invention can comprise from about 0% to about 10% by weight of the lubricating agent, and preferably from about 1% to about 5%.

[0121] Sweetening agents can be used to improve the palatability of the composition by masking any unpleasant tastes it may have. Examples of suitable sweetening agents include, without limitation, compounds selected from the saccharide family such as the mono-, di-, tri-, poly-, and oligosaccharides; sugars such as sucrose, glucose (corn syrup), dextrose, invert sugar, fructose, maltodextrin, and polydextrose; saccharin and salts thereof such as

sodium and calcium salts; cyclamic acid and salts thereof; dipeptide sweeteners; chlorinated sugar derivatives such as sucralose and dihydrochalcone; sugar alcohols such as sorbitol, sorbitol syrup, mannitol, xylitol, hexa-resorcinol, and the like, and combinations thereof. Hydrogenated starch hydrolysate, and the potassium, calcium, and sodium salts of 3,6-dihydro-6-methyl-1-1,2,3-oxathiazin-4-one-2,2-dioxide may also be used. Of the foregoing, sorbitol, mannitol, and xylitol, either alone or in combination, are preferred sweetening agents. The compositions of the present invention can comprise from about 0% to about 80% by weight of the sweetening agent, preferably from about 5% to about 75%, and more preferably from about 25% to about 50%.

[0122] Flavoring agents can also be used to improve the palatability of the composition. Examples of suitable flavoring agents include, without limitation, natural and/or synthetic (*i.e.,* artificial) compounds such as peppermint, spearmint, wintergreen, cinnamon, menthol, cherry, strawberry, watermelon, grape, banana, peach, pineapple, apricot, pear, raspberry, lemon, grapefruit, orange, plum, apple, fruit punch, passion fruit, chocolate (*e.g.,* white, milk, dark), vanilla, caramel, coffee, hazelnut, combinations thereof, and the like. Coloring agents can be used to color code the composition, for example, to indicate the type and dosage of the therapeutic agent therein. Suitable coloring agents include, without limitation, natural and/or artificial compounds such as FD & C coloring agents, natural juice concentrates, pigments such as titanium oxide, silicon dioxide, and zinc oxide, combinations thereof, and the like. The compositions of the present invention can comprise from about 0% to about 10% by weight of the flavoring and/or coloring agent, preferably from about 0.1% to about 5%, and more preferably from about 2% to about 3%.

1. Chewing Gums

[0123] When the dosage form is a chewing gum, the compositions of the present invention comprise a 5-HT agonist or a pharmaceutically acceptable salt thereof, a carrier such as a gum base, a binary or ternary buffer system, and optionally a protecting agent. The chewing gum composition may further comprise lubricating agents, wetting agents, emulsifying agents, suspending agents, preserving agents, sweetening agents, flavoring agents, and coloring agents. Typically, the chewing gum composition comprises from about 0.001% to about 10.0% by weight of the 5-HT agonist (in whatever chosen form, measured as per its free base form), more typically from about 0.01% to about 5.0%, and still more typically from about 0.1% to about 3.0%. One skilled in the art understands that the foregoing percentages will vary depending upon the particular source of 5-HT agonist utilized, the

amount of 5-HT agonist desired in the final formulation, as well as on the particular release rate of 5-HT agonist desired. The binary or ternary buffer system of the chewing gum composition provides for a final salivary pH in excess of at least about 9.5, preferably at least about 9.9, and more preferably in the range of from about 9.9 to about 11. The chewing gum composition typically comprises from about 20% to about 95% by weight of the gum base, more typically from about 30% to about 85%, and most typically from about 50% to about 70% of the gum base.

[0124] The chewing gum composition may further comprise a protecting agent. The protecting agent coats at least part of the therapeutic agent, typically upon the mixing of the two agents. The protecting agent may be mixed with the therapeutic agent in a ratio of from about 0.1 to about 100 by weight, preferably in a ratio of from about 1 to about 50, and more preferably in a ratio of about 1 to about 10. Without being bound to any particular theory, the protecting agent reduces the adhesion between the therapeutic agent and the gum base so that the therapeutic agent may be more easily released from the gum base. In this way, the therapeutic agent may be delivered across the mucous membranes of the oral cavity within about 5 to about 20 minutes of chewing, preferably within about 10 minutes of chewing. A variety of different protecting agents may be used. Examples of suitable protecting agents include, without limitation, calcium stearate, glycerin monostearate, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type I, light mineral oil, magnesium lauryl sulfate, magnesium stearate, mineral oil, poloxamer, polyethylene gycol, sodium benzoate, sodium chloride, sodium lauryl sulfate, stearic acid, cab-o-sil, talc, zinc stearate, and combinations thereof.

[0125] The gum base may additionally include plasticizers such as softeners or emulsifiers. Such plasticizers may, for example, help reduce the viscosity of the gum base to a desirable consistency and improve its overall texture and bite. Plasticizers may also facilitate the release of the therapeutic agent upon mastication. Non-limiting examples of plasticizers include lecithin, mono- and diglycerides, lanolin, stearic acid, sodium stearate, potassium stearate, glycerol triacetate, glycerol monostearate, glycerin, and combinations thereof. The gum base typically comprises from about 0% to about 20% by weight of the plasticizer, and more typically from about 5% to about 15%.

[0126] The gum base may further comprise waxes such as beeswax and microcrystalline wax, fats or oils such as soybean and cottonseed oil, and combinations thereof. Typically, the

gum base comprises from about 0% to about 25% by weight of these waxes and oils, and more typically comprises from about 15% to about 20%.

[0127] In addition, the gum base may further comprise one or more elastomeric solvents such as rosins and resins. Non-limiting examples of such solvents include methyl, glycerol, and pentaerythritol esters of rosins, modified rosins such as hydrogenated, dimerized or polymerized rosins, or combinations thereof (*e.g.*, pentaerythritol ester of partially hydrogenated wood rosin, pentaerythritol ester of wood rosin, glycerol ester of wood rosin, glycerol ester of partially dimerized rosin, glycerol ester of polymerized rosin, glycerol ester of tall oil rosin, glycerol ester of wood rosin and partially hydrogenated wood rosin and partially hydrogenated methyl ester of rosin such as polymers of alpha-pinene or beta-pinene; terpene resins including polyterpene, and combinations thereof). Typically, the gum base comprises from about 0% to about 75% by weight of the elastomeric solvent, and more typically less than about 10%.

[0128] The gum base may further comprise a filler material to enhance the chewability of the final chewing gum composition. Fillers that are substantially non-reactive with other components of the final chewing gum formulation are preferable. Examples of suitable fillers include, without limitation, calcium carbonate, magnesium silicate (*i.e.*, talc), dicalcium phosphate, metallic mineral salts (*e.g.*, alumina, aluminum hydroxide, and aluminum silicates), and combinations thereof. Typically, the gum base comprises from about 0% to about 30% by weight of the filler, and more typically from about 10% to about 20%.

[0129] One skilled in the art will appreciate that the gum base need not be prepared from its individual components. For example, the gum base can be purchased with the desired ingredients contained therein, and can be modified to include additional agents. Several manufacturers produce gum bases suitable for use with the described chewing gum compositions. Examples of such gum bases include, without limitation, Pharmgum™ M, S, or C (SPI Pharma Group; New Castle, DE). In general, Pharmagum™ comprises a mixture of gum base, sweetening agent, plasticizer, and sugar.

[0130] In certain instances, the chewing gum composition includes a therapeutic agent centerfill. A centerfill may be particularly suitable when immediate release of the therapeutic agent is preferred. In addition, encapsulating the therapeutic agent in a centerfill may help to mask any undesirable taste that the therapeutic agent may have. In these instances, the gum base surrounds, at least in part, a centerfill. The centerfill comprises at least one therapeutic

agent, and may be a liquid or semi-liquid material. The centerfill material can be a synthetic polymer, a semi-synthetic polymer, low-fat, or fat-free and contain one or more sweetening agents, flavoring agents, coloring agents, and/or scenting agents. Preferably, the centerfill includes a binary or ternary buffer system as described herein. Methods for preparing a centerfill chewing gum are described, for example, in U.S. Pat. No. 3,806,290, which is hereby incorporated by reference in its entirety.

[0131] The chewing gum compositions can have any desired shape, size, and texture. For example, the composition can have the shape of a stick, tab, gumball, and the like. Similarly, the chewing gum can be any desirable color. For example, the chewing gum can be any shade of red, blue, green, orange, yellow, violet, indigo, and mixtures thereof, and can be color coded to indicate the type and dosage of the therapeutic agent therein. The chewing gum can be individually wrapped or grouped together in pieces for packaging by methods well known in the art.

2. Tablets

[0132] When the dosage form is a tablet such as a dissolving tablet (*i.e.*, disintegrating tablet) or chewable tablet, the compositions of the present invention comprise a 5-HT agonist or a pharmaceutically acceptable salt thereof, a carrier such as a binder, and a binary or ternary buffer system. The tablet composition may further comprise lubricating agents, wetting agents, emulsifying agents, suspending agents, preserving agents, sweetening agents, flavoring agents, coloring agents, and disintegrating agents. Typically, the tablet compositions of the present invention comprise from about 0.001% to about 10.0% by weight of the 5-HT agonist (in whatever chosen form, measured as per its free base form), and more typically from about 1.0% to about 5.0%. In some embodiments, about 3.5% by weight of the 5-HT agonist is used. One skilled in the art understands that the foregoing percentages will vary depending upon the particular source of 5-HT agonist utilized, the amount of 5-HT agonist desired in the final formulation, as well as on the particular release rate of 5-HT agonist desired. The buffer system of the tablet composition provides for a final salivary pH in excess of at least about 9.5, preferably at least about 9.9, and more preferably in the range of from about 9.9 to about 11.

[0133] In certain embodiments, the tablet is a dissolving tablet such as a slow-dissolving or quick-dissolving tablet that is dissolved by a subject's saliva, without the need for chewing. For example, a dissolving tablet placed on the subject's tongue can be used for buccal

delivery of the therapeutic agent. Alternatively, a dissolving tablet placed underneath the subject's tongue can be used for sublingual delivery of the therapeutic agent. This type of dosage form may be particularly desirable for pediatric and geriatric patients, since small children and aged individuals often have difficulty chewing certain items. Typically, the dissolving tablet is formulated to dissolve within about 1 to about 15 minutes, preferably within about 2 to about 10 minutes, *e.g.,* within about 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes, following administration. One skilled in the art will understand that quick-dissolving tablets dissolve faster than slow-dissolving tablets, which are typically dissolved gradually rather than rapidly by a subject's saliva. In a preferred embodiment, the slow-dissolving or quick-dissolving tablet delivers the therapeutic agent across the sublingual mucosa.

[0134] In certain other embodiments, the tablet is a chewable tablet that is chewed by a subject and formulated to dissolve either rapidly or gradually. For example, a chewable tablet placed on the subject's tongue can be used for buccal delivery of the therapeutic agent. During chewing, the chewable tablet can be moved around within the mouth and can sometimes be parked between the gums and the cheeks or underneath the tongue. As a result, at least a portion of the therapeutic agent contained within a chewable tablet may also be delivered sublingually (*i.e.,* across the sublingual mucosa). Typically, the chewable tablet is formulated to dissolve within about 1 to about 15 minutes, preferably within about 2 to about 10 minutes, *e.g.,* within about 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes, following administration.

[0135] As described above, the dissolving and chewable tablets of the present invention are typically formulated to dissolve within about 1 to 15 minutes following administration. However, while these time frames are amenable to maximum exposure of the therapeutic agent to the oral mucosa (*e.g.,* to the sublingual and/or buccal mucosa), they are not always amenable to user compliance (*e.g.,* users may swallow too frequently and, therefore, hinder maximal transmucosal absorption). Consequently, in certain instances, it may be desirable to strike a balance between patient compliance and maximum exposure time of the therapeutic agent to the oral mucosa. This can be accomplished, for example, by reducing the tablet size (*e.g.,* from about 700-800 mg to about 200-300 mg) without reducing the concentration or amount per unit dose of the buffer system or the therapeutic agent. In addition, subtle changes to the tablet formulation such as, for example, replacing one flavoring agent for another (*e.g.,* chocolate for spearmint) or replacing one binder or sweetening agent for another (*e.g.,* lactose for mannitol or sorbitol) may be used to reduce salivation.

[0136] The carrier present in the tablets of the present invention is typically a binder that is useful in keeping the tablet in a semi-solid state, and may be a solid or a liquid, and may for example be a high-melting point fat or waxy material. Materials suitable as binders are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention. In addition, binders such as mannitol, sorbitol, lactose, sucrose, and inositol can impart properties to the tablet that permit or enhance its disintegration in the mouth.

[0137] The tablet composition may further comprise a protecting agent. The protecting agent coats at least part of the therapeutic agent, typically upon the mixing of the two agents. The protecting agent may be mixed with the therapeutic agent in a ratio of from about 0.1 to about 100 by weight, preferably in a ratio of from about 1 to about 50, and more preferably in a ratio of about 1 to about 10. Without being bound to any particular theory, the protecting agent reduces the adhesion between the therapeutic agent and the binder so that the therapeutic agent may be more easily released from the binder. In this way, the therapeutic agent may be delivered across the mucous membranes of the oral cavity within about 5 to about 20 minutes, preferably within about 10 minutes. Materials suitable as protecting agents are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention.

[0138] The tablet composition may also comprise one or more elastomeric solvents such as rosins and resins. Non-limiting examples of such solvents are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention. In addition, the tablet composition may further comprise waxes such as beeswax and microcrystalline wax, fats or oils such as soybean and cottonseed oil, and combinations thereof. Moreover, the tablet composition may additionally include plasticizers such as softeners or emulsifiers. Such plasticizers may, for example, help reduce the viscosity of the salivary solution of the dissolved tablet to a desirable consistency and improve its overall texture and bite and help facilitate the release of the therapeutic agent. Non-limiting examples of such plasticizers are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention.

[0139] In certain instances, the tablet composition includes a therapeutic agent centerfill. A centerfill may be particularly suitable when immediate release of the therapeutic agent is preferred. In addition, encapsulating the therapeutic agent in a centerfill may help to mask

any undesirable taste that the therapeutic agent may have. In these instances, the binder surrounds, at least in part, a centerfill. The centerfill comprises at least one therapeutic agent, and may be a liquid or semi-liquid material. The centerfill material can be low-fat or fat free and contain one or more sweetening agents, flavoring agents, coloring agents, and/or scenting agents. Preferably, the centerfill includes a binary or ternary buffer system as described herein.

[0140] In certain other instances, the tablet composition of the present invention is multilayered. In this way, the dissolving or chewable tablet can be designed to provide more than one therapeutic agent, *e.g.,* two or more 5-HT agonists or one or more 5-HT agonists in combination with one or more non-5-HT agonist therapeutic agents. For example, with a bi-layered tablet, the first layer contains a 5-HT agonist and the second layer contains the same or different 5-HT agonist or a non-5-HT agonist therapeutic agent. Typically, the first layer comprises the dissolving or chewable portion of the tablet, and the second (*i.e.,* subsequent) layer is coated by the first layer. This type of formulation may be particularly suitable when immediate release of the 5-HT agonist, followed by gastrointestinal absorption of a second therapeutic agent, is desirable. Gastrointestinal absorption of the second therapeutic agent may be desirable, for example, in order to mitigate co-morbid symptoms or to sustain the therapeutic benefit of the 5-HT agonist in the dissolving or the chewable portion of the tablet. Alternatively, the second layer is present as a layer lateral to the first layer. The second layer typically comprises at least one therapeutic agent, and can also comprise one or more sweetening agents, flavoring agents, coloring agents, and scenting agents as described above. In some instances, the second layer further includes a binary or ternary buffer system as described herein.

[0141] In still other instances, the combination of 5-HT agonists with or without non-5-HT agonist therapeutic agents need not take the form of a multilayered tablet, but instead comprises a single homogenous tablet layer. This type of formulation may also be used in the case where gastrointestinal absorption of at least one therapeutic agent is desirable. In this case, the relative extent of ionization of the two or more therapeutic agents determines how they are to be absorbed. For example, those therapeutic agents that are un-ionized are absorbed through the oral mucosa, while the ionized agents are swallowed for gastrointestinal absorption.

[0142] The tablet compositions can have any desired shape, size, and texture. For example, the tablet can have the shape of a stick, tab, pellet, sphere, and the like. Similarly, the tablet can be any desirable color. For example, the tablet can be any shade of red, blue, green, orange, yellow, violet, indigo, and mixtures thereof, and can be color coded to indicate the type and dosage of the therapeutic agent therein. The tablets can be individually wrapped or grouped together in pieces for packaging by methods well known in the art.

3. Lozenges

[0143] When the dosage form is a lozenge or candy, the compositions of the present invention comprise a 5-HT agonist or a pharmaceutically acceptable salt thereof, a carrier such as a binder, and a binary or ternary buffer system. The lozenge or candy composition may further comprise lubricating agents, wetting agents, emulsifying agents, suspending agents, preserving agents, sweetening agents, flavoring agents, coloring agents, and disintegrating agents. A general discussion of lozenges and candies is provided, *e.g.*, in *Pharmaceutical Dosage Forms, Volume 1: Tablets*, 2nd Ed., Marcel Dekker, Inc., New York, N.Y., pages 75-418 (1989).

[0144] Typically, the lozenge or candy compositions of the present invention comprise from about 0.001% to about 10.0% by weight of the 5-HT agonist (in whatever chosen form, measured as per its free base form), preferably from about 1.0% to about 5.0%, and more preferably from about 2.5% to about 4.5%. One skilled in the art understands that the foregoing percentages will vary depending upon the particular source of 5-HT agonist utilized, the amount of 5-HT agonist desired in the final formulation, as well as on the particular release rate of 5-HT agonist desired. The buffer system for the lozenge or candy composition is typically a binary or ternary buffer system comprising amorphous magnesium oxide with a carbonate salt and/or a bicarbonate salt. For example, a ternary buffer system typically comprises from about 4.0% to about 7.0% by weight sodium carbonate; from about 8.0% to about 12.0% by weight dessicant-coated sodium bicarbonate; and from about 20% to about 30% by weight amorphous magnesium oxide. The buffer system provides for a final salivary pH in excess of at least about 9.5, preferably at least about 9.9, and more preferably in the range of from about 9.9 to about 11. In a preferred embodiment, the lozenge or candy composition comprises about 3.5% by weight 5-HT agonist, about 5.5% by weight sodium carbonate, about 9.0% by weight dessicant-coated sodium bicarbonate, and about 25% by weight amorphous magnesium oxide. Examples of sumatriptan lozenge compositions are provided in Example 5 below.

[0145] In certain embodiments, the lozenge or candy is dissolved by a subject's saliva, without the need for chewing. For example, a lozenge placed on the subject's tongue can be used for buccal delivery of the therapeutic agent. Alternatively, a lozenge placed underneath the subject's tongue can be used for sublingual delivery of the therapeutic agent. This type of dosage form may be particularly desirable for pediatric and geriatric patients, since small children and aged individuals often have difficulty chewing certain items. Typically, the lozenge is formulated to dissolve within about 1 to about 15 minutes, preferably within about 2 to about 10 minutes, *e.g.,* within about 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes, following administration. In a preferred embodiment, the lozenge or candy delivers the therapeutic agent across the sublingual mucosa.

[0146] As described above, the lozenges the present invention are typically formulated to dissolve within about 1 to 15 minutes following administration. However, while these time frames are amenable to maximum exposure of the therapeutic agent to the oral mucosa (*e.g.,* to the sublingual and/or buccal mucosa), they are not always amenable to user compliance (*e.g.,* users may swallow too frequently and, therefore, hinder maximal transmucosal absorption). Consequently, in certain instances, it may be desirable to strike a balance between patient compliance and maximum exposure time of the therapeutic agent to the oral mucosa. This can be accomplished, for example, by reducing the lozenge size (*e.g.,* from about 700-800 mg to about 200-300 mg) without reducing the concentration or the amount per unit dose of the buffer system or the therapeutic agent. In addition, subtle changes to the lozenge formulation such as, for example, replacing one flavoring agent for another (*e.g.,* chocolate for spearmint) or replacing one binder or sweetening agent for another (*e.g.,* lactose for mannitol or sorbitol) may be used to reduce salivation.

[0147] The carrier present in the lozenges of the present invention is typically a binder that is useful in keeping the lozenge in a semi-solid state, and may be a solid or a liquid, and may for example be a high-melting point fat or waxy material. Materials suitable as binders are discussed in detail above and may be used alone or in combination in the lozenge compositions of the present invention. In addition, binders such as mannitol, sorbitol, lactose, sucrose, and inositol can impart properties to the lozenge that permit or enhance its disintegration in the mouth.

[0148] The lozenge composition may further comprise a protecting agent. The protecting agent coats at least part of the therapeutic agent, typically upon the mixing of the two agents.

The protecting agent may be mixed with the therapeutic agent in a ratio of from about 0.1 to about 100 by weight, preferably in a ratio of from about 1 to about 50, and more preferably in a ratio of about 1 to about 10. Without being bound to any particular theory, the protecting agent reduces the adhesion between the therapeutic agent and the binder so that the therapeutic agent may be more easily released from the binder. In this way, the therapeutic agent may be delivered across the mucous membranes of the oral cavity within about 5 to about 20 minutes, preferably within about 10 minutes. Materials suitable as protecting agents are discussed in detail above and may be used alone or in combination in the lozenge compositions of the present invention.

[0149] The lozenge composition may also comprise one or more elastomeric solvents such as rosins and resins. Non-limiting examples of such solvents are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention. In addition, the lozenge composition may further comprise waxes such as beeswax and microcrystalline wax, fats or oils such as soybean and cottonseed oil, and combinations thereof. Moreover, the lozenge composition may additionally include plasticizers such as softeners or emulsifiers. Such plasticizers may, for example, help reduce the viscosity of the salivary solution of the dissolved lozenge to a desirable consistency and improve its overall texture and bite and help facilitate the release of the therapeutic agent. Non-limiting examples of such plasticizers are discussed in detail above and may be used alone or in combination in the lozenge compositions of the present invention.

[0150] In certain instances, the lozenge composition includes a therapeutic agent centerfill. A centerfill may be particularly suitable when immediate release of the therapeutic agent is preferred. In addition, encapsulating the therapeutic agent in a centerfill may help to mask any undesirable taste that the therapeutic agent may have. In these instances, the binder surrounds, at least in part, a centerfill. The centerfill comprises at least one therapeutic agent, and may be a liquid or semi-liquid material. The centerfill material can be a synthetic polymer, a semi-synthetic polymer, low-fat, or fat free and contain one or more sweetening agents, flavoring agents, coloring agents, and/or scenting agents. Preferably, the centerfill includes a binary or ternary buffer system as described herein.

[0151] In certain other instances, the lozenge composition of the present invention is multilayered. In this way, the lozenge can be designed to provide more than one therapeutic agent, *e.g.,* two or more 5-HT agonists or one or more 5-HT agonists in combination with one

or more non-5-HT agonist therapeutic agents. For example, with a bi-layered lozenge, the first layer contains a 5-HT agonist and the second layer contains the same or different 5-HT agonist or a non-5-HT agonist therapeutic agent. Typically, the first layer comprises the dissolving portion of the lozenge, and the second (*i.e.,* subsequent) layer is coated by the first layer. This type of formulation may be particularly suitable when immediate release of the 5-HT agonist, followed by gastrointestinal absorption of a second therapeutic agent, is desirable. Gastrointestinal absorption of the second therapeutic agent may be desirable, for example, in order to mitigate co-morbid symptoms or to sustain the therapeutic benefit of the 5-HT agonist in the dissolving portion of the lozenge. Alternatively, the second layer is present as a layer lateral to the first layer. The second layer typically comprises at least one therapeutic agent, and can also comprise one or more sweetening agents, flavoring agents, coloring agents, and scenting agents as described above. In some instances, the second layer further includes a binary or ternary buffer system as described herein.

[0152] In still other instances, the combination of 5-HT agonists with or without non-5-HT agonist therapeutic agents need not take the form of a multilayered lozenge, but instead comprises a single homogenous lozenge layer. This type of formulation may also be used in the case where gastrointestinal absorption of at least one therapeutic agent is desirable. In this case, the relative extent of ionization of the two or more therapeutic agents determines how they are to be absorbed. For example, those therapeutic agents that are un-ionized are absorbed through the oral mucosa, while the ionized agents are swallowed for gastrointestinal absorption.

[0153] The lozenge compositions can have any desired shape, size, and texture. For example, the lozenge can have the shape of a stick, tab, pellet, sphere, and the like. Similarly, the lozenge can be any desirable color. For example, the lozenge can be any shade of red, blue, green, orange, yellow, violet, indigo, and mixtures thereof, and can be color coded to indicate the type and dosage of the therapeutic agent therein. The lozenges can be individually wrapped or grouped together in pieces for packaging by methods well known in the art.

[0154] In addition to the preferred dosage forms described above, the compositions of the present invention can also take to form of a solution formulation for delivery of a 5-HT agonist across the oral mucosa. For example, the solution formulation can be administered sublingually by using a two-chamber syringe delivery system, in which the upper chamber

contains an unbuffered 5-HT agonist solution, the lower chamber contains the dry buffer system components, and a non-permeable membrane separates the upper and lower chambers. Depressing the syringe ruptures the non-permeable membrane and allows mixing of the unbuffered 5-HT agonist solution with the dry buffer system components. The resulting buffered 5-HT agonist solution is then released from the tip of the syringe. As such, by simply placing the tip of the syringe anywhere underneath a subject's tongue and depressing the syringe, a solution formulation of the present invention can be used to deliver the 5-HT agonist across the subject's sublingual mucosa.

[0155] Accordingly, the present invention further provides A composition for delivery of a 5-HT agonist across the oral mucosa, said composition comprising: (a) a 5-HT agonist or a pharmaceutically acceptable salt thereof, preferably sumatriptan; (b) a carrier; and (c) a binary buffer system comprising a carbonate salt and a bicarbonate salt, wherein the binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva. Preferably, the composition is a solution that is prepared just prior to administration to the oral mucosa. In certain preferred embodiments, the binary buffer system comprises sodium bicarbonate and sodium carbonate wherein the ratio of sodium bicarbonate to sodium carbonate is from about 2:1 to about 5:1 by weight. In other embodiments, sodium carbonate is used in an amount that is equivalent to, or in excess of sodium bicarbonate. More particularly, the compositions are those that provide peak plasma levels of sumatriptan in less than 15 minutes (e.g, about 1-15 minutes), preferably in about 5 minutes to about 10 minutes.

D. Methods of Administration

[0156] The compositions of the present invention are useful in therapeutic applications, *e.g.,* for treating a migraine. Importantly, the compositions of the present invention provide the rapid delivery of a 5-HT agonist across the oral mucosa by raising the pH of saliva to a pH greater than about 9.9, irrespective of the starting pH of saliva. In particular, the delivery of the therapeutic agent across the oral mucosa avoids hepatic first pass metabolism, degradation within the gastrointestinal tract, and drug loss during absorption. As a result, the therapeutic agent reaches the systemic circulation in a substantially shorter period of time and at a substantially higher concentration than with traditional oral (*e.g.,* tablet) administration.

[0157] The compositions of the present invention have particular utility in the area of human and veterinary therapeutics. Generally, administered dosages will be effective to deliver picomolar to micromolar concentrations of the 5-HT agonist to the appropriate site.

[0158] Administration of the compositions of the present invention is preferably carried out via any of the accepted modes of administration to the mucous membranes of the oral cavity. Examples of suitable sites of administration within the oral mucosa include, without limitation, the mucous membranes of the floor of the mouth (sublingual mucosa), the cheeks (buccal mucosa), the gums (gingival mucosa), the roof of the mouth (palatal mucosa), the lining of the lips, and combinations thereof. These regions differ from each other with respect to their anatomy, drug permeability, and physiological response to drugs. Preferably, the compositions of the present invention are administered to the sublingual mucosa, buccal mucosa, or a combination thereof.

[0159] The oral mucosa, possessing a rich blood supply and suitable drug permeability, is an especially attractive route of administration for systemic drug delivery. Furthermore, delivery of a therapeutic agent across the oral mucosa bypasses hepatic first pass metabolism, avoids enzymatic degradation within the gastrointestinal tract, and provides a more suitable enzymatic flora for drug absorption. As used herein, the term "sublingual delivery" refers to the administration of a therapeutic agent across the mucous membranes lining the floor of the mouth and/or the ventral tongue. The term "buccal delivery" as used herein refers to the administration of a therapeutic agent across the mucous membranes lining the cheeks.

[0160] The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Beneath this layer lies a basement membrane, *i.e.,* the lamina propria, followed by the submucosa as the innermost layer. The epithelium of the oral mucosa is similar to the stratified squamous epithelia found in the rest of the body in that it contains a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium (Gandhi *et al.*, *Ind. J. Pharm. Sci.*, 50:145-152 (1988)). For example, the epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer cell layers. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

[0161] The turnover time for buccal mucosal epithelium, estimated at 5-6 days, is representative of the turnover time for sublingual mucosal epithelium as well as other

epithelia in the oral mucosa (Harris *et al.*, *J. Pharm. Sci.*, 81:1-10 (1992)). The thickness of the oral mucosa varies depending on the site in the oral cavity. For example, the buccal mucosa measures at about 500-800 μm in thickness, while the hard and soft palatal mucosa, the sublingual mucosa, the ventral tongue, and the gingival mucosa measure at about 100-200 μm in thickness. The composition of the epithelium also varies depending on the site in the oral cavity. For example, the mucosae of areas subject to mechanical stress (*i.e.*, the gingivae and hard palate) are keratinized similar to the epidermis. However, the mucosae of the soft palate, the sublingual region, and the buccal region are not keratinized (Harris *et al.*, *supra*). The keratinized epithelia contain neutral lipids like ceramides and acylceramides, which have been associated with providing a barrier function. As a result, these epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as sublingual and buccal epithelia, do not contain acylceramides and have only small amounts of ceramide (Wertz *et al.*, *Crit. Rev. Ther. Drug Carr. Sys.*, 8:237-269 (1991); Squier *et al.*, *J. Invest. Dermat.*, 96:123-126 (1991); Squier *et al.*, in *Oral Mucosal Drug Delivery*, Ed. M. J. Rathbone, Marcel Dekker, Inc., New York, New York, 1-26 (1996)). Non-keratinized epithelia also contain small amounts of neutral but polar lipids, *e.g.*, cholesterol sulfate and glucosyl ceramides. As such, these epithelia have been found to be considerably more permeable to water than keratinized epithelia (Harris *et al.*, *supra*; Wertz *et al.*, *supra*; Squier *et al.*, *supra*, 1991).

[0162] In general, the oral mucosa is a somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. For example, the permeability of the buccal mucosa is estimated to be about 4-4000 times greater than that of skin (Galey *et al.*, *J. Invest. Dermat.*, 67:713-717 (1976)). The permeability of different regions of the oral mucosa generally decrease in the order of sublingual mucosa greater than buccal mucosa, and buccal mucosa greater than palatal mucosa (Harris *et al.*, *supra*). This permeability is generally based upon the relative thickness and degree of keratinization of these membranes, with the sublingual mucosa being relatively thin and non-keratinized, the buccal mucosa being thicker and non-keratinized, and the palatal mucosa being intermediate in thickness, but keratinized.

[0163] The epithelial cells of the oral mucosa are surrounded by mucus comprising primarily complexes of proteins and carbohydrates that may or may not be attached to certain regions on the cell surface. The mucus may play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another (Tabak *et al.*, *J. Oral Pathol.*, 11:1-17 (1982)). In stratified squamous epithelia found elsewhere in the body, mucus is

synthesized by specialized mucus secreting cells such as goblet cells; however, in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva (Tabak *et al.*, *supra*; Rathbone *et al.*, *Adv. Drug Del. Rev.*, 13:1-22 (1994)). At physiological pH, the mucus network carries a negative charge due to the sialic acid and sulfate residues present on the carbohydrates. At this pH, mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer (Gandhi *et al.*, *supra*). Without being bound to any particular theory, the buffer systems of the present invention neutralize the sialic acid residues present on the carbohydrates and prevent them from interacting with the therapeutic agent, thereby further enhancing drug permeation.

[0164] Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. Saliva is an aqueous fluid with about 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate, which in turn depends upon factors such as the time of day, the type of stimulus, and the degree of stimulation. The salivary pH typically ranges from about 5.5 to about 7.0, depending on the flow rate. For example, at high flow rates, the sodium and bicarbonate concentrations increase, leading to an increase in the pH. Because the daily salivary volume is between about 0.5 to about 2 liters, the oral cavity provides an aqueous environment for the hydration and/or dissolution of the oral mucosal dosage forms of the present invention.

[0165] The sublingual mucosa is the most highly permeable region of the oral cavity, and provides rapid absorption and high bioavailability of a drug in a convenient, accessible, and well-accepted route of administration (Harris *et al.*, *supra*). Suitable sublingual dosage forms include, without limitation, tablets (*e.g.*, quick-dissolving, slow-dissolving), lozenges, candy, and soft gelatin capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the sublingual mucosa. As a result, the sublingual mucosa is particularly well-suited for producing a rapid onset of action, and sublingual dosage forms can be used to deliver drugs with shorter delivery period requirements and/or less frequent dosing regimens. Although the buccal mucosa is considerably less permeable than the sublingual area, rapid absorption and high bioavailability of a drug can also be observed with buccal administration. Suitable buccal dosage forms include, without limitation, chewing gums, tablets (*e.g.*, quick-dissolving, slow-dissolving), lozenges, candy, and the like. Both the buccal mucosa and the

sublingual mucosa are far superior to the gastrointestinal tract for providing increased absorption and bioavailability of a drug.

[0166] To increase the permeability of drugs through the oral mucosa, penetration enhancers can be included in the dosage forms of the present invention. The penetration enhancers may be of the type that alters the nature of the oral mucosa to enhance penetration, or of the type that alters the nature of the therapeutic agent to enhance penetration through the oral mucosa. Suitable penetration enhancers include, without limitation, polyoxyethylene 23-lauryl ether, aprotin, azone, benzalkonium chloride, cetylpyridinium chloride, cetyltrimethylammonium bromide, cyclodextrin, dextran sulfate, lauric acid, propylene glycol, lysophosphatidylcholine, menthol, methoxysalicylate, methyloleate, oleic acid, phosphatidylcholine, polyoxyethylene, polysorbate 80, sodium ethylenediaminetetraacetic acid ("EDTA"), sodium deoxycholate, sodium glycocholate, sodium glycodeoxycholate, sodium lauryl suflate, sodium salicylate, sodium taurocholate, sodium taurodeoxycholate, as well as certain sulfoxides and glycosides, and combinations thereof.

IV. Examples

[0167] The following examples are offered to illustrate, but not to limit, the claimed invention.

Example 1. Sumatriptan Membrane Assay.

[0168] This example illustrates the beneficial effects of pH adjustment on membrane penetration for a sumatriptan dosage form.

[0169] The effect of pH adjustment on the extent of ionization, and hence, the extent to which a therapeutic agent will traverse the mucous membrane can be demonstrated using a membrane assay; *see, e.g.,* Kansy *et al., J. Med. Chem.*, 41:1007-1010 (1998); and Avdeef, *Curr. Topics Med. Chem.*, 1:277-351 (2001). This assay uses a lipid-coated membrane to predict lipid mucosal membrane penetration. The membrane apparatus consists of a dodecane membrane sandwiched between a donor and acceptor cell. The lipid-coated membrane is less porous then the mucous membrane of the oral cavity. Thus, the enhancement seen in the membrane assay is very likely to be magnified *in vivo*.

[0170] The dissociation constant (pKa) of sumatriptan is 9.5, and therefore the drug would be 100% un-ionized at pH 11.5 and 90% at pH 10.5. Membrane assays were performed

using sumatriptan succinate at pH values of 9.0, 9.5, and 10.0. The final pH values of these solutions were adjusted using freshly prepared 0.01 M sodium bicarbonate/sodium carbonate buffer. Permeation was measured by determining the concentration of sumatriptan in the acceptor cell, and is expressed as P_e (effective permeability in centimeters per second). As shown in Table 3 below, the effective permeability of sumatriptan increased with pH.

Table 3: Effective permeability (P_e) of sumatriptan in a membrane assay.

pH	P_e (cm/s)
9.0	5.99
9.5	9.45
10.0	15.61

Example 2. Sumatriptan Pharmacokinetic Study.

[0171] This example illustrates the pharmacokinetic profile of a sumatriptan solution of the present invention as compared to a dose equivalent commercial oral tablet.

[0172] Because the lipid-coated membrane is less porous than the mucous membrane of the oral cavity, the enhancement seen in the membrane assay is very likely to be magnified *in situ*, resulting in enhanced buccal absorption and higher bioavailability of sumatriptan relative to a dose equivalent commercial oral tablet. To evaluate the pharmacokinetic profile of a buccally administered sumatriptan formulation, a 25 mg sumatriptan succinate solution buffered at pH 10 with 150 mg sodium bicarbonate and 50 mg sodium carbonate (Formulation A) was compared to a dose equivalent commercial oral tablet formulation (Formulation B), *i.e.*, Imitrex® (GlaxoSmithKline; Research Triangle Park, NC), in four healthy subjects following a 10 hour overnight fast. Subject demographics are shown in Table 4 below.

Table 4. Subject demographics.

Number of Subjects	4 (1 female; 3 male)
Average Age (yr)	32 (min. 19; max. 45)
Frame	medium
Average Weight (kg)	75 (min. 62; max. 82)
Average Height (cm)	176 (min. 165; max. 182)

[0173] A single dose, open-label, randomized, two treatment, two-way crossover study with a three day washout period between treatments was performed. The sample size used in this study is typical for assessing safety/tolerability (Simon *et al.*, *J. Natl. Cancer Inst.*, 89:1138-1147 (1997)) and for comparing routes of administration (Chang *et al.*, *Ann. Pharmacother.*, 33:781-786 (1999)). Furthermore, due to the crossover nature of this study, each subject acts as his or her own control. As a result, variables such as age, gender, and differences in physiology and enzymology are controlled; *see, e.g.,* Chow *et al.*, Marcel Dekker, 1992, page 30). For Formulation A, blood samples were taken at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 360 minutes following administration. For Formulation B, blood samples were taken at 0, 10, 20, 30, 45, 60, 90, 120, 180, 240, and 360 minutes following administration. High pressure liquid chromatography (HPLC)-tandem mass spectrometry (MS) assays were performed to determine plasma sumatriptan levels. The assay parameters are shown in Table 5 below.

Table 5. Sumatriptan assay parameters.

Molecular Ions Analyzed	296.4 (parent); 58 (daughter)
Calibration Curve Concentration Range	1-200 ng/ml plasma
Curve and Coefficient of Correlation	Power curve (log-log straight line) with linearity $r^2 > 0.996$
Minimum Detectable Concentration	0.1 ng/ml
Typical Plasma Volume	100 µl

[0174] Figure 1 shows the mean plasma concentration over time for Formulation A (25 mg buccal sumatriptan succinate solution) and Formulation B (25 mg sumatriptan succinate oral tablet). Table 6 below shows the pharmacokinetic parameters determined for both formulations. This study demonstrates that delivery of sumatriptan across the oral mucosa produced plasma sumatriptan concentrations that were over three times greater than those observed for the commercial oral tablet during the hour immediately following administration. In addition, peak plasma sumatriptan concentrations were achieved within 10 minutes following buccal administration, while peak plasma sumatriptan concentrations were not achieved until 60 minutes following commercial oral tablet administration. As such, the present study shows that sumatriptan from the buffered solution is rapidly absorbed and has substantially better bioavailability than the commercial oral tablet.

Table 6. Pharmacokinetic parameters for Formulation A and Formulation B.

Formulation	Formulation A (sumatriptan succinate solution)	Formulation B (Imitrex®)
C_{max} (ng/ml)	55.6 ± 24.2 (31.3; 88.3)	20.1 ± 5.2 (15.2; 27.5)
T_{max} (hr)	0.17	1.06 ± 0.31 (0.8; 1)
$AUC_{0\text{-}6\ hr}$ (ng.hr/ml)	107.4 ± 37.8 (79.8; 160.9)	68.9 ± 12.1 (57.7; 84.5)
$AUC_{0\text{-}1\ hr}$ (ng.hr/ml)	31.9 ± 11.5 (21.6; 47.9)	10.2 ± 2.1 (8.1; 13.2)

Values represent the mean ± standard deviation (SD). The numbers in parentheses represent the minimum and maximum values, respectively.

Example 3. Sumatriptan Gum Compositions.

[0175] This example illustrates the sumatriptan chewing gum compositions of the present invention.

[0176] Sumatriptan can be formulated as a chewing gum composition as described above. In these embodiments, the unit dose or serving of the chewing gum comprises from about 0.1 to about 100 milligrams (mg) sumatriptan (as measured in its free base form), preferably from about 1 to about 50 mg, and more preferably from about 2 to about 25 mg. In other embodiments, the unit dose comprises from about 2 to about 20 mg sumatriptan, preferably from about 5 to about 15 mg. Extra sumatriptan, for example, up to from about 10% to about 25% by weight, can be added as "overage" or as the amount that may be expected to be "washed away" and not otherwise released or absorbed during mastication.

[0177] Given in weight percentages, the sumatriptan chewing gum composition comprises from about 0.001% to about 2.0% sumatriptan (in whatever chosen form, measured as per its free base form), and preferably from about 0.002% to about 1.0%. In some embodiments, about 0.008% sumatriptan is used. One skilled in the art understands that the foregoing percentages will vary depending upon the particular source of sumatriptan utilized, the amount of sumatriptan desired in the final formulation, as well as on the particular release rate of sumatriptan desired. The buffer system of the sumatriptan chewing gum composition provides for a final salivary pH in excess of at least about 9.5, preferably at least about 9.9, and more preferably in the range of from about 9.9 to about 11.

[0178] A sumatriptan chewing gum was made according to the following procedure. Silicon dioxide USP (0.35 kg) was passed through a #20 mesh screen and then loaded into a blender containing 0.810 kg mannitol granular USP and 9.430 kg Pharmagum C. The material was blended for 10 minutes. Sumatriptan succintate EP (0.173 kg) was ground with silicon dioxide (0.02 kg) using a mortar and pestle. The remaining silicon dioxide, along with 0.228 kg magnesium stearate, was added into the mortar while continuing to grind. The ground materials were transferred into a plastic bag, and the mortar was rinsed using 0.01 kg silicone dioxide, and transferred into the bag. The contents of the bag were then blended for five minutes.

[0179] Equal parts of the blended bag contents and the blended mannitol gum base mixture were blended for an additional five minutes. This process was repeated until all the sumatriptan and gum base mixture had been blended together. Sodium carbonate (0.110 kg), sodium bicarbonate (0.570 kg), gum acacia (0.43 kg), xanthan gum (0.013 kg), and aspartame (0.072 kg), were then loaded into the blender with natural and artificial flavors and blended for ten minutes with 0.090 kg of silicon dioxide. The flavors used were as follows: natural

and artificial grape flavor S.D. (0.215 kg); natural and artificial cherry flavor (0.108 kg); natural and artificial fruit punch flavor S.D. (0.180 kg); natural cherry WONF DURAROME® flavor (0.215 kg); and natural passion fruit type DURAROME® flavor (0.035 kg).

[0180] The blend was passed through a #12 mesh screen and then blended for an additional 15 minutes. Magnesium stearate (0.114 kg) was passed through a #20 mesh screen, added to the blend, and blended for five minutes. The blend was collected and placed in plastic bags. Two silica gel desiccant bags were placed around the plastic bags to absorb ambient moisture. The blend was then compressed and compacted using a tablet press. By using the above-described procedure, the average particle size of the drug (*i.e.,* sumatriptan) in the chewing gum is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In addition, the average particle size of the drug in the chewing gum is less than or equal to the average particle size of the carrier ingredients (*e.g.,* gum base, binders, *etc.*).

[0181] The sumatriptan chewing gum compositions of the present invention can be used, *e.g.,* for treating a migraine. After introduction of a serving size piece of the gum composition into the mouth, the subject chews the gum as is normally done with any non-medicated type of chewing gum for about 20-30 minutes, at approximately an average rate of about 10-45 chews per minute. The gum is then discarded.

[0182] A serving of the sumatriptan chewing gum is typically designed to cause a loaded sumatriptan concentration level in the bloodstream of at least about 5 to about 300 nanograms (ng) of sumatriptan per milliliter (ml) of plasma. The ratio of the maximum plasma concentration (C_{max}) to the time to achieve that maximum plasma concentration (T_{max}) is preferably within a range of about 10 ng/ml x hr to about 1000 ng/ml x hr, and more preferably within a range of about 100 ng/ml x hr to about 500 ng/ml x hr. The chewing gum compositions of the present invention provide a convenient, reliable, practical, and painless system for delivering sumatriptan across the oral mucosa. Notably, the chewing gum compositions are capable of rapidly delivering sumatriptan so that a therapeutically effective amount of sumatriptan enters the bloodstream within 20 minutes, 10 minutes, or even within 1-2 minutes after sumatriptan is released from the carrier.

Example 4. Sumatriptan Quick-Dissolving Tablet Compositions.

[0183] This example illustrates the quick-dissolving sumatriptan tablet compositions of the present invention.

[0184] Given in weight percentages, the sumatriptan quick-dissolving tablet composition typically comprises from about 0.001% to about 10.0% sumatriptan (in whatever chosen form, measured as per its free base form), and more typically from about 1.0% to about 5.0%. In some embodiments, about 3.5% sumatriptan is used. One skilled in the art understands that the foregoing percentages will vary depending upon the particular source of sumatriptan utilized, the amount of sumatriptan desired in the final formulation, as well as on the particular release rate of sumatriptan desired. The buffer system of the sumatriptan quick-dissolving tablet composition provides for a final salivary pH in excess of at least about 9.5, preferably at least about 9.9, and more preferably in the range of from about 9.9 to about 11.

[0185] A sumatriptan quick-dissolving tablet was made according to the following procedure. Mannitol (3.633 kg) and sorbitol (0.330 kg) were blended for ten minutes. Sodium bicarbonate (0.330 kg), sodium carbonate (0.165 kg), natural peppermint flavor (0.125 kg), natural menthol flavor (0.025 kg), and sucralose (0.020 kg) were blended separately for ten minutes. Stearic acid (0.125 kg), magnesium stearate (0.075 kg), and sumatriptan succinate (0.172 kg) were blended for ten minutes and then passed through a #12 mesh screen. The blended mixtures were then added together and compressed into tablets. By using this procedure, the average particle size of the drug (*i.e.*, sumatriptan) in the quick-dissolving tablet is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In addition, the average particle size of the drug in the quick-dissolving tablet is less than or equal to the average particle size of the carrier ingredients (*e.g.*, gum base, binders, *etc.*).

[0186] The sumatriptan quick-dissolving tablets of the present invention can be used, *e.g.*, for treating a migraine. As such, the quick-dissolving tablets provide a convenient, reliable, practical, and painless system for delivering sumatriptan across the oral mucosa. Notably, the quick-dissolving tablets are capable of rapidly delivering sumatriptan so that a therapeutically effective amount of sumatriptan enters the bloodstream within 20 minutes, 10 minutes, or even within 1-2 minutes after sumatriptan is released from the carrier.

Example 5. Sumatriptan Lozenge Compositions.

[0187] This example illustrates the sumatriptan lozenge compositions of the present invention.

[0188] Given in weight percentages, the sumatriptan lozenge composition typically comprises from about 0.001% to about 10.0% sumatriptan (in whatever chosen form, measured as per its free base form), preferably from about 1.0% to about 5.0% sumatriptan, and more preferably from about 2.5% to about 4.5% sumatriptan. The buffer system for the sumatriptan lozenge composition is typically a binary or ternary buffer system comprising amorphous magnesium oxide with a carbonate salt and/or a bicarbonate salt. For example, a ternary buffer system typically comprises from about 4.0% to about 7.0% sodium carbonate; from about 8.0% to about 12.0% dessicant-coated sodium bicarbonate; and from about 20% to about 30% amorphous magnesium oxide. In a preferred embodiment, the sumatriptan lozenge composition comprises about 3.5% sumatriptan, about 5.5% sodium carbonate, about 9.0% dessicant-coated sodium bicarbonate, and about 25% amorphous magnesium oxide. The buffer system provides for a final salivary pH in excess of at least about 9.5, preferably at least about 9.9, and more preferably in the range of from about 9.9 to about 11.

[0189] A sumatriptan sublingual lozenge was made according to the formulation shown in Table 7. Briefly, mannitol and sorbitol were blended. Sodium carbonate, dessicant-coated sodium bicarbonate, magnesium oxide, natural and artificial spearmint flavor, and sucralose were blended separately. Magnesium stearate and sumatriptan were blended and then passed through a #12 mesh screen. The blended mixtures were then added together and compressed to produce white round lozenges. By using this procedure, the average particle size of the drug (*i.e.,* sumatriptan) in the lozenge is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In addition, the average particle size of the drug in the lozenge is less than or equal to the average particle size of the carrier ingredients (*e.g.,* gum base, binders, *etc.*). The unit weight for each lozenge was 250 mg.

Table 7. Sumatriptan lozenge formulation.

Material	Unit Quantity (mg)	Batch Quantity (g)
Sodium Carbonate, NF	14.000	294.000
Sodium Bicarbonate (Effer Soda)	23.000	483.000
Sumatriptan	9.000	189.000
Mannogem EZ (Mannitol), USP	40.000	840.000
Sorbogem 712 (Sorbitol), NF	80.000	1680.000
Magnesium Oxide @ Mg = 57%	63.400	1331.400
Natural & Artificial Spearmint Flavor	6.500	136.500
Sucralose, NF	1.100	23.100
Silicon Dioxide, USP	5.500	115.500
Magnesium Stearate, NF	7.500	157.500

The batch quantity formulation produces 21,000 unit doses.

[0190] As shown in Figure 2, the sublingual lozenge containing 9 mg sumatriptan had a pH of above 10.2 and maintained a stable pH at 25°C and 60% relative humidity (RH). A sublingual lozenge containing 12.5 mg sumatriptan had a pH of about 9.9 and maintained a stable pH (*see,* Figure 2).

[0191] The sumatriptan lozenges of the present invention can be used, *e.g.,* for treating a migraine. As such, the lozenges provide a convenient, reliable, practical, and painless system for delivering sumatriptan across the oral mucosa. For example, the sumatriptan lozenges are simply kept in the mouth (*i.e.,* under the tongue) for about two or more minutes. Preferably, the sumatriptan lozenges dissolve within about 6 minutes following administration.

[0192] The use of a ternary buffer system comprising sodium carbonate, sodium bicarbonate, and magnesium oxide in the lozenges of the present invention raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva, thus allowing for the rapid delivery across the oral mucosa (*e.g.,* sublingual mucosa) of a therapeutically effective amount of sumatriptan. As a result, sumatriptan enters the bloodstream within 20 minutes, 10 minutes, or even within 1-2 minutes after being released from the carrier. Notably, the magnesium oxide in the ternary buffer system serves several important functions including, for example, raising the pH of the formulation, masking the corrosiveness of

sodium carbonate, serving as a secondary binding agent thereby eliminating the need for stearic acid, and lowering the amount of sodium carbonate needed to produce the desired pH.

[0193] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A composition for delivery of a 5-HT agonist across the oral mucosa, said composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a metal oxide,

wherein said ternary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

2. A composition of claim **1**, wherein said ternary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11 irrespective of the starting pH of saliva.

3. A composition of claim **1**, wherein said 5-HT agonist is selected from the group consisting of sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, and combinations thereof.

4. A composition of claim **1**, wherein said carbonate salt is selected from the group consisting of sodium carbonate and potassium carbonate.

5. A composition of claim **1**, wherein said bicarbonate salt is selected from the group consisting of sodium bicarbonate and potassium bicarbonate.

6. A composition of claim **1**, wherein said metal oxide is selected from the group consisting of magnesium oxide and aluminum oxide.

7. A composition of claim **6**, wherein said magnesium oxide is amorphous magnesium oxide.

8. A composition of claim **1**, wherein said ternary buffer system comprises sodium carbonate, sodium bicarbonate, and amorphous magnesium oxide.

9. A composition of claim **1**, wherein said carrier is selected from the group consisting of a binder, a gum base, and combinations thereof.

10. A composition of claim **9**, wherein said gum base comprises at least one hydrophobic polymer and at least one hydrophilic polymer.

11. A composition of claim **9**, wherein said binder is selected from the group consisting of a sugar, a sugar alcohol, and combinations thereof.

12. A composition of claim **11**, wherein said sugar alcohol is selected from the group consisting of mannitol, sorbitol, xylitol, and combinations thereof.

13. A composition of claim **1**, wherein said composition is a dosage form selected from the group consisting of a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet.

14. A composition of claim **13**, wherein said dissolving tablet is selected from the group consisting of a slow-dissolving tablet and a quick-dissolving tablet.

15. A composition of claim **1**, wherein said oral mucosa is selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof.

16. A composition of claim **1**, further comprising a 5-HT antagonist.

17. A composition of claim **1**, further comprising a non-steroidal anti-inflammatory drug (NSAID).

18. A composition of claim **1**, wherein the average particle size of said 5-HT agonist or a pharmaceutically acceptable salt thereof is less than or equal to the average particle size of said carrier.

19. A composition of claim **1**, wherein said 5-HT agonist is sumatriptan and said ternary buffer system comprises sodium carbonate, sodium bicarbonate, and amorphous magnesium oxide.

20. A composition of claim **19**, wherein said composition is a lozenge or a dissolving tablet.

21. A composition of claim **20**, wherein said composition is administered sublingually.

22. A composition of claim **19**, wherein said sodium bicarbonate is dessicant-coated sodium bicarbonate.

23. A composition of claim **19**, wherein the weight percent of amorphous magnesium oxide is greater than the combined weight percent of sodium carbonate and sodium bicarbonate.

24. A composition of claim **23**, wherein said composition comprises from about 2.5 to about 4.5 weight percent sumatriptan; from about 4.0 to about 7.0 weight percent sodium carbonate; from about 8.0 to about 12.0 weight percent dessicant-coated sodium bicarbonate; and from about 20 to about 30 weight percent amorphous magnesium oxide.

25. A composition of claim **24**, wherein composition comprises about 3.5 weight percent sumatriptan; about 5.5 weight percent sodium carbonate; about 9.0 weight percent dessicant-coated sodium bicarbonate; and about 25 weight percent amorphous magnesium oxide.

26. A composition for delivery of a 5-HT agonist across the oral mucosa, said composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a citrate, phosphate, or borate salt,

wherein said ternary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

27. A composition of claim **26**, wherein said ternary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11 irrespective of the starting pH of saliva.

28. A composition of claim **26**, wherein said 5-HT agonist is selected from the group consisting of sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, and combinations thereof.

29. A composition of claim **26**, wherein said carbonate salt is selected from the group consisting of sodium carbonate and potassium carbonate.

30. A composition of claim **26**, wherein said bicarbonate salt is selected from the group consisting of sodium bicarbonate and potassium bicarbonate.

31. A composition of claim **26**, wherein said citrate salt is selected from the group consisting of sodium citrate, potassium citrate, calcium citrate, magnesium citrate, and ammonium citrate.

32. A composition of claim **26**, wherein said phosphate salt is selected from the group consisting of monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, dibasic potassium phosphate, monobasic calcium phosphate, dibasic calcium phosphate, monobasic magnesium phosphate, dibasic magnesium phosphate, monobasic ammonium phosphate, and dibasic ammonium phosphate.

33. A composition of claim **26**, wherein said borate salt is selected from the group consisting of sodium borate, potassium borate, calcium borate, magnesium borate, and ammonium borate.

34. A composition of claim **26**, further comprising a metal oxide.

35. A composition of claim **26**, wherein said carrier is selected from the group consisting of a binder, a gum base, and combinations thereof.

36. A composition of claim **26**, wherein said composition is a dosage form selected from the group consisting of a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet.

37. A composition of claim **36**, wherein said dissolving tablet is selected from the group consisting of a slow-dissolving tablet and a quick-dissolving tablet.

38. A composition of claim **26**, wherein said oral mucosa is selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof.

39. A composition of claim **26**, wherein the average particle size of said 5-HT agonist or a pharmaceutically acceptable salt thereof is less than or equal to the average particle size of said carrier.

40. A composition of claim **26**, wherein said 5-HT agonist is sumatriptan and said ternary buffer system comprises sodium carbonate, sodium bicarbonate, and a citrate, phosphate, or borate salt.

41. A composition of claim **40**, wherein said composition is a lozenge or a dissolving tablet.

42. A composition of claim **41**, wherein said composition is administered sublingually.

43. A composition for delivery of a 5-HT agonist across the oral mucosa, said composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a buffer system comprising a carbonate salt or a bicarbonate salt and two or more buffering agents selected from the group consisting of a metal oxide, a citrate salt, a phosphate salt, and a borate salt,

wherein said buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

44. A composition of claim **43**, wherein said ternary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11 irrespective of the starting pH of saliva.

45. A composition of claim **43**, wherein said 5-HT agonist is selected from the group consisting of sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, and combinations thereof.

46. A composition of claim **43**, wherein said carbonate salt is selected from the group consisting of sodium carbonate and potassium carbonate.

47. A composition of claim **43**, wherein said bicarbonate salt is selected from the group consisting of sodium bicarbonate and potassium bicarbonate.

48. A composition of claim **43**, wherein said carrier is selected from the group consisting of a binder, a gum base, and combinations thereof.

49. A composition of claim **43**, wherein said composition is a dosage form selected from the group consisting of a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet.

50. A composition of claim **49**, wherein said dissolving tablet is selected from the group consisting of a slow-dissolving tablet and a quick-dissolving tablet.

51. A composition of claim **43**, wherein said oral mucosa is selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof.

52. A composition of claim **43**, wherein the average particle size of said 5-HT agonist or a pharmaceutically acceptable salt thereof is less than or equal to the average particle size of said carrier.

53. A composition of claim **43**, wherein said composition is administered sublingually.

54. A composition for delivery of a 5-HT agonist across the oral mucosa, said composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt or a bicarbonate salt and a metal oxide,

wherein said binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

55. A composition of claim **54**, wherein said binary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11 irrespective of the starting pH of saliva.

56. A composition of claim **54**, wherein said 5-HT agonist is selected from the group consisting of sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, and combinations thereof.

57. A composition of claim **54**, wherein said carbonate salt is selected from the group consisting of sodium carbonate and potassium carbonate.

58. A composition of claim **54**, wherein said bicarbonate salt is selected from the group consisting of sodium bicarbonate and potassium bicarbonate.

59. A composition of claim **54**, wherein said metal oxide is selected from the group consisting of magnesium oxide and aluminum oxide.

60. A composition of claim **59**, wherein said magnesium oxide is amorphous magnesium oxide.

61. A composition of claim **54**, wherein said binary buffer system comprises sodium carbonate and amorphous magnesium oxide.

62. A composition of claim **54**, wherein said binary buffer system comprises sodium bicarbonate and amorphous magnesium oxide.

63. A composition of claim **54**, wherein said carrier is selected from the group consisting of a binder, a gum base, and combinations thereof.

64. A composition of claim **54**, wherein said composition is a dosage form selected from the group consisting of a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet.

65. A composition of claim **56**, wherein said dissolving tablet is selected from the group consisting of a slow-dissolving tablet and a quick-dissolving tablet.

66. A composition of claim **54**, wherein said oral mucosa is selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof.

67. A composition of claim **54**, wherein the average particle size of said 5-HT agonist or a pharmaceutically acceptable salt thereof is less than or equal to the average particle size of said carrier.

68. A composition of claim **54**, wherein said 5-HT agonist is sumatriptan and said binary buffer system comprises sodium carbonate or sodium bicarbonate and amorphous magnesium oxide.

69. A composition of claim **68**, wherein said composition is a lozenge or a dissolving tablet.

70. A composition of claim **69**, wherein said composition is administered sublingually.

71. A composition of claim 68, wherein the weight percent of amorphous magnesium oxide is greater than the weight percent of sodium carbonate or sodium bicarbonate.

72. A composition for delivery of a 5-HT agonist across the oral mucosa, said composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt or a bicarbonate salt and a citrate, phosphate, or borate salt,

wherein said binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

73. A composition of claim 72, wherein said binary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11 irrespective of the starting pH of saliva.

74. A composition of claim 72, wherein said 5-HT agonist is selected from the group consisting of sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, and combinations thereof.

75. A composition of claim 72, wherein said carbonate salt is selected from the group consisting of sodium carbonate and potassium carbonate.

76. A composition of claim 72, wherein said bicarbonate salt is selected from the group consisting of sodium bicarbonate and potassium bicarbonate.

77. A composition of claim 72, wherein said carrier is selected from the group consisting of a binder, a gum base, and combinations thereof.

78. A composition of claim 72, wherein said composition is a dosage form selected from the group consisting of a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet.

79. A composition of claim 78, wherein said dissolving tablet is selected from the group consisting of a slow-dissolving tablet and a quick-dissolving tablet.

80. A composition of claim **72**, wherein said oral mucosa is selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof.

81. A composition of claim **72**, wherein the average particle size of said 5-HT agonist or a pharmaceutically acceptable salt thereof is less than or equal to the average particle size of said carrier.

82. A composition of claim **72**, wherein said 5-HT agonist is sumatriptan and said binary buffer system comprises sodium carbonate or sodium bicarbonate and and a citrate, phosphate, or borate salt.

83. A composition of claim **82**, wherein said composition is a lozenge or a dissolving tablet.

84. A composition of claim **83**, wherein said composition is administered sublingually.

85. A composition for delivery of a 5-HT agonist across the oral mucosa, said composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a metal oxide and a citrate, phosphate, or borate salt,

wherein said binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

86. A composition of claim **85**, wherein said binary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11 irrespective of the starting pH of saliva.

87. A composition of claim **85**, wherein said 5-HT agonist is selected from the group consisting of sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, and combinations thereof.

88. A composition of claim **85**, wherein said metal oxide is selected from the group consisting of magnesium oxide and aluminum oxide.

89. A composition of claim **88**, wherein said magnesium oxide is amorphous magnesium oxide.

90. A composition of claim **85**, wherein said carrier is selected from the group consisting of a binder, a gum base, and combinations thereof.

91. A composition of claim **85**, wherein said composition is a dosage form selected from the group consisting of a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet.

92. A composition of claim **91**, wherein said dissolving tablet is selected from the group consisting of a slow-dissolving tablet and a quick-dissolving tablet.

93. A composition of claim **85**, wherein said oral mucosa is selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof.

94. A composition of claim **85**, wherein the average particle size of said 5-HT agonist or a pharmaceutically acceptable salt thereof is less than or equal to the average particle size of said carrier.

95. A composition of claim **85**, wherein said 5-HT agonist is sumatriptan and said binary buffer system comprises amorphous magnesium oxide and a citrate, phosphate, or borate salt.

96. A composition of claim **95**, wherein said composition is a lozenge or a dissolving tablet.

97. A composition of claim **96**, wherein said composition is administered sublingually.

98. A composition for delivery of a 5-HT agonist across the oral mucosa, said composition comprising:

(a) a 5-HT agonist or a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt and a bicarbonate salt,

wherein said binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

99. A composition of claim **98**, wherein said 5-HT agonist is sumatriptan and said binary buffer system is combined with sumatriptan to form a solution just prior to delivery of sumatriptan to the oral mucosa.

100. A composition of claim **98**, wherein said 5-HT agonist is sumatriptan and said binary buffer system comprises sodium bicarbonate and sodium carbonate wherein the ratio of sodium bicarbonate to sodium carbonate is from about 2:1 to about 5:1 by weight.

101. A composition of claim **100**, said composition delivering a peak plasma concentration within about 1-15 minutes following administration.

102. A method for treating a migraine in a subject in need thereof, said method comprising:

administering to said subject a composition comprising a therapeutically effective amount of sumatriptan or a pharmaceutically acceptable salt thereof, a carrier, and a binary buffer system comprising a carbonate salt and a bicarbonate salt, wherein said binary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

103. A method in accordance with claim **102**, wherein said composition is a solution composition.

104. A method in accordance with claim **103**, wherein said binary buffer system comprises sodium bicarbonate and sodium carbonate wherein the ratio of sodium bicarbonate to sodium carbonate is from about 2:1 to about 5:1 by weight, and said composition provides a peak plasma concentration within about 1-15 minutes following administration to said subject.

105. A method for treating a migraine in a subject in need thereof, said method comprising:

administering to said subject a composition comprising a therapeutically effective amount of a 5-HT agonist or a pharmaceutically acceptable salt thereof, a carrier,

and a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a metal oxide, wherein said ternary buffer system raises the pH of saliva to a pH greater than about 9.9 irrespective of the starting pH of saliva.

106. A method of claim **105**, wherein said ternary buffer system raises the pH of saliva to a pH of from about 9.9 to about 11 irrespective of the starting pH of saliva.

107. A method of claim **105**, wherein said composition delivers said 5-HT agonist across the oral mucosa.

108. A method of claim **107**, wherein said oral mucosa is selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof.

109. A method of claim **105**, wherein said migraine is selected from the group consisting of a migraine without aura and a migraine with aura.

110. A method of claim **105**, wherein said 5-HT agonist is selected from the group consisting of sumatriptan, naratriptan, rizatriptan, eletriptan, almotriptan, zolmitriptan, frovatriptan, and combinations thereof.

111. A method of claim **105**, wherein said carbonate salt is selected from the group consisting of sodium carbonate and potassium carbonate.

112. A method of claim **105**, wherein said bicarbonate salt is selected from the group consisting of sodium bicarbonate and potassium bicarbonate.

113. A method of claim **105**, wherein said metal oxide is selected from the group consisting of magnesium oxide and aluminum oxide.

114. A method of claim **113**, wherein said magnesium oxide is amorphous magnesium oxide.

115. A method of claim **105**, wherein said ternary buffer system comprises sodium carbonate, sodium bicarbonate, and amorphous magnesium oxide.

116. A method of claim **105**, wherein said carrier is selected from the group consisting of a binder, a gum base, and combinations thereof.

117. A method of claim **105**, wherein said composition is a dosage form selected from the group consisting of a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet.

118. A method of claim **117**, wherein said dissolving tablet is selected from the group consisting of a slow-dissolving tablet and a quick-dissolving tablet.

119. A method of claim **105**, wherein said oral mucosa is selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof.

120. A method of claim **105**, further comprising a 5-HT antagonist.

121. A method of claim **105**, further comprising a non-steroidal anti-inflammatory drug (NSAID).

122. A method of claim **105**, wherein the average particle size of said 5-HT agonist or a pharmaceutically acceptable salt thereof is less than or equal to the average particle size of said carrier.

123. A method of claim **105**, wherein said 5-HT agonist is sumatriptan and said ternary buffer system comprises sodium carbonate, sodium bicarbonate, and amorphous magnesium oxide.

124. A method of claim **123**, wherein said composition is a lozenge or a dissolving tablet.

125. A method of claim **124**, wherein said composition is administered sublingually.

126. A method of claim **123**, wherein the weight percent of amorphous magnesium oxide is greater than the combined weight percent of sodium carbonate and sodium bicarbonate.

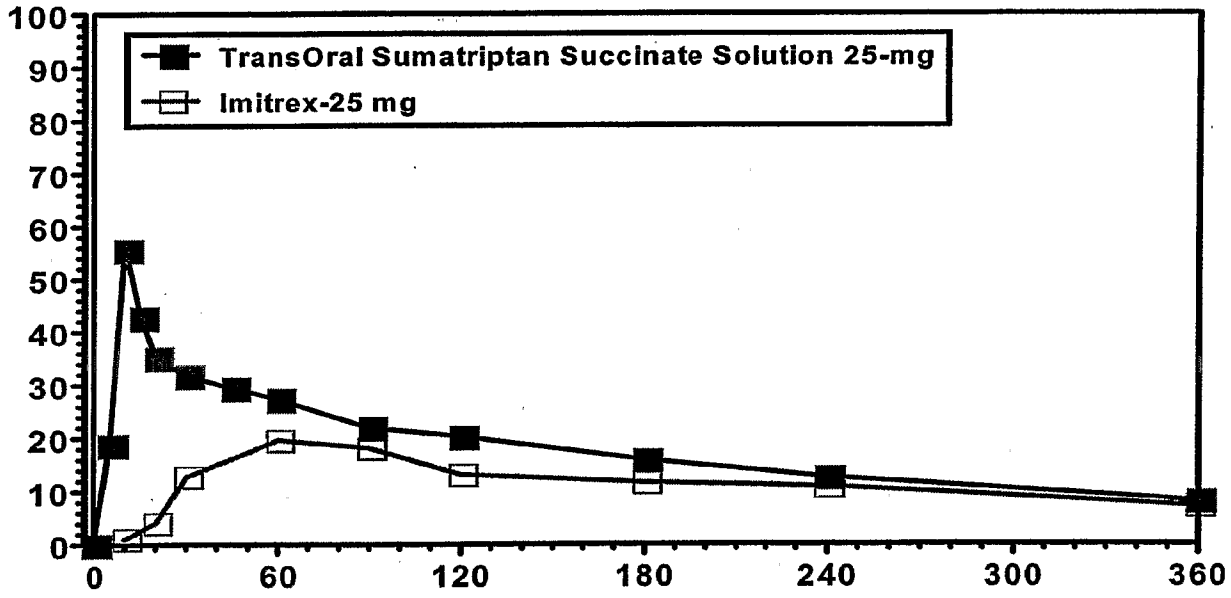

TransOral Sumatriptan Succinate Solution 25-mg
Imitrex-25 mg
100
90
80
70
60
50
40
30
20
10
0
0
60
120
180
240
300
360

FIG. 1

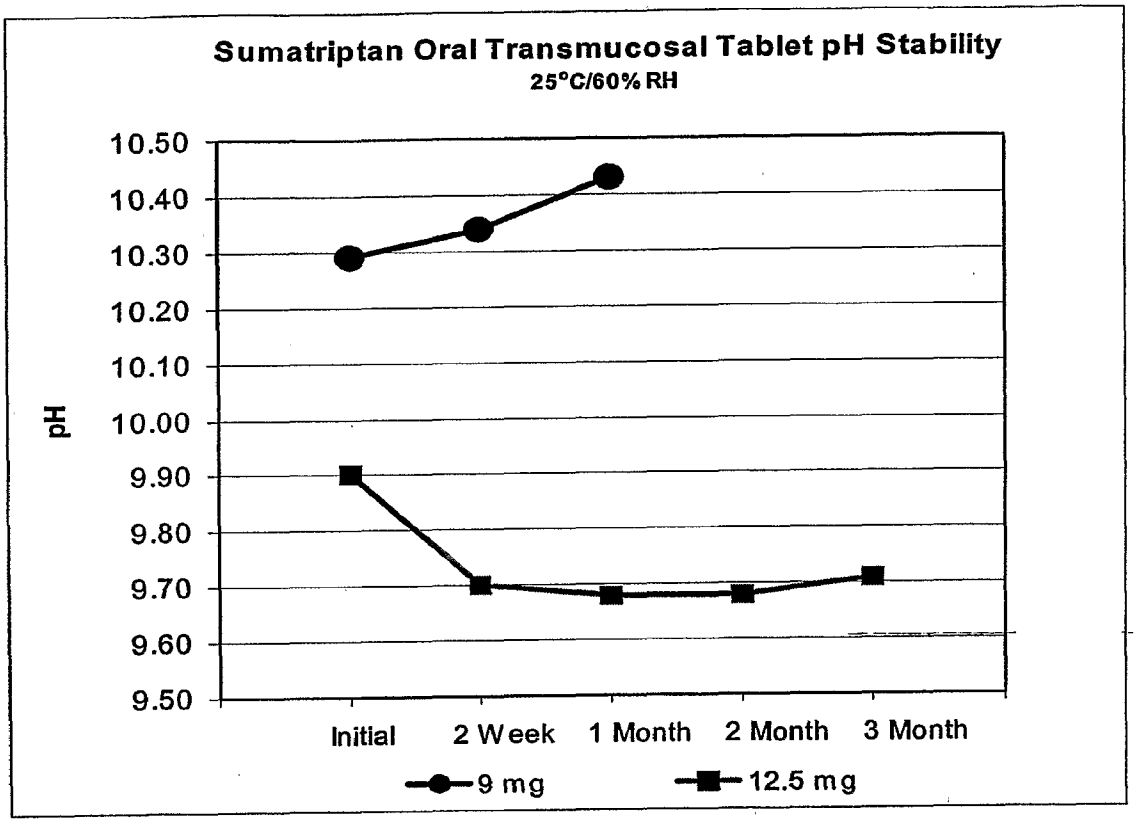

Sumatriptan Oral Transmucosal Tablet pH Stability
25°C/60% RH
pH
10.50
10.40
10.30
10.20
10.10
10.00
9.90
9.80
9.70
9.60
9.50
Initial
2 Week
1 Month
2 Month
3 Month
9 mg
12.5 mg

FIG. 2

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(54) Title: PHARMACEUTICAL COMPOSITIONS OF BENZODIAZEPINES AND METHODS OF USE THEREOF

(57) Abstract: The present invention includes benzodiazepine compositions formulated for intranasal administration, comprising a binary solvent system comprising a first solvent in which the benzodiazepine is soluble, the first solvent capable of penetrating nasal mucosal tissue, and a second solvent in which the benzodiazepine in less soluble. The compositions of the present invention may be used to treat a variety of disorders including, but not limited to, panic attacks, muscle spasms, anxiety, and seizures. In one aspect, the present invention relates to a fast-acting, clonazepam composition for transnasal administration that can be used for the treatment of seizure clusters.

Pharmaceutical Compositions of Benzodiazepines and Methods of Use Thereof

Technical Field

[0001] The present invention relates to formulations, including compositions and dosage forms of benzodiazepines. Described herein are compositions that are useful and efficacious for transmucosal delivery, including intranasal delivery, as well as methods of use and methods of manufacturing for such compositions.

Background of the Invention

[0002] Benzodiazepines are a class of antidepressants, anti-panic agents, and muscle relaxants used to ameliorate anxiety, treat panic disorders, induce sleep, relax muscles, and relieve seizures and muscle spasms. Benzodiazepine medications produce these effects by depressing the central nervous system. Clonazepam, alprazolam, chlordiazepoxide, diazepam, lorazepam, oxazepam, estazolam, midazolam, and triazolam are examples of benzodiazepine medications.

[0003] Clonazepam is marketed by Hoffman-La Roche under the trade names KLONOPIN® (Hoffmann-La Roche Inc., New Jersey) in the United States and RIVOTRIL® (Hoffmann-La Roche Inc., New Jersey) in Canada, South America, and Europe. The pharmacological profile of clonazepam resembles that of other anxiolytic/sedative benzodiazepine medications, and its anticonvulsive characteristics are like those of other diazepines. Clonazepam can suppress the spike-wave discharge accompanying absence seizures (i.e., petit mal seizures) and reduce amplitude, frequency, duration, and discharge spreading in small-scale motor seizures.

[0004] Lorazepam was first introduced in the late 1970's by Wyeth Pharmaceuticals under the trade name Ativan®. It is now manufactured by Wyeth Laboratories, Pennsylvania and distributed by Biovail Pharmaceuticals, New Jersey and is indicated for the management of anxiety disorders or for the short term relief of the symptoms of anxiety or anxiety associated with depressive symptoms. Injectable lorazepam is useful as an initial anticonvulsant medication for the control of status epilepticus.

[0005] Diazepam was first marketed as Valium® by Hoffman-LaRoche in the 1960's. Valium is now distributed by Roche Pharmaceuticals, New Jersey. Valium is indicated for the management of anxiety disorder and relief of symptoms of anxiety, for

symptomatic relief of acute alcohol withdrawal, adjunctively for relief of skeletal muscle spasm, and adjunctively in convulsive disorders.

[0006] Clonazepam is well absorbed orally; maximum blood concentrations typically occur in one to two hours. It is metabolized by the liver and reduced to inactive metabolites that are excreted primarily in the urine. The amount excreted unchanged in the urine is less than 0.5% of a dose. In addition, 9% to 27% of a dose of clonazepam is excreted in the feces. Clonazepam exhibits a half-life that varies from about 18 hours to 50 hours.

[0007] Lorazepam is well absorbed orally; maximum blood concentrations typically occur in one to four hours. It is metabolized by the liver and reduced to inactive metabolites that are excreted primarily in the urine. Lorazepam exhibits a half-life that varies from about 8 hours to 24 hours.

[0008] Diazepam is well absorbed orally; maximum blood concentrations typically occur in one to two hours. It is metabolized by the liver and reduced to inactive metabolites that are excreted primarily in the urine. Diazepam exhibits a half-life of about 100 hours.

[0009] Clonazepam exhibits strong anxiolytic properties and euphoric side effects; therefore, it is considered a "highly potent" benzodiazepine. Specifically, 0.25 mg of clonazepam is roughly equal to 1.0 mg of lorazepam and 5.0 mg of diazepam. Clonazepam's sedative effects are relatively weak in comparison with its strong anticonvulsant and anxiolytic effects. The sedative effects of clonazepam are also weaker than that of other benzodiazepines. Clonazepam appears to act by simulating the central nervous system actions of GABA, like other benzodiazepines.

[0010] Clonazepam is commonly prescribed to treat epilepsy, anxiety disorders, panic attacks, Restless Legs Syndrome (RLS), chronic fatigue syndrome, REM behavior disorder, night terrors, and Tourette's Syndrome. In the treatment of anxiety disorders, low-dose, long-term treatment with clonazepam may be required because of the chronic nature of anxiety. Although benzodiazepines have some potential for abuse, the use of clonazepam in long-term treatment of anxiety disorders is therapeutic and should not be confused with dependence or addiction. Clonazepam also is used for the initial treatment of mania in combination with medications such as lithium, risperidone, or haloperidol. In addition, clonazepam is prescribed to treat the symptoms of Parkinson's disease and

schizophrenia and for twitching and pain management. Clonazepam has also been used to reduce and manage Tourette's Syndrome motor tics. In another application, clonazepam has been used to treat Hallucinogen Persisting Perception Disorder (HPPD). Clonazepam is not typically used to treat insomnia because of its relatively weak sedative effects.

[0011] For epilepsy patients, clonazepam is indicated for use alone or as an adjunct therapy, and as primary therapy and for refractory patients. Epilepsy is a disorder characterized by transient but recurrent disturbances of brain function that may or may not be associated with impairment or loss of consciousness and abnormal movements or behavior. The primary objective of caring for patients with epilepsy is to restore their functional capacity to its maximal potential. To do this, physicians use a stable regimen of anti-epileptic drugs (AED). Approximately 30% of patients continue to be refractory to AED treatment and often have recurrent seizures that may occur in clusters. Some of these patients may also experience continued seizure activity without regaining consciousness for a prolonged period of time, a condition called status epilepticus. In addition to being life threatening, recurrent seizures and status epilepticus can impact cognition and permanently damage other brain function.

[0012] Patients with refractory epilepsy including episodes of seizure clusters and status epilepticus often present at the emergency room where they are treated with IV benzodiazepines, phenytoin and barbiturates. The goal of treatment in the ER is the prompt cessation of seizure activity. Prior to the ER, there are limited treatment options available to these patients and caregivers.

[0013] Epileptic seizures are often classified in two types: primary generalized seizures, (seizures that begin with a widespread electrical discharge involving both sides of the brain) and partial seizures (seizures involving one area of the brain). Included among primary generalized seizures are: absence (also known as petit-mal) seizures, myoclonic seizures, atonic and tonic seizures, clonic and clonic-tonic (also known as grand-mal) seizures. Included among partial seizures are simple and complex seizures and secondary generalized seizures.

[0014] Clonazepam has been used in the treatment many different epilepsy syndromes and for different types of seizures including Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. Clonazepam is also useful in patients with absence seizures. In Europe, clonazepam, available in IV formulation, is also used in the

acute treatment of seizures in the emergency setting. Often patients with history of cluster seizures and status epilepticus will present to the emergency room.

[0015] A rectal gel formulation of diazepam is commercially available (Diastat®) for outpatient treatment of increased seizure activity in patients on stable anti-epileptic drug regimen. Diastat® is administered to patients by caregivers and has been effective in aborting seizure activity and thereby reducing ER visits. However, due to the mode of administration, Diastat® has primarily been used in the pediatric population where a parent can rectally administer to their child. Ideally, an outpatient rescue treatment for these epileptic patients would have a quick onset of action terminating the ongoing seizure and prevent recurrence of seizure activity through a long enough duration of effect. The treatment should also be easily administered by caregivers in a culturally acceptable mode of administration that is easily accessible.

[0016] The nasal mucosa offers an alternative to oral and parenteral administration; intranasal administration is a practical way to achieve the therapeutic effect of many medications. Advantages of this method are that drugs can be administered readily and simply, and either a localized or a systemic effect can be achieved. Intranasal administration suffers from a significant problem, however: Most drug molecules diffuse slowly and poorly through the nasal mucosa. Therefore, therapeutic levels of the medication cannot be achieved or may not be achieved in time with the progression of the incidence. A further constraint is that the administration volume must be small; usually it is maximally about 150 μL per nostril. If a greater volume of medication is administered, it may drain into the pharynx and be swallowed.

[0017] Various intranasal benzodiazepine compositions have been developed. However, some of these compositions exhibit a delayed time to peak plasma concentration, poor absorption, or poor bioavailability. This is unacceptable for treatment or prevention of some disorders, illnesses and symptoms. Some intranasal midazolam formulations, for example, are produced at a pH that causes nasal irritation and burning in many patients.

[0018] Accordingly, there is a need for intranasal benzodiazepine compositions with improved properties such as, for example, rapid absorption, time to peak concentration, and bioavailability. Further, a need exists for vehicles in which the

solubility of the drug is high but which are non-damaging to the nasal mucosa. There also is a need for intranasal compositions that improve patient compliance.

Summary of the Invention

[0019] In one aspect, the invention is directed to a pharmaceutical composition for transmucosal administration to a mammal, comprising a solvent system comprising a first solvent in which a benzodiazepine is soluble, the first solvent capable of penetrating nasal mucosal tissue, and a second solvent in which the benzodiazepine is less soluble than in the first solvent, wherein the solvent system comprises 10% (weight/weight) or less of an aqueous buffer solution with the caveat that the solvent system does not comprise free polyethylene glycol polymers; and a therapeutically effective amount of a benzodiazepine.

[0020] In other embodiments, the pharmaceutical the solvent system may be substantially a single phase and substantially homogeneous, may be substantially free of aqueous buffer, the first solvent may be diethylene glycol monoethylether (DEGEE) or tetrahydrofurfuryl alcohol polyethyleneglycol ether (glycofurol), the first solvent may be present at a weight percent of between about 30% to about 70%, the second solvent may be glycerol triacetate or propylene glycol, and the benzodiazepine may be present at a weight percent of between about 0.1% to about 10%.

[0021] In further embodiments, the first and second solvents may be present in equal weight percents, the pH of the aqueous buffer solution may be between about pH 4 to about pH 7, the composition may further comprise one or more components selected from the group consisting of a surfactant, anti-oxidant, pharmaceutically acceptable polymer, polyalcohol, lipid, mucosa penetration enhancing agent, colorant, flavoring agent, anesthetic agent, co-solvent, and agent to adjust osmolarity, the composition may be formulated to be sprayable and the composition may be sprayable at temperatures between -15° and 30°C.

[0022] In another aspect, the invention is directed to a pharmaceutical composition for transmucosal administration to a mammal, comprising a solvent system comprising a first solvent comprising one or more components selected from the group consisting of diethylene glycol monoethylether and tetrahydrofurfuryl alcohol polyethyleneglycol ether, and a second solvent comprising one or more component

selected from the group consisting of glycerol triacetate or propylene glycol, wherein the solvent system comprises 10% (weight/weight) or less of an aqueous buffer solution with the caveat that the solvent system does not comprise free polyethylene glycol polymers; and a therapeutically effective amount of a benzodiazepine wherein the composition is a single phase and homogeneous.

[0023] In further embodiments the composition may be used at a unit therapeutic dose of between about 50 μL and 300 μL, or between 25 and 150 μL.

[0024] In another embodiment, the pharmaceutical composition of the invention comprises a benzodiazepine for intranasal administration to a mammal comprising an ethyl ether solvent and a therapeutically effective amount of the benzodiazepine, wherein the composition is a single phase and homogeneous.

[0025] In yet another aspect, the pharmaceutical composition of the invention comprises a benzodiazepine for transmucosal administration to a mammal, characterized by (i) a T_{max} of a benzodiazepine, after a single intranasal administration, of no more than 2 hours, and (ii) a bioavailability of the benzodiazepine, after a single intranasal administration, of no less than 30% of the bioavailability of an equivalent dose of the benzodiazepine delivered orally.

[0026] In still another aspect, the pharmaceutical composition of the invention comprises a benzodiazepine for transmucosal administration to a mammal, characterized by (i) a C_{max} of the benzodiazepine, after a single intranasal administration, of at least about 75% the C_{max} of an equivalent dose of the benzodiazepine delivered orally, and (ii) a bioavailability of the benzodiazepine, after a single intranasal administration, of no less than 30% of the bioavailability of an equivalent dose of the benzodiazepine delivered orally.

[0027] In a further aspect, the pharmaceutical composition of the invention comprises a benzodiazepine for intranasal administration to a mammal, characterized by (i) a ratio of the AUC of the benzodiazepine, after a single intranasal administration, (AUC_{in}) to the AUC of an equivalent dose of the benzodiazepine delivered orally (AUC_{oral}) of at least about AUC_{in}:AUC_{oral} = 1:3.3, wherein the AUC values are determined over the same time period.

[0028] In other aspects, the invention is directed to a method for administering an active agent to a mammal in need thereof, the method comprising delivery of a

benzodiazepine to the mammal's bloodstream via the nasal mucosa of the mammal in a dosage form comprising the compositions described above, and the invention is directed to a method of treating a mammal suffering seizures, the method comprising delivery of the benzodiazepine to the mammal's bloodstream via the nasal mucosa of the mammal, wherein the benzodiazepine is delivered in a dosage form comprising a composition described above.

[0029] In other embodiments, delivery of the active agent occurs at the onset of the symptoms of seizures, and one or more unit doses may be administered.

[0030] In yet another aspect, the invention is directed to a method of manufacturing a benzodiazepine composition, the method comprising mixing a solvent system and benzodiazepine to provide a single-phase, homogeneous solution suitable for intranasal administration of the benzodiazepine.

[0031] Still another aspect, the invention is directed to a method of administering an active agent to a mammal in need thereof, wherein a composition described above is administered to a mammal suffering from anxiety attacks selected from the group consisting of panic attacks, social phobia, social anxiety and performance anxiety.

[0032] These and other embodiments of the present invention will readily occur to those of ordinary skill in the art in view of the disclosure herein.

Brief Description of the Figures

[0033] Figure 1 presents a graphic representation of the mean cumulative amount of diazepam, lorazepam and clonazepam permeated per unit area over a period of 7 hours (h). In the figure, the horizontal axis is Time given in hours (h) and the vertical axis is the mean permeated amount of permeated drug per unit area ($\mu g/cm^2$). The legend for the plot of data is as follows: lorazepam, diamonds; clonazepam, squares; and diazepam, triangles.

[0034] Figure 2 presents the solubility of clonazepam in mixtures of triacetin or propylene glycol and glycofurol. In the figure, the vertical axis is CLO (clonazepam) solubility in mg/mL, and the horizontal axis is the percent (%) triacetin (TA) or propylene glycol (PG) and glycofurol (GF). In the figure, the linear regression for PG/GF was $y = -0.6539x + 66.185$, with a correlation coefficient of $R^2 = 0.9904$; and the linear regression for TA/GF was $y = -0.6229x + 67.597$, with a correlation coefficient of $R^2 = 0.999$.

[0035] Figure 3 presents irritation data for five clonazepam formulations. Comparison of irritation values is given relative to acetic acid solutions and a setron formulation. In the figure, the vertical axis is the blood pressure integrated as a function of time (Integral) and the horizontal axis is the formulations tested at 50 μL doses, as follows: CLZ2080 -- 10 mg/mL clonazepam, 20% Transcutol® (TC), 80% Polyethylene Glycol (PEG); CLZ5050 -- 10 mg/mL clonazepam, 50% TC, 50% PEG; CLZ70G30T -- 10 mg/mL clonazepam, 70% GF, 30% TA; CLZ20T80P02T, 10 mg/mL clonazepam, 10% TC, 90% PEG 200 and 0.2% Tween 20; Saline (negative control); Acetic Acid (HOAc) 0.3% (positive control); Acetic Acid (HOAc) 1.5% (positive control); Setron (positive control).

[0036] Figure 4 presents that data for irritation scores of eight clonazepam formulations and control formulations based on the mean blood pressure changes. The columns for saline, acetic acid solutions and a setron formulation (i.e., the right-most four columns) represented data from previous experiments and were inserted for comparison. In the figure, the vertical axis is the blood pressure integrated as a function of time (Integral) and the horizontal axis corresponds to the tested formulations (the formulations are set forth in Table 11). Saline was a negative control; 0.3% Acetic Acid (HOAc) and 0.9% HOAc were positive irritation controls; and setron was a positive irritation control.

[0037] Figure 5 presents pharmacokinetic data in a rabbit study. In the figure, the vertical axis is concentration of clonazepam (CLZ conc. (ng/mL)), and the horizontal axis is time in minutes (Time (min.)). The legend for the plot of data is as follows: Formulation I, closed circles; Formulation II, closed squares; Formulation III; upright triangles; and Formulation IV, light x's. The top data line with dark x's corresponds to the data for intravenous administration.

[0038] Figure 6 summarizes the histopathology results for the nasal cavities of test animals to which clonazepam compositions of the present invention were administered. In the figure, the vertical axis is the number of affected animals; and the horizontal axis are the test groups organized by groups of three bar graphs. In each bar graph the order of the vertical bars is as follows: Score 0; Score 1; and Score 2.

[0039] Figure 7 shows the correlation between plume area at 3 cm and viscosity of non-aqueous solvent matrices. Data for water is shown for comparison (□).

Composition of solvent matrices is presented in Table 19. In the figure, the vertical axis is plume area in cm and the horizontal axis is viscosity (cP).

[0040] Figure 8 shows the correlation between spray angle and viscosity of non-aqueous solvent matrices. Data for water is shown for comparison (□). Composition of solvent matrices is presented in Table 19. In the figure, the vertical axis is spray angle (in degrees) and the horizontal axis is viscosity (cP).

[0041] Figure 9 shows the correlation between plume asymmetry (D_{max}/D_{min}) and viscosity of non-aqueous solvent matrices. Data for water is shown for comparison (□). Composition of solvent matrices is presented in Table 19. In the figure, the vertical axis is (D_{max}/D_{min}) and the horizontal axis is viscosity (cP).

Detailed Description of the Invention

[0042] All patents, publications, and patent applications cited in this specification are herein incorporated by reference as if each individual patent, publication, or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

1.0.0 Definitions

[0043] It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting. As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a solvent" includes a combination of two or more such solvents, reference to "a compound" includes one or more compounds, mixtures of compounds, and the like.

[0044] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although other methods and materials similar, or equivalent, to those described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

[0045] In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

[0046] The term "dosage form" as used herein refers to a pharmaceutical composition comprising an active agent, such as a benzodiazepine, and optionally containing inactive ingredients, e.g., pharmaceutically acceptable excipients such as

suspending agents, surfactants, solvents, co-solvents, permeation enhancers, binders, diluents, lubricants, stabilizers, anti-oxidants, osmotic agents, colorants, plasticizers, coatings and the like, that may be used to manufacture and deliver active pharmaceutical agents.

[0047] The term "gel" as used herein refers to a semi-solid dosage form that contains a gelling agent in, for example, an aqueous, alcoholic, or hydroalcoholic vehicle and the gelling agent imparts a three-dimensional cross-linked matrix ("gellified") to the vehicle. The term "semi-solid" as used herein refers to a heterogeneous system in which one solid phase is dispersed in a second liquid phase. In preferred embodiments of the present invention, the benzodiazepine (e.g., clonazepam) compositions formulated for intranasal delivery are not gellified.

[0048] The pH measurements for formulations and compositions described herein, wherein the formulations or compositions do not comprise a predominantly aqueous environment, are more aptly described as "apparent pH" values as the pH values are not determined in a predominantly aqueous environment. In such cases, the influence of, for example, organic solvents on the pH measurement may result in a shift of pH relative to a true aqueous environment.

[0049] The term "mucoadhesive" as used herein refers to adhesion to mucous membranes that are covered by mucus, for example, those in the nasal cavity.

[0050] The term "carrier" or "vehicle" as used herein refers to carrier materials (other than the pharmaceutically active ingredient) suitable for administration of a pharmaceutically active ingredient, for example, transmucosal administration via nasal mucosa. A vehicle may comprise, for example, solvents, cosolvents, permeation enhancers, pH buffering agents, antioxidants, additives, or the like, wherein components of the vehicle are nontoxic and do not interact with other components of the total composition in a deleterious manner.

[0051] The term "transdermal" delivery, as used herein refers to both transdermal (or "percutaneous") and transmucosal administration, that is, delivery by passage of a drug through a skin or mucosal tissue surface and ultimately into the bloodstream. Transmucosal administration includes, but is not limited to, nasal, oral, rectal, and vaginal administration of a composition for delivery of an active drug (e.g., clonazepam) to the blood stream of the subject to which it is administered.

[0052] The phrase "therapeutically effective amount" as used herein refers to a nontoxic but sufficient amount of a drug, agent, or compound to provide a desired therapeutic effect, for example, one or more doses of benzodiazepine that will be effective in treatment of seizures including seizure clusters and status epilepticus or for the treatment of anxiety states including but not limited to panic attacks, social phobia, social anxiety and performance anxiety, acute mania, psychosis, and drug withdrawal, including but not limited to nicotine withdrawal, opiate withdrawal, and alcohol withdrawal.

[0053] The phrase "seizure clusters" as used herein refers to closely related groups of seizures in some epilepsy patients. Typically seizure cluster patients experience this increased frequency of seizures in unique patterns. It is not uncommon for some of these patients to experience 3 or more seizures in a 24-48 hour period.

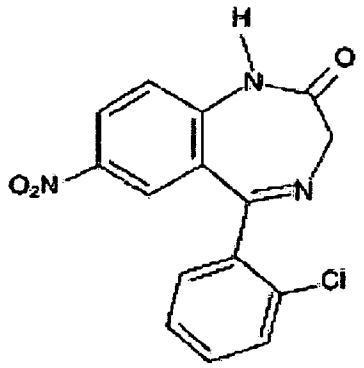
[0054] The term "benzodiazepine" as used herein refers to a class of drugs with sedative, hypnotic, anxiolytic, anticonvulsant, amnestic and/or muscle relaxant properties. Typically, benzodiazepines comprise a structure composed of a benzene ring fused to a seven-membered diazepine ring. Most of the important benzodiazepines contain an aryl substituent ring and a 1, 4-diazepine ring. Generally, benzodiazepine refers to aryl-1,4-benzodiazepines. The actions of benzodiazepines are usually the result of increased activation of receptors by gamma-aminobutyric acid (GABA). The term benzodiazepine includes benzodiazepines and pharmaceutically acceptable salts thereof.

[0055] Benzodiazepines are commonly divided into three groups related to the period of time for which the drug has an evident effect: short-acting benzodiazepines typically act for less than six hours; intermediate-acting benzodiazepines typically act for 6-10 hours; and long-acting benzodiazepines have strong sedative effects that persist. The following list is a partial list of benzodiazepines. The list is arranged in an approximate order of the shortest acting to the longest acting benzodiazepine: alprazolam; bromazepam; chlordiazepoxide; clobazam; clonazepam; clorazepate; diazepam; estazolam; flunitrazepam; flurazepam; halazepam; ketazolam; loprazolam; lorazepam; lormetazepam; medazepam; midazolam; nitrazepam; nordazepam; oxazepam; prazepam; quazepam; temazepam; tetrazepam; and triazolam.

[0056] Benzodiazepines typically have the following effects, though some may be relatively stronger anxiolytics and others relatively stronger amnesics: anxiolytic (reduce

anxiety, e.g., treatment of panic attacks); anticonvulsant (e.g., treatment of seizures); antispasmodic (e.g., muscle relaxant); sedative / hypnotic; antidepressant; and, amnesic (produce anterograde amnesia).

[0057] The term "clonazepam" as used herein includes clonazepam and its active pharmaceutically acceptable derivatives and metabolites, as well as pharmaceutically acceptable salts thereof. Clonazepam's pharmacological profile is similar to other anxiolytic/sedative benzodiazepines. Further, the basic anticonvulsive properties of clonazepam are similar to those of other diazepines. Clonazepam is capable of suppressing the spike and wave discharge in absence seizures (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in minor motor seizures. Clonazepam can be used for the treatment of seizure clusters associated with epilepsy. Chemically, clonazepam is 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one. It is a light yellow crystalline powder. Clonazepam has a molecular weight of 315.72 and the following molecular formula: $C_{15}H_{10}ClN_3O_3$. The structure of clonazepam is as follows:



[0058] The term "alkyl solvent" as used herein includes alkyl ethers of 2-5 carbons in length and includes but is not limited to 1,2-dimethoxyoethane, di(ethylene glycol) methyl ether, diethylene glycol monoethyl ether and di(ethyleneglycol) diethyl ether.

[0059] The phrase "permeation enhancer" or "penetration enhancer" as used herein refers to an agent that improves the rate of transport of a pharmacologically active agent (e.g., clonazepam) across the mucosal or skin surface. Typically a penetration enhancer increases the permeability of mucosal tissue or skin to a pharmacologically active agent. Penetration enhancers, for example, increase the rate at which the

pharmacologically active agent permeates through mucosal tissue and enters the bloodstream. Enhanced permeation effected through the use of penetration enhancers can be observed, for example, by measuring the flux of the pharmacologically active agent across animal or human tissue as described in the Examples herein below. An "effective" amount of a permeation enhancer as used herein means an amount that will provide a desired increase in nasal mucosal tissue permeability to provide, for example, the desired depth of penetration of a selected compound, rate of administration of the compound, and amount of compound delivered.

[0060] The term "subject" as used herein refers to any warm-blooded animal, particularly including a member of the class Mammalia such as, without limitation, humans and non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rabbits and rodents such as mice, rats and guinea pigs, and the like. The term does not denote a particular age or sex.

[0061] The term "delivery rate" as used herein refers to the quantity of drug delivered, typically to plasma, per unit time, for example, nanograms of drug released per hour (ng/hr) *in vivo*.

[0062] In the context of plasma blood concentration of active agent, the term "C" as used herein refers to the concentration of drug in the plasma of a subject, generally expressed as mass per unit volume, typically nanograms per milliliter (this concentration may be referred to as "plasma drug concentration" or "plasma concentration" herein which is intended to be inclusive of drug concentration measured in any appropriate body fluid or tissue). The plasma drug concentration at any time following drug administration is typically referred to as C_{time} as in C_{10h} or C_{20h}, etc. The term "C_{max}" refers to the maximum observed plasma drug concentration following administration of a drug dose, and is typically monitored after administration of a first dose and/or after steady-state delivery of the drug is achieved. The following terms are used herein as follows: "C_{avg}" refers to average observed plasma concentration typically at steady state, C_{avg} at steady state is also referred to herein as "C_{ss}"; "C_{min}" refers to minimum observed plasma concentration typically at steady state.

[0063] The term "AUC" or area under the curve as used herein refers to total amount of drug absorbed by the body and is the area under the curve in a plot of

concentration of drug in plasma against time and in this case is calculated for humans for 24 hours after administration orally (AUC_{oral}), intranasally (AUC_{in}) or intraveneously (AUC_{iv}).

[0064] The term "T_{max}" as used herein refers to the time to maximum plasma concentration and represents the time that elapses between administration of the formulation and a maximum plasma concentration of drug (i.e., a peak in a graph of plasma concentration vs. time, see, for example, Figure 5). T_{max} values may be determined during an initial time period (for example, related to administration of a single dose of the drug) or may refer to the time period between administration of a dosage form and the observed maximum plasma concentration during steady state.

[0065] The term "steady state" as used herein refers to a pattern of plasma concentration versus time following consecutive administration of a constant dose of active agent at predetermined intervals. During "steady state" the plasma concentration peaks and plasma concentration troughs are substantially the same within each dosing interval.

[0066] The term "spray" as used herein means a liquid composition expressed from a device under pressure in the form of an aerosol, a fine mist, liquid droplets, a fine stream, or combinations thereof. The precise form of the liquid composition is dependent upon the viscosity and other physical properties, as well as the manner in which a force (manual or other) is applied to a device containing the liquid composition to discharge the liquid composition. Some characteristics of a spray of a liquid composition are described in "Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry" and further in "Manufacturing, and Controls Documentation" (July 2002), and the Examples, herein below, and include, but are not limited to spray pattern, droplet size, and plume geometry. Typically, the spray is homogeneous, however a heterogeneous spray is acceptable as long as the sprayed volume is effectively adsorbed by the nasal mucosa.

[0067] The phrase "with the caveat that the solvent system does not comprise free polyethylene glycol polymers" as used herein refers to a composition comprising one or more solvents that do not contain polyethylene glycol (PEG) polymers free in the solution of the solvent system, that is the composition does not contain PEG polymers that are not an intrinsic part of a larger chemical entity. Accordingly, free polyethylene glycol

polymers (e.g., PEG 200, PEG 300, PEG 400) are not added as separate components to the solvent system. However, a composition that does not comprise free polyethylene glycol polymers may comprise molecules that contain substituent polyethyelene glycol polymers as part of their intrinsic molecular structure (e.g., glycofurol and mono- or di-glycerides that contain PEG polymers as substituent groups (see, for example, published P.C.T. International Application Nos. WO 03/070273, WO 03/070280, and U.S. Patent Nos. 6,855,332 and 5,942,237)).

[0068] The term "free of aqueous buffer" intends a composition that is substantially free of aqueous buffer in that aqueous buffer is not added to the composition.

[0069] The term "homogeneous" as used herein refers to a composition that is substantially uniform visually and macroscopically, substantially free of particulates and does not settle or separate over time.

[0070] The term "single phase" as used herein refers to a composition that substantially contains one thermodynamic state, and is chemically and physically uniform throughout.

[0071] The term "bioavailability" or "F" refers to relative bioavailability and intends the ratio of AUC_{in} to $AUC_{oral,}$ in the case of human subjects and intends the ratio of AUC_{in} to AUC_{iv} in the case of rabbits.

[0072] The term "unit dose" as used herein refers to the amount of the transmucosal clonazepam required for a therapeutically effective dose. The unit dose may be given in one or more sprays, and for intranasal delivery, may be given in one or both nostrils.

[0073] One of ordinary skill in the art appreciates that plasma drug concentrations obtained in individual subjects will vary due to inter-subject variability in many parameters affecting, for example, drug absorption, distribution, metabolism, and excretion. Accordingly, mean values obtained from groups of subjects are typically used for purposes of comparing plasma drug concentration data and for analyzing relationships between *in vitro* dosage assays and *in vivo* plasma drug concentrations.

2.0.0 General Overview of the Invention

[0074] A seizure cluster can be described as an ictal pattern wherein several seizures occur within a short period, usually days. This period of seizure activity is

typically followed by a longer seizure-free interval of weeks to months. According to epidemiologic studies, approximately 50% of epilepsy patients experience seizure clusters. Clustering may be quasi-weekly or quasi-monthly (Tauboll, E., *et al.*, "Temporal distribution of seizures in epilepsy," Epilepsy Res. **8**(2), pages 153-165 (1991); Bauer, J., *et al.*, "Course of chronic focal epilepsy resistant to anticonvulsant treatment," Seizure **10**(4), pages 239-246 (2001)).

[0075] A preferred treatment for seizure clusters would have a rapid action and long duration of action. Further, the treatment should be relatively non-sedating. In addition, the ability to self-administer treatment is often compromised during seizure and oral administration may not be possible. One common treatment in the United States is rectal diazepam gel (Dreifuss, F.E., *et al.*, "A comparison of rectal diazepam gel and placebo for acute repetitive seizures," N. Engl. J. Med. **338**(26), pages, 1869-1875 (1998)). Non-oral routes of administration are desirable in that it is often a family member, significant other, or other second party who may recognize the onset of acute repetitive seizures. Oral administration of some benzodiazepines has been used for the treatment of seizure clusters (for example, diazepam given at 5 mg to 10 mg dose, lorazepam given at 1 mg to 2 mg dose, and clonazepam given at 0.5 mg to 2 mg dose. Some benzodiazepine formulations for buccal (e.g., U.S. Patent No. 6,699,849), transdermal (e.g., Mura, P., *et al.*, "Evaluation of Transcutol® as a clonazepam Transdermal Permeation Enhancer," Eur. J. Pharma. Sci. **9**, pages 365-372 (2000)) and mucosal administration (e.g., U.S. Patent No. 6,488,953) have been described. Further, some benzodiazepine formulations for intranasal administration have been described (see, for example, Hou, H., *et al.*, "Enhanced Permeation of Diazepam through Artificial Membranes from Supersaturated Solutions," J. Pharma. Sciences **95(4)**, pages 896-905 (2001); Schols-Hendriks, M.W.G., *et al.*, J. Clin. Pharmac. **39**, pages 449-451 (1995); U.S. Patent Nos. 6,193,985, 6,610,271, 6,627,211; U.S. Published Patent Application No. 2004/0176359; Published P.C.T. International Application Nos. WO 2004/110403 and WO 03/070208); however, nasal formulations prior to those of the present invention have had a number of short comings, for example, the formulations comprise benzodiazepines with relatively high sedation properties, formulations have relied on supersaturated solutions that do not store well and may crystallize, serum drug concentrations after administration have been too low to be therapeutically effective, the formulations

comprised non-homogeneous systems that present complications for spray delivery, some formulations do not have acceptable tolerability or irritation profiles, or they contain components that lead to degradation of the benzodiazepine.

[0076] Some treatments, for example, treatment with oral lorazepam or diazepam, often cause drowsiness and delay the ability of the subject being treated to return to her/his normal activities.

[0077] Since the treatment described herein would be relative fast acting and non-sedating, it is also contemplated the intranasal benzodiazepines could be useful to treat other conditions that require fast onset and minimal side effects. These include anxiety states including but not limited to panic attacks, social phobia, social anxiety and performance anxiety; acute mania; psychosis; and drug withdrawal, including but not limited to nicotine withdrawal, opiate withdrawal, and alcohol withdrawal. The treatment may also be useful for patents that are unconscious, semiconscious, and/or unable to swallow.

[0078] Some advantages for intranasal delivery of benzodiazepines include the following. Intranasal administration is convenient, simple, easy, non-invasive and virtually pain-free. It neither generates biohazardous waste nor risk of needle-stick accidents. Intranasal formulations can be delivered in precise, metered doses. Further, smaller doses can be administered, for example, serially, to obtain the desired clinical result with fewer side effects (e.g., intestinal) than medication delivered in tablet form. Intranasal administration can provide rapid, efficient absorption and more consistent bioavailability. It also provides flexibility for health care workers, patients, and their caregivers. Unit doses, for example, can reduce abuse potential. Also, intranasal administration avoids first pass metabolism of the benzodiazepine.

[0079] Before describing the present invention in detail, it is to be understood that this invention is not limited to particular embodiments described herein, for example, particular benzodiazepines (including, without limitation, clonazepam, diazepam and lorazepam), solvent(s), cosolvent(s), hydrophilic polymer(s), surfactant(s) (including, ionic and non-ionic surfactant(s)), polyalchohol(s), solublizing agent(s), antioxidant(s), penetration enhancer(s), and/or buffering agent(s), and the like, as use of such particulars may be selected in view of the teachings of the present specification by one of ordinary skill in the art. It is also to be understood that the terminology used herein is for the

purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

2.1.0 Exemplary Formulations of the Present Invention and Components Thereof

2.1.1 Transmucosal Formulations and Methods of Use

[0080] In one aspect, the present invention includes a pharmaceutical composition of benzodiazepine (e.g., clonazepam) for transmucosal administration to a mammal. Example 1 presents data obtained in support of the present invention that demonstrated the ability of clonazepam, diazepam and lorazepam as a exemplary benzodiazepines, to penetrate nasal mucosa. The permeation of saturated solutions of the benzodiazepines across nasal sheep mucosa *in vitro* is described in the example, as are preliminary stability data. Figure 1 presents a graphic representation of the mean cumulative amount of benzodiazepines permeated per unit area over a period of Example 1. The benzodiazepines were shown to have acceptable stability in the context of use for transmucosal administration, as well as acceptable permeation characteristics through nasal mucosa.

[0081] The solubility of clonazepam in a number of neat solvents were determined (Example 2) as part of a determination of suitable solvents for use in benzodiazepine formulations of the present invention for intranasal administration. Good solvents were identified as useful for achieving a target solubility of clonazepam of about 10 to about 20 mg/mL. Further, the solubility of clonazepam in binary solvent mixtures of diethylene glycol mono-ethyl ether, triacetin, glycofurol and propylene glycol was evaluated. The data presented in Figure 2, for example, demonstrated a linear relationship between the solubility and percent composition of the binary mixtures of triacetin or propylene glycol and glycofurol. The data presented in Figure 2 demonstrated the usefulness of solvent solutions comprising binary solvent mixtures to solubilize clonazepam for use in formulation of intranasal pharmaceutical compositions.

[0082] The solvent systems set forth Example 2 provide examples of formulations of minimum number of solvent components in the system, which helps reduce possible interactions. These solvent combinations also increase the chemical potential and system thermodynamics helping to ensure that the drug (e.g., clonazepam) prefers to leave the solvent system to cross the nasal membrane rather than being swallowed, particularly

when mixed with water in the nasal mucosa (i.e., mucocilliary clearance). The solvent systems described in Example 2 also provide guidance concerning avoiding components that may provide a thermodynamic sink (e.g., polyethylene glycol polymers and cyclodextrins).

[0083] The stability of clonazepam in exemplary solvent systems was further examined (Example 3). The data suggested that formulations comprising polyethylene glycol polymers provided the least drug (clonazepam) stability. Further, formulations that contained water without buffer also demonstrated color development, indicative of degradation of the clonazepam. Other solvent systems (for example, including diethylene glycol monoethylether, tetrahydrofurfuryl alcohol polyethyleneglycol ether, glycerol triacetate, propylene glycol, and buffered aqueous solutions) provided good stability for clonazepam.

[0084] The data presented in Example 3 also suggested that addition of an anti-oxidant to the formulations of the present invention used for intranasal delivery of benzodiazepines may provide desirable drug protective benefits to such formulations. Further, the data indicated drug protective effects resulting from the inclusion of pH modifiers when an aqueous solvent was used.

[0085] In order for benzodiazepine (e.g., clonazepam) formulations to be useful for administration to mucosal membranes, the formulations should have acceptable irritation and tolerance profiles. The preliminary nasal irritation data (Example 4) and the nasal discomfort reports of the human pharmacokinetic study (Example 14) suggested that the benzodiazepine formulations of the present invention were suitable for intranasal delivery. The data shown in Figure 3 and Figure 4 demonstrated slight, transient nasal irritation in the test animals. After instillation of compositions, irritation typically lasted less than about two minutes in rats. Irritation was generally greater than saline and similar to irritation from tolerable concentrations of acetic acid. Veterinary evaluation of the data resulted in the conclusion that nasal irritation from these formulations was not significant. Further, the data presented in Example 4 suggests that non-ionic surfactants may possibly be used to reduce nasal irritation in some formulations.

[0086] The pharmacokinetics of a large number of clonazepam formulations were evaluated (Example 5, see, for example, Table 12A and 12B). The pharmacokinetic data presented in the example illustrated that clonazepam compositions formulated for

intranasal administration are pharmaceutically efficacious to deliver clinically relevant amounts of clonazepam into the bloodstream in a relatively short time period -- making such intranasal formulations clinically useful, for example, for the treatment of seizure clusters. The values of the pharmacokinetic parameters vary between the different formulations and one of ordinary skill in the art, following the guidance of the present specification, may select formulations suitable for a variety of treatment purposes, for example, use in adults (generally higher C_{max}, and AUC, is desirable), use in children (lower C_{max}, and AUC, may be desirable relative to formulations for use in adults), different dosage forms and serial administration (e.g., starting with administration of rapid onset, early T_{max}, and following with a second administration of a formulation with slower onset, later T_{max}), etc.

[0087] Experiments performed in support of the present invention demonstrated that the compositions of the present invention may comprise a solvent matrix of two solvents, for example, a first solvent that provides high solublization of clonazepam (for example, Transcutol® (diethylene glycol monoethylether) and similar monoethylethers, Glycofurol (ethoxylated furanyl alcohol or tetrahydrofurfuryl alcohol polyethyleneglycol ether) and similar ethoxylated tetrahydrofurfuryl alcohols that, after application to nasal mucosa, is absorbed by the nasal mucosa leading to clonazepam super saturation in the nasal cavity, and a second solvent (for example, triacetin and propylene glycol or the like) in which clonazepam has lower solubility relative to the first solvent.

[0088] The pharmacokinetics and tolerability of four clonazepam compositions comprising binary solvent systems were evaluated in further detail (Example 5, Table 13). The intranasal PK profiles of the formulations (Figure 5) demonstrated a rapid absorption of clonazepam such that clinically relevant amounts of clonazepam reach the bloodstream in a short period of time. Lower bioavailability in some formulations can be compensated for with, for example, use of a higher initial dose. An advantage of a higher dose and low short term bioavailability may be passage of the drug that is not absorbed intranasally into the gastro-intestinal tract resulting in the remainder of the drug undergoing classical GI absorption leading to a sustained release profile.

[0089] Further, experiments performed in support of the present invention evaluated the local tolerance in the upper and lower respiratory tract of four clonazepam compositions of the present invention. Tolerance was assessed using a rabbit model

(Example 5). The data presented in Figure 6 summarizes the histopathology results for the nasal cavities of the animals. The results of necropsy and histopathological examination, including comparison of severity scores, suggested that clonazepam compositions of the present invention have acceptable tolerability for pharmaceutical use for administration to nasal mucosal tissue.

[0090] Pharmacokinetic and tolerability were expected to be similarly desirable in humans and were shown to be desirable in 15 human volunteers. Experiments to evaluate pharmacokinetics and tolerability in humans are prophetically described in Example 8, Example 9, and Example 10. Actual experiments and their results are described in Examples 14, 15 and 16.

[0091] As one intended use of the formulations of the present invention is for intranasal administration, sprayability (including plume geometry, spray angle, and plume symmetry) and viscosity of exemplary formulations of the present invention were evaluated (Example 6, Figure 7, Figure 8, and Figure 9). The results demonstrated that at 20-25°C all solvent matrices tested sprayed well from manually activated unit dose devices (e.g., obtained from Pfeiffer, manufactured by Pfeiffer of America, Princeton, N.J.). The results also suggested that viscosity of the formulations of the present invention is a good predictor of sprayability and that the formulations retained their sprayability at temperatures below 40°C, and between -15°C and 30°C .

[0092] In view of the experimental findings discussed herein, the compositions of the present invention of benzodiazepine (e.g., clonazepam, diazepam or lorazepam) for transmucosal administration to a mammal may, for example, comprise a solvent system and a therapeutically effective amount of a benzodiazepine (e.g., clonazepam, diazepam or lorazepam). In one embodiment the solvent system comprises a first solvent in which benzodiazepine (e.g., clonazepam, diazepam or lorazepam) is soluble, the first solvent capable of penetrating nasal mucosal tissue, and a second solvent in which benzodiazepine (e.g., clonazepam, diazepam or lorazepam) is less soluble than in the first solvent. The solvent system may comprise about 40% or less aqueous solvent, about 30% or less, preferably about 20% or less, more preferably about 10%, or less, about 8% or less, about 5% or less, or about 2% or less. The aqueous solvent is preferably a buffered aqueous solution, for example, with a pH of the aqueous buffer solution between about pH 4 to about pH 7, more preferably between about pH 4 to pH 5.5. In preferred

embodiments, the solvent system does not comprise free polyethylene glycol polymers. Preferred compositions are a single phase and homogeneous.

[0093] In one embodiment, the solvent system is substantially free of aqueous buffer.

[0094] In a second embodiment, the solvent system may comprise a single alkyl ether solvent. Such solvent may be selected from the group consisting of 1,2-dimethoxyoethane, di(ethylene glycol) methyl ether, diethylene glycol monoethyl ether and di(ethyleneglycol) diethyl ether. In a particular embodiment, the single alkyl ether solvent is diethylene glycol monoethyl ether.

[0095] Examples of the first binary solvent of the solvent system include, but are not limited to, diethylene glycol monoethylether or tetrahydrofurfuryl alcohol polyethyleneglycol ether. The first solvent may be, for example, present at a weight percent of between about 30% to about 70%. Examples of the second solvent of the solvent system include, but are not limited to, glycerol triacetate or propylene glycol. The second solvent may be, for example, present at a weight percent of between about 70% and about 30%. In some embodiments the second solvent is less capable of penetrating nasal mucosa than the first solvent.

[0096] The solvent system may, for example, consist essentially of the first solvent and the second solvent. In another embodiment, the solvent system may consist essentially of the first solvent, the second solvent, and an aqueous buffer solution (e.g., 10% (weight/weight) or less) and may further comprise additional components (e.g., an anti-oxidant).

[0097] The active drug, for example, the benzodiazepine, is typically present at a weight percent of between about 0.1% to about 20% and often between 0.1% and 10% often 0.25% to 6%.

[0098] In one embodiment, the first and second solvents are present in equal weight percents.

[0099] In addition to the components just described, pharmaceutical compositions comprising the benzodiazepine (e.g., clonazepam, diazepam or lorazepam) of the present invention, for example, for intranasal administration to a mammal, may further comprise one or more components including, but not limited to, a surfactant, anti-oxidant, pharmaceutically acceptable polymer, polyalcohol, lipid, mucosa penetration enhancing

agent, colorant, flavoring or olfactory agent, anesthetic agent, co-solvent, and agent to adjust osmolarity.

[00100] In preferred embodiments of the present invention, the pharmaceutical compositions of benzodiazepine (e.g., clonazepam, diazepam or lorazepam) are formulated to be sprayable, for example, from a manually actuated spray device, and at temperatures between -15°C and 30°C.

[00101] In a second aspect, the present invention includes a pharmaceutical composition for intranasal administration of a benzodiazepine to a mammal, for example, a human. In this aspect, the solvent system may comprise a single alkyl ether solvent or a first solvent, comprising one or more component selected from the group consisting of diethylene glycol monoethylether and tetrahydrofurfuryl alcohol polyethyleneglycol ether, and a second solvent, comprising one or more component selected from the group consisting of glycerol triacetate or propylene glycol. The solvent system may further comprise an aqueous buffer solution (e.g., 10% (weight/weight) or less, wherein the pH of the aqueous buffer solution is between about pH 4 to about pH 7, more preferably between about pH 4 to about pH 6.5). In preferred embodiments, there is a caveat that the solvent system does not comprise free polyethylene glycol polymers. The pharmaceutical compositions of the present invention for transmucosal administration of a benzodiazepine also comprise a therapeutically effective amount of the benzodiazepine. Typically, the composition is a single phase and homogeneous. In one embodiment of the benzodiazepine is lorazepam, in another embodiment it is diazepam.

[00102] In one embodiment, the solvent system is a binary solvent system, that is, a solvent system consisting essentially of two solvents. Such binary solvent systems may be, for example, substantially free of an aqueous component. In some embodiments of the present invention, the first solvent consists essentially of diethylene glycol monoethylether or tetrahydrofurfuryl alcohol polyethyleneglycol ether. The first solvent may be present at a weight percent of, for example, between about 30% to about 70%. In some embodiments, the second solvent consists essentially of glycerol triacetate or propylene glycol. The second solvent may be present, for example, at a weight percent of between about 70% and about 30%. In another embodiment the pharmaceutical composition may include a single alkyl ether solvent such as diethylene glycol monoethyl ether Typically, the benzodiazepine is present at a weight percent of between about 0.1%

to about 20%, more preferably at a weight percent of between about 0.1% to about 10%, more preferably at a weight percent of between about 0.25% to about 6%. In yet a further embodiment, the solvent system consists essentially of the first solvent and the second solvent. In another embodiment, the solvent system consists essentially of the first solvent, the second solvent, and an aqueous buffer solution (e.g., 10% (weight/weight) or less). The aqueous buffer may further comprise one or more additional components, for example, an anti-oxidant and/or surfactant.

[00103] In some embodiments of this aspect of the present invention, the first and second solvents are present in equal weight percents.

[00104] The pharmaceutical compositions of the present invention for intranasal administration of a benzodiazepine to a mammal may include further components, for example, less than about 10% (weight/weight) of one or more components including, but not limited to, a surfactant, anti-oxidant, pharmaceutically acceptable polymer, polyalcohol, lipid, mucosa penetration enhancing agent, colorant, flavoring agent, anesthetic agent, co-solvent, and agent to adjust osmolarity.

[00105] Examples of suitable pharmaceutically acceptable polymers include, but are not limited to, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, xanthane gum, tragacantha, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, and combinations thereof.

[00106] Surfactants useful in the practice of the present invention are typically, but not exclusively, non-ionic. Examples of suitable surfactants include, but are not limited to, TWEEN (i.e., polyoxyethylene sorbitan fatty acid ester), an alpha-hydro-omega-hydroxypoly(oxyethylene) poly(oxypropylene)poly(oxyethylene) block copolymer, a polyoxyethylene alkyl ether, a polyoxyethylene castor oil derivative, and combinations thereof.

[00107] Examples of suitable polyalcohols include, but are not limited to, glycerol, propylene glycol, glycerol monoesters with fatty acids, and combinations thereof. In preferred embodiments, the compositions of the present invention do not include free polyethlylene glycol polymers.

[00108] Examples of suitable solublizing agent agents include, but are not limited to, lipids (e.g., fats, oils, waxes, sterols, triglycerides, and combinations thereof).

[00109] The compositions of the present invention may further comprise a mucosal penetration enhancing agent. Examples of mucosal penetration enhancing agents include, but are not limited to, N-methyl-2-pyrrolidone, 2-pyrrolidone, propylene glycol, dimethylformamide, dimethyl sulfoxide, caprolactam, oleic acid, decylmethylsulfoxide, 1-dodecylazacycloheptan-2-one, isopropyl myristate, hexamethylene palmitamide, hexamethylene lauramide, aliphatic acids, esters, and combinations thereof.

[00110] Antioxidants typically provide enhanced stability to the composition as a whole and/or specifically contribute to stability of the active agent (e.g., the benzodiazepine). Addition of anti-oxidants may serve to protect the benzodiazepine from oxidative damage in some embodiments of the present invention. Accordingly, the compositions of the present invention may further comprise an anti-oxidant (e.g., edetic acid or sodium edetate, butylhydroxytoluene, propyl gallate, sodium metabisulfite, butylhydroxyanisole, tocopherols, and combinations thereof), in particular the antioxidant may be butylhydroxytoluene (BHT) at concentrations of 100-300 ppm more often 500-2000 ppm.

[00111] Further, one or more additional components may be added to the compositions of the present invention. Such additional components will be apparent to one of ordinary skill in the art in view of the teachings of the present specification. Such further components include, but are not limited to, a colorant, flavorant, and anesthetic agent.

[00112] In preferred embodiments, the benzodiazepine compositions of the present invention are formulated to be sprayable, for example, using a manually or electronically actuated spray device or a passive device that is actuated by the patient's act of inhalation. For sprayable compositions that are intended for delivery to the nasal cavity of a mammal, the composition may be used at a unit therapeutic dose of between about 50 μL and 300 μL, often between 25 μL and 150 μL and more preferably at a unit therapeutic dose of about 100 μL.

[00113] A therapeutically effective amount of clonazepam in the compositions of the present invention may be, for example, between about 0.1 mg and about 5.0 mg per unit dose, more preferably between about 1.0 mg and about 4.0 mg per unit dose. A therapeutically effective amount of lorazepam in the compositions of the present invention may be, for example between about 0.5 mg and about 10.0 mg per unit dose,

more preferably between about 1.0 mg and about 5.0 mg per unit dose. A therapeutically effective amount of diazepam in the compositions of the present invention may be, for example between about 1.0 mg and about 40.0 mg per unit dose, more preferably between about 2.0 mg and about 10.0 mg per unit dose.

[00114] Some exemplary formulations of clonazepam compositions of the present invention are presented in Example 7, Table 20. In the example, methods of making the compositions are also described.

[00115] A third aspect of the present invention relates to a pharmaceutical composition comprising a benzodiazepine for transmucosal administration to a mammal, wherein the composition is characterized by T_{max} of the benzodiazepine, after a single intranasal administration, and bioavailability of the benzodiazepine. In one embodiment, the composition is characterized by (i) a T_{max} of the benzodiazepine, after a single intranasal administration, of no more than 2 hours and (ii) a bioavailability of the benzodiazepine, after a single intranasal administration, of no less than about 30% of the bioavailability of an equivalent dose of the benzodiazpine delivered orally. In other embodiments, the T_{max} is less than or equal to 30 minutes and the bioavailability is greater than or equal to 55% of the bioavailability of orally delivered benzodiazepine. Exemplary T_{max} and bioavailability data for some embodiments of the present invention are presented herein below in Example 5, Tables 12A and 12B, Figure 5 and Example 14 T_{max} may be less than or equal to 2 hours or less than or equal to 1 hour or less than or equal to 30 minutes or less than 15 minutes.

[00116] A fourth aspect of the present invention relates to a pharmaceutical composition comprising the benzodiazepine for transmucosal administration to a mammal, wherein the composition is characterized by C_{max} of the benzodiazepine, after a single intranasal administration, and bioavailability of the benzodiazepine. In one embodiment, the composition is characterized by (i) a C_{max} of the benzodiazepine, after a single intranasal administration, of at least about 75% of the C_{max} of an equivalent dose of clonazepam delivered orally, and (ii) a bioavailability of the benzodiazepine, after a single intranasal administration, of no less than about 30% of the bioavailability of an equivalent dose of the benzodiazepine delivered orally. Exemplary C_{max} and bioavailability data for some embodiments of the present invention are presented herein below in Example 5, Tables 12A and 12B, and Figure 5. In other embodiments, the C_{max}

of intranasally delivered benzodiazepine is greater than or equal to 75% or greater than or equal to 80% of orally delivered benzodiazepine, or may be greater than or equal to 90% of the C_{max} of the orally delivered benzodiazepine. In further embodiments the bioavailability is greater than or equal to 30% or greater than or equal to 40% of the bioavailability of orally delivered benzodiazepine or greater than 55% of orally delivered benzodiazepine.

[00117] A fifth aspect of the present invention relates to a pharmaceutical composition comprising a benzodiazepine for intranasal administration to a mammal, wherein the composition is characterized by a ratio of the AUC of the benzodiazepine, after a single intranasal administration, (AUC_{in}) to the AUC of an equivalent dose of the benzodiazepine delivered orally (AUC_{oral}) calculated for 24 hours after administration. In one embodiment, the composition is characterized by (i) a ratio of the AUC of a benzodiazepine, after a single intranasal administration, (AUC_{in}) to the AUC of an equivalent dose of the benzodiazepine delivered orally (AUC_{oral}) of at least about AUC_{in}:AUC_{oral} = 1:3.3, wherein the AUC values are determined over the same time period (for example, 24 hours for human subjects). Exemplary AUC data for some embodiments of the present invention are presented herein below in Example 5, Tables 12A and 12B, Figure 5 and Example 14. AUC_{in}:AUC_{oral} can be at least about 1:3.3 or often at least about 1:2.5 or 1:1.8.

[00118] In addition to pharmaceutical compositions comprising a benzodiazepine for transmucosal administration to a mammal, the present invention further includes a method for administering an active agent (e.g., a benzodiazepine) to a mammal in need thereof. In the method, the benzodiazepine is delivered to the mammal's bloodstream by crossing the nasal mucosa of the mammal and entering the blood stream. The benzodiazepine may be delivered transmucosally using dosage forms described herein. The benzodiazepine may be administered to a mammal to treat a variety of conditions including, but not limited to, depression, panic disorders (including acute panic attacks), muscle spasms, insomnia, and seizures (including seizure clusters). The benzodiazepine compositions of the present invention may be self-administered or administered by a second party, for example, a health care professional, a family member, or significant other.

[00119] In one embodiment, the compositions of the present invention are used to treat a mammal suffering seizure clusters by, for example, delivery of a benzodiazepine to the mammal's bloodstream via nasal mucosa of the mammal, wherein the benzodiazepine is delivered in an intranasal dosage form of the present invention. Administration of the compositions of the present invention may be performed, for example, at the onset of the symptoms of seizures. One or more unit doses may be administered to the mammal. In preferred embodiments the mammal is a human.

[00120] The present invention also includes methods of manufacturing a benzodiazepine composition useful for intranasal delivery of a benzodiazepine. A general method of making exemplary compositions of the present invention is described herein below in Example 7. Typically, the method includes mixing the solvent system and the benzodiazepine under conditions to provide a single-phase, homogeneous solution suitable for intranasal administration of the benzodiazepine. The benzodiazepine may be first dissolved in the solvent in which it has higher solubility, for example, the first solvent. The second solvent may be added with stirring. Mixing of the solution compositions of the present invention may be carried out under conditions that reduce exposure of the benzodiazepine to oxidative conditions, for example, by mixing under nitrogen or in a reduced oxygen environment.

[00121] After preparation of the solution compositions of the present invention, the solution may be dispensed into one or more containers (e.g., a unit dose container or a multiple dose container). The container may be a manually actuated spray device or a spray device wherein the contents are maintained under pressure and released by depressing an actuator or a device that is actuated by the patient's act of inhalation.

[00122] Typical unit doses delivered by these spray devices for intranasal delivery are between about 50 μL to about 300 μL, often 25 μL to about 150 μL, preferably a volume of about 100 μL, but for certain devices can be up to 5 mL. The spray pattern and plume geometry of the compositions as delivered from the spray device are suitable for intranasal delivery to a mammal (e.g., human). Parameters related to sprayability and viscosity of solvent matrices (solvent systems) related to the practice of the present invention are described in Example 6.

2.1.2 Manufacturing and Packaging

[00123] Preparation of the benzodiazepine compositions of the present invention, for example, formulated for intranasal administration, may be performed following the teachings of the present specification in view of teachings known to those of ordinary skill in the art. For example, according to the present invention, the benzodiazepine compositions may be prepared generally as follows. A solvent is selected in which the selected benzodiazepine is soluble, for example, clonazepam is very soluble in diethylene glycol monoethylether and/ or tetrahydrofurfuryl alcohol polyethyleneglycol ether. The desired amount of the benzodiazepine is added with stirring to obtain a substantially single phase, substantially homogeneous solution. A second solvent (for example, triacetin and/or propylene glycol and/or an aqueous buffered solution) may then be added to the solution comprising the first solvent and the benzodiazepine. The mixture is stirred to obtain a substantially single phase, substantially homogeneous solution. Additional components are typically first dissolved in the solvent in which they have the highest solubility.

[00124] As another example, the desired amount of the benzodiazepine may be dissolved in a solvent (e.g., diethylene glycol monoethylether and/ or tetrahydrofurfuryl alcohol polyethyleneglycol ether) and stirred to obtain a substantially single phase, substantially homogeneous solution. A second solvent, for example, an aqueous buffered solution may be prepared with additional components. Such additional components may include, but are not limited to, anti-oxidant (e.g., sodium metabisulfite) and/or surfactant (e.g., TWEEN). The buffering agent (or buffering system) should be able to maintain the pH of the formulation in the target range. After the addition of some buffering agents, further adjustment of pH may be desirable by addition of a second agent to achieve pH values in the target range. In view of the fact that the compositions of the present invention are directed to pharmaceutical use, the buffering agent or system should not be substantially irritating to mucosal tissue to which the composition is being applied. Buffering agents include organic and non-organic buffering agents. Exemplary buffering agents include, but are not limited to, phosphate buffer solutions, carbonate buffers, citrate buffers, phosphate buffers, acetate buffers, sodium hydroxide, hydrochloric acid, lactic acid, tartaric acid, diethylamine, triethylamine, diisopropylamine, and aminomethylamine. Ultimately buffering agents are used at a concentration to achieve the

desired target pH range; accordingly weight percent amounts of buffering agents may vary as may be determined by one of ordinary skill in the art in view of the teachings of the present specification.

[00125] The aqueous buffered solution (possibly comprising further components) is stirred to obtain a substantially single phase, substantially homogeneous solution. Aqueous solutions may be degassed; but degassing is not typically necessary. The aqueous buffered solution is then slowly added to the first solvent in which the benzodiazepine was dissolved to obtain a substantially single phase, substantially homogeneous solution.

[00126] As another example, the benzodiazepine may be dissolved in a first solvent (for example, diethylene glycol monoethylether and/ or tetrahydrofurfuryl alcohol polyethyleneglycol ether). A second solvent may be added (for example, triacetin and/or propylene glycol), and may be followed by the addition of, for example, an aqueous buffered solution, with or without additional components.

[00127] Mixing may be carried out under normal conditions or under a slight vacuum and/or nitrogen blanketing.

[00128] The methods of manufacturing of the present invention may further include dispensing compositions of the present invention into appropriate containers. The compositions of the present invention may be packaged, for example, in unit dose or multi-dose containers. The container typically defines an inner surface that contains the composition. Any suitable container may be used. The inner surface of the container may further comprise a liner or be treated to protect the container surface and/or to protect the composition from adverse affects that may arise from the composition being in contact with the inner surface of the container. Liners or coating material are typically substantially impermeable to the composition and typically to the individual components of the composition.

[00129] A number of types of suitable containers commercially available and known in the art, for example, as manufactured by Pfeiffer of America, Princeton, N.J. (e.g., U.S. Patent Nos. 5,584,417, 6,705,493, 6,446,839, 6,478,196), and Valois of America Inc., Greenwich, CN (e.g., U.S. Patent Nos. 5,328,099, 6,742,677, 7,080,759).

[00130] Containers/Delivery systems for the compositions of the present invention may include unit dose or multi-dose containers providing, for example, a fixed or variable

metered dose application. Multi-dose containers include, but are not limited to, a metered dose aerosol, a stored-energy metered dose pump, or a manual metered dose pump. In preferred embodiments, the container/delivery system is used to deliver metered doses of the compositions of the present invention for application to the nasal cavity of a subject. Metered dose containers may comprise, for example, an actuator nozzle that accurately controls the amount and/or uniformity of the dose applied. The delivery system may be propelled by, for example, a pump pack or by use of propellants (e.g., hydrocarbons, hydro fluorocarbons, nitrogen, nitrous oxide, or carbon dioxide). Devices such as those sold by Kurve® Technology described as ViaNase ™ atomizers, which allow for electronic dosing and nasal cavity saturation may be used. Further, devices such as passive devices sold by OptiNose (Oslo, Norway) may be actuated by the patient's inhalation. In preferred embodiments of the present invention, the container is a single-use, unit-dose, manually actuated spray device.

[00131] Example 6 describes methods to evaluate sprayability and viscosity of the benzodiazepine formulations of the present invention. The results obtained from experiments performed in support of the present invention demonstrated that the benzodiazepine formulations described herein are suitable for intranasal delivery.

[00132] Nasal tissue comprises a single epithelial layer and has a limited area suitable for absorption of drugs delivered intranasally. Typically the nasal tissue area in adult humans is about 20 cm^2. Volume per unit dose of compositions delivered intranasally is typically limited to between about 25 µl and about 150 µl, per nostril, and if delivered to 2 nostrils, a unit dose may be 50 µL to 300 µL. A unit dose of about 100 µl is suitable for many applications which dose may be delivered 50 µL per nostril or 100 µL in one nostril. A preferred droplet size distribution for intranasal delivery is typically in the range of about 10 µm to about 50 µm, but may vary as long as sufficient transnasal absorption of the active drug is effected.

[00133] In a preferred embodiment, airless packaging with excellent barrier properties is used to prevent oxidation of the benzodiazepine, for example, airless single-dose manually actuated spray devices. Accurate dosing from such pumps ensures reproducibility of dose.

2.1.3 Further Dosage Forms

[00134] In another aspect of the present invention, benzodiazepines are delivered to mucosal tissue, for example, intranasally, using dry powder formulations. Such dry powder formulations may comprise micronized particles of a selected benzodiazepine (e.g., clonazepam).

[00135] Intranasal administration of benzodiazepines may be accomplished, for example, as described herein, by solublizing a selected benzodiazepine in a suitable solvent system then using an intranasal spray device intended for use with a liquid form. Examples of liquid forms useful for such applications include, but are not limited to, an emulsion, a suspension, or a true solution. Due to the highly lipophilic nature of the benzodiazepines a combination of surfactants, strong solublizing solvents, and carrier solutions are often used. An alternative to such liquid forms is a dry powder formulation of benzodiazepine (e.g., diazepam, lorazepam, midazolam, clonazepam, and the like) that may be administered intranasally as a dry powder or a blend.

[00136] Intranasal delivery of particulate benzodiazepines would likely result in an acceptable delivery profile for benzodiazepines due to the intrinsic permeation properties of the substances. Benzodiazepines tend to be highly lipophilic, thus compatible with adsorption to and absorption by mucosal tissues. Particle sizes ranging from about 5 μm to about 20 μm would allow a dry-powder dispensing device to deliver sufficient quantities of selected benzodiazepines to effect pharmacological action in a short time frame. Methods of preparing dry powders of benzodiazepines with suitable size distribution (e.g., micronized powders) include, but are not limited to, anti-solvent precipitation, fluid bed drying, spray drying, size sorting, as well as combinations thereof.

[00137] Benzodiazepine, for example, clonazepam, dry powders may also be blended with suitable carriers for nasal administration to improve wetting, mucoadhesion and permeability (see, for example, European Patent Application Nos. EP1587514A1, EP1652518A1, EP 0324725B1, for examples of such carriers). In this aspect, benzodiazepines may be formulated in an ordered mixture where the core is an inert carrier such as a sugar and the surface is a combination of mucoadhesives and drug.

[00138] Advantages of this dry powder drug delivery approach include excellent stability and possibly greater intranasal residence time leading to improved drug uptake. A suitable dry powder intranasal delivery system may be used.

[00139] Dry powder formulations of the present invention may employ microparticles of a benzodiazepine of less than about 15-20 microns, more preferably of between about 5 and about 10 microns. The microparticles of the benzodiazepine may be combined with carrier particles as described above. Preferably, a mucoadhesion promoting agent is added to the carrier particles. The mucoadhesion promoting agent is effective in making the benzodiazepine adhere to the nasal mucosa. The mucoadhesion promoting agent is typically present on the surface of the carrier particles, but it may also be present within the particles.

[00140] In one embodiment, the carrier particles contain from about 0.1 to about 30 weight percent, preferably between about 1 to about 20 weight percent, of mucoadhesion agents, based on the total weight percent composition of the dry composition. The preferred mucoadhesive agent is typically a polymeric substance, preferably having an average molecular weight above 5,000 (weight average). The hydration of mucoadhesive agents also makes them useful as absorption enhancers according to the invention.

[00141] Carrier particle size is typically from about 50 μm to about 800 μm, preferably from about 50 μm to about 500 μm. Exemplary carrier particle substances include, but are not limited to, carbohydrates, such as sugar, mannitol and lactose, or pharmaceutically acceptable inorganic salts, such as sodium chloride or calcium phosphate, or mixtures thereof.

[00142] Dry powder compositions of the present invention may include a pharmaceutically acceptable surfactant (such as those described above). The increased wetting effect of the surfactant in the composition can enhance the hydration of the carrier particles. This enhanced hydration may result in faster initiation of mucoadhesion. Typically, the surfactant is in a finely dispersed form and intimately mixed with the clonazepam. The amount of surfactant may be, for example, from about 0.5 to about 5 weight percent of the dry composition, and preferably from about 0.5 to about 3 weight percent.

[00143] A variety of polymers known in the art can be used as mucoadhesive agents and examples are listed above included in the list of pharmaceutically acceptable polymers. The mucoadhesive polymers are typically hydrophilic, water-dispersible, or hydrophilic and water-dispersible. The ability of the polymer to swell in the presence of water is sometimes desirable. Mucoadhesiveness of substances can be determined *in*

vitro, for example, as described by Sala, G., et al., Proceed. Int. Symp. Contr. Release. Bioact. Mat. **16**:420 (1989).

[00144] Devices for the intranasal delivery of fine, powdered compositions are known in the art (for example, U.S. Patent Nos. 6,948,492, 6,824,080, 6,752,147, 6,715,485, 6,488,648, 5,901,703, 4,227,522, 4,192,309, 4,105,027) and may be used for delivery of the powdered compositions of the present invention comprising a benzodiazepine.

[00145] These dosage forms may be used in similar methods of use/treatment to those described above.

[00146] These aspects are described herein below with reference to clonazepam as an exemplary benzodiazepine. These examples are not intended to be limiting. Other objects of the invention may be apparent to one of ordinary skill upon reviewing the teachings of the specification and preferred embodiments of the invention described herein.

Experimental

[00147] As is apparent to one of skill in the art, various modifications and variations of the above embodiments can be made without departing from the spirit and scope of this invention. Such modifications and variations are within the scope of this invention. Some of the above-described aspects of the present invention are described herein below with reference to clonazepam as an exemplary benzodiazepine.

[00148] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the devices, methods, and formulae of the present invention, and are not intended to limit the scope of what the inventors regard as the invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[00149] The compositions produced according to the present invention meet the strict specifications for content and purity required of pharmaceutical products.

Materials and Methods

[00150] A. Pharmaceuticals and Reagents: The pharmaceuticals and reagents used in the following examples can be obtained from commercial sources, for example, as follows: active drug, e.g., clonazepam (from Lake Chemicals, India, or F.I.S. - Fabbrica Italiana Sintetici SpA, Vicenza, Italy) where delivered orally, the tablet is half of a Rivotril® 2 mg scored tablet (Hoffman-La Roche, New Jersey) diazepam and lorazepam (from Cambrex Profarmaco, Milan, Italy); penetration enhancers and solvents (e.g., diethylene glycol monoethylether, also called TRANSCUTOL®, from Gattefossé Corporation, Paramus, NJ); antioxidants (e.g., butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), sodium metabisulfite, from Sigma-Aldrich Corporation, St. Louis, MO); pharmaceutically acceptable polymers (e.g., hydroxypropyl cellulose, from Hercules, Inc., Wilmington, DE); excipients, solublizers, and solvents,e.g., triacetin (also called glycerol triacetate or 1,2,3-Propanetriol, triacetate) from Mallinckrodt Baker, Inc., Phillipsburg NJ; propylene glycol, from Apotekproduksjon, Norway; GLYCOFUROL™ (also called ethoxylated furanyl alcohol or tetrahydrofurfuryl alcohol polyethyleneglycol ether) and similar ethoxylated tetrahydrofurfuryl alcohols, from Agrar, Italy); and standard pharmaceutical and chemical reagents (e.g., colorants, solvents, and surfactants, from Sigma-Aldrich Corporation, St. Louis, MO, Fisher Scientific, UK, and Merck, Germany: for example, propylene glycol, PEG 200 (ICI Americas Inc., Bridgewater New Jersey) and TWEEN® 20, from Merck, Germany; Citric acid from Riedel-de-Haen, Germany; triacetin from Abitec, USA; and water (WFI) from Fresenius Kabi, Norway). Analytical reagents are also available from a number of commercial sources, for example, citric acid, from Acros Organics, UK; hydrochloric acid, acetonitrile (HPLC grade), methanol (HPLC grade), orthophosphoric acid, potassium chloride, potassium hydrogen phthalate, potassium dihydrogen orthophosphate, ethanol, from Fisher Scientific, UK; and disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate, from Merck, Germany.

[00151] B. HPLC Analytical Methods: The HPLC system for detection of clonazepam was as follows: Waters 2487 Dual λ Absorbance Detector, Waters 600 Controller, Waters 717 plus Autosampler, Waters Millennium Chromatograph Manager Software (Waters Corporation, Milford, MA); Column, Chromolith Performance RP-18e 100 x 4.6 mm, and Guard Column, Chromolith Guard Cartridge RP-18e 5 x 4.6 mm

(Merck KgaA, Frankfurt, Germany); Detection, λ = 220 nm; Sample Temperature, 20 ± 2°C; Column Temperature, Ambient temperature; Flow Rate, 2.0 mL/min; Mobile Phase, Isocratic, Mobile Phase, KH_2PO_4 35 mM in deionized water (pH 2.1 adjusted with orthophosphoric acid) : acetonitrile – 70:30; Injection Volume, 100 µL; Run Time, 10-20 min; and Needle Wash, 90:10 (methanol:water).

[00152] The limit of detection (LOD) and quantification (LOQ) were calculated according to Equations 1 and 2:

[00153] LOD = (3.3*STEYX)/S (Equation 1)

[00154] LOQ = (10*STEYX)/S (Equation 2)

[00155] where, STEYX = the standard deviation of the y-intercepts of regression lines, obtained from the respective calibration curve and S = the gradient of the calibration curve.

[00156] Preliminary stability studies of drug standard solution were performed in phosphate buffered saline (PBS) containing 10% ethanol. In parallel, the stability of drug in various buffer pH values (pH 2 to 8) was also investigated. Because clonazepam was poorly soluble in water, 10% ethanol was added to each buffer system in order to aid solubility. The stability of drug in each buffer system was determined over a period of 72 hours at 37°C and 2-8°C.

[00157] The preparation of buffers was as follows. The preparation of buffers pH 2 to 4 are summarized in Table 1.

Table 1

Composition of buffers pH 2 to 4

Buffer pH	Potassium chloride (mL)	Potassium hydrogen phthalate (mL)	Hydrochloric acid 1M (mL)	Deionized water (mL)	Actual pH recorded
2	50	0	7.8	142.2	2.11
3	0	50	15.7	134.3	3.17
4	0	50	0.1	149.9	3.98

[00158] Potassium chloride solution was prepared by adding 14.9 g of solid into a 1 L volumetric flask and made up to volume with deionized water. Potassium hydrogen phthalate solution was prepared by adding 40.8 g of solid into a 1 L volumetric flask and made up to volume with deionized water.

[00159] The preparation of buffers pH 5 to 7 is summarized in Table 2.

Table 2

Composition of buffers pH 5-7

Buffer pH	Citric acid (mL)	Sodium dihydrogen phosphate (mL)	Deionized water (mL)	Actual pH recorded
5	24.3	25.7	50	5.2
6	16.9	33.1	50	6.09
7	6.5	43.6	49.9	6.98

[00160] Citric acid solution was prepared by adding 21.01 g of solid into a 1 L volumetric flask and made up to volume with deionized water. Sodium dihydrogen phosphate solution was prepared by adding 13.8 g of solid into a 1 L volumetric flask and made up to volume with deionized water.

[00161] The preparation of buffer pH 8 is summarized in Table 3.

Table 3

Composition of buffers pH 8

Buffer pH	Sodium dihydrogen phosphate (mL)	Disodium hydrogen phosphate (mL)	Deionized water (mL)	Actual pH recorded
8	94.7	5.3	100	8.13

[00162] Disodium hydrogen phosphate dehydrate was prepared by adding 35.6 g of solid into a 1 L volumetric flask and made up to volume with deionized water. Sodium dihydrogen phosphate solution was prepared by adding 13.8 g of solid into a 1 L volumetric flask and made up to volume with deionized water.

[00163] The percentage drug recovered was calculated using Equation 3:

[00164] % drug recovered = (drug concentration at t=X/drug concentration at t=0) x 100 (Equation 3)

[00165] where, X = specific time point and temperature.

[00166] Following the stability studies, a suitable receiver fluid was developed in order to ensure that sink conditions for tested drug were such that the drug release was limited by the solubility of the drug in the receiver fluid. The saturated solubility (at 37°C) for drug was performed in 3 solvent/co-solvent systems, namely, pH 6 buffer, 10% ethanol in pH 6 buffer and 20% ethanol in pH 6 buffer. Briefly, drug was saturated into different receiver fluid systems by adding excess drug and allowed to stir with a magnetic flea over a period of 2 h at 37°C. Each saturated solution was then filtered using a 0.2 μm syringe filter and the resultant solution was assayed via HPLC.

[00167] C. *In vitro* Permeation Methodology: *In vitro* permeation was carried out by standard methods (e.g., Franz, T.J., "Percutaneous absorption: on the relevance of *in vitro* data," J. Invest Dermatol 64:190-195 (1975); Franz, T.J., "The finite dose technique as a valid *in vitro* model for the study of percutaneous absorption in man," In: Skin: Drug Application and Evaluation of Environmental Hazards, Current Problems in Dermatology, vol. 7, G. Simon, Z. Paster, M Klingberg, M. Kaye (Eds), Basel, Switzerland, S. Karger, pages 58-68 (1978)).

[00168] Freshly excised sheep nasal mucosa was used and prepared following a standard protocol. The excised sheep nasal mucosa was cleaned by rinsing with de-

ionized water and either used fresh or placed flat over a filter paper and stored frozen until used.

[00169] (i) Drug recovery, degradation and binding to nasal sheep mucosa: The effect of drug recovery, degradation and binding to sheep nasal mucosa was determined. Briefly, a known surface area (approx. 1 cm^2) of sheep nasal mucosa was added into a glass vial containing a known concentration (10 μg/mL) of each drug prepared in the receiver fluid (10% ethanol in pH 6 buffer). The content of the vial was allowed to equilibrate at 37°C over a period of 48 h. At 24 h intervals, a sample was removed and assayed via HPLC. The percentage of drug recovered was calculated using Equation 4:

[00170] % drug recovered = (drug concentration at t=Y/drug concentration at t=Z) x 100 (Equation 4)

[00171] where, Y = specific time point at 37°C (in the presence of nasal sheep mucosa); and Z = specific time point at 37°C (in the absence of nasal sheep mucosa).

[00172] (ii) Dosing and Sample Collection -- Franz cell studies: Individually calibrated Franz cells with an average surface area and volume of approximately 0.6 cm^2 and 2 mL, respectively, were employed to determine the permeation characteristics of drug. The nasal sheep mucosa was mounted between the two halves of the Franz cell with the mucosal side facing the donor compartment. The receptor compartment was filled with receiver fluid, stirred constantly with a PTFE-coated magnetic follower driven by a submersible magnetic stirrer bed and maintained at 37°C in a water bath. Approximately 1 mL (infinite dose) of saturated drug solution was placed into the donor compartment and covered with PARAFILM® (Pechiney Plastic Packaging, Inc., Chicago, IL) throughout the study. Following the application of the drug solution, the receiver fluid (200 μL) was removed from the receptor compartment via the sampling arm after sampling times (t=1, 2, 3, 4, 5, 6 and 7 h) and analyzed via HPLC. Each sample removed was replaced by an equal volume of fresh pre-warmed (37°C) receiver fluid. A total of eight repetitions (n=8) were performed on the drug solution and a single control experiment where no drug was present in the donor compartment was also performed.

[00173] D. Neurocognative Tests: The Cognitive Drug Research (CDR) computerized assessment system is specifically designed to evaluate the effects of compounds on the quality of cognitive functioning in subjects and patients in all phases of

clinical development. The CDR system is a widely used computerized cognitive assessment system (see, for example, Ebert U, et al., "Pharmacokinetics and pharmacodynamics of scopolamine after subcutaneous administration," *Journal of Clinical Pharmacology* **38**: 720-726 (1998); Harrington F, et al., "Cognitive Performance in Hypertensive and Normotensive Older Subjects," *Hypertension* **36**: 1079-1082 (2000); Preece AW, et al., "Effect of a 915-MHz simulated mobile phone signal on cognitive function in man," *International Journal of Radiation Biology* **75**: 447-456 (1999); and Walker MP, et al., "Quantifying fluctuation in Dementia with Lewy Bodies, Alzheimer's disease and vascular dementia," *Neurology* 54: 1616-1625 (2000)) and has been used to evaluate a diverse range of pharmaceutical compounds.

[00174] E. Electroencephalography (EEG) Methods: Drug and placebo are administered, for example, at a five-minute intravenous (i.v.) infusion. During 15 minutes following the beginning of the administration EEG is registered. The EEG is registered again at 30, 60, 90, 120, and 180 minutes. Subjects are typically in a quiet laboratory (soundproof and electrically shielded room). During acquisition of EEG measurements subjects recline in an armchair. Usually twenty-eight EEG leads (issued, for example, from a 10-20 system; Jasper, H.H., et al., "Studies of clinical and electrical responses to deep temporal stimulation in men with some considerations of functional anatomy," Res Publ Assoc Res Nerv Ment Dis. **36**:316-34 (1958); Japser, H.H., "Progress and problems in brain research," J Mt Sinai Hosp N Y. **25**(3):244-53 (1958)) are used for recording. An ear linked reference, as well as four artifact channels (detection of eye movement, muscle activity, and other potentials for artifacts) may be used. Silver-plated disc electrodes are attached to subject's scalp, for example, with quick drying collondion. Impedance (for example, of 2000-5000 ohms) is checked before each recording session. A calibration signal is used, before each subject is tested, in order to adjust all the recorded leads thus allowing the construction of EEG or event-related-potentials (ERP) maps. EEGs are taken under resting recording conditions (i.e., subjects are asked to relax with their eyes closed). An example of data analysis used is the method of Dago, et al. (Dago, KT, et al., "Statistical Decision Tree: a tool for studying pharmaco-EEG effects of CNS-active drugs," Neuropsychobiology, 29(2):91-6 (1994)) which involves a statistical comparison of data obtained during active treatment versus placebo treatment. Typically,

topographic mapping of mean EEG parameters and statistical evaluation of treatment effects is carried out in a selected number of healthy volunteers.

Example 1

Absorption of Benzodiazepines Through Nasal Mucosa *in vitro*

[00175] The following experiments, performed in support of the present invention, demonstrate the ability of benzodiazepines to penetrate nasal mucosa. The permeation of saturated solutions of clonazepam, diazepam and lorazepam across sheep nasal mucosa *in vitro* is described herein below.

[00176] HPLC detection of clonazepam showed the principal eluted peak had a retention time of 7.5 minutes; for lorazepam 7.3 minutes; and for diazepam 14 minutes. Calibration curves for clonazepam were constructed between 0.2 to 10 μg/mL with appropriate replicates to ensure repeatability and linearity. The saturated solubility for clonazepam in the receiver solution (10% ethanol in buffer pH 6, see Materials and Methods) was 29.32 μg/mL; for lorazepam, 125.79 μg/mL; and for diazepam 129.47 μg/mL. In buffer pH 6 the saturated solubility for clonazepam was 13.66 μg/mL; for lorazepam 78.49 μg/mL; and diazepam 62.93 μg/mL and in 20% ethanol in buffer pH6 the saturated solubility for clonazepam was 82.28 μg/mL; for lorazepam 308.92 μg/mL; and for diazepam was 362.06 μg/mL.

[00177] Standards were prepared in receiver fluid (10% ethanol in buffer 6). Although the solubility of drug in 10% ethanol/buffer pH 6 was not extremely high, it was selected over the 20% ethanol/buffer pH 6 because it was considered that the latter may perturb the nasal mucosa. It should also be noted that although the saturated solubility was determined at 37°C, the filtration of the saturated system was performed at room temperature. The filtration at room temperature was performed as quickly as possible to minimize any drug precipitation as the temperature dropped from 37°C during filtration.

[00178] The linearity for the calibrations was found to be excellent (r^2 greater than or equal to 0.999). The limit of detection (LOD) and quantification (LOQ) for clonazepam was shown to be LOD (μg/mL) 0.269 and LOQ (μg/mL) 0.898; for lorazepam LOD (μg/mL) 0.376 and (μg/mL) 1.252; and for diazepam LOD (μg/mL) 0.204 and LOQ (μg/mL) 0.681.

[00179] Preliminary stability studies were performed in 10% ethanol in phosphate buffer (PBS). The data are summarized in Table 4 for drug stability studies at 2-8°C and 37°C in the presence of nasal sheep mucosa.

Table 4

Preliminary stability data for standards prepared in 10% ethanol/PBS

Drug	Conc (μg/mL)	Ave % recovery at 2-8°C			Ave % recovery at 37° C		
		T=24h	T=48h	T=72h	T=24h	T=48h	T=72h
Lorazepam	10.02	100.69 ± 0.09	99.46 ± 0.12	94.25 ± 0.59	97.50 ± 0.42	88.68 ± 0.25	68.37 ± 1.33
Diazepam	9.94	102.27 ± 0.17	101.77 ± 0.12	100.37 ± 0.31	102.76 ± 0.97	102.86 ± 0.50	99.72 ± 2.23
Clonazepam	9.96	100.21 ± 0.01	100.64 ± 0.17	105.16 ± 7.32	101.07 ± 0.65	101.86 ± 1.13	100.55 ± 0.77

[00180] The data clearly suggested that the benzodiazepines are stable at both temperatures over the 72 h period.

[00181] Following the preliminary stability study, the stability of prepared drug solution was repeated over a range of buffer pH values. The percent drug recovered as a result of drug stability or degradation is summarized in Table 5.

Table 5

Percentage (%) drug recovered from stability studies

Drug	*Buffer pH	% recovery 2-8°C			% recovery 37°C		
Lorazepam		T=24 h	T=48 h	T=72 h	T=24 h	T=48 h	T=72 h
	2	98.46	98.39	97.17	73.96	55.75	16.82
	3	99.67	93.17	98.84	88.76	68.71	43.08
	4	100.38	92.11	100.21	96.24	80.34	74.38
	5	99.83	98.41	100.25	97.89	90.29	84.38
	6	99.32	95.31	99.69	96.65	80.97	83.18
	7	99.27	94.32	99.79	95.41	80.23	77.72
	8	101.39	92.86	99.46	92.22	74.23	59.65
Diazepam	2	98.94	97.02	101.11	97.29	98.10	100.62
	3	100.38	98.13	99.95	101.00	100.61	100.33
	4	99.89	97.84	99.97	100.28	100.67	98.02
	5	98.95	98.11	98.24	99.84	100.70	100.32
	6	99.06	98.15	97.67	98.53	99.57	102.01
	7	98.30	97.15	96.34	98.98	99.21	102.10
	8	99.31	98.69	98.36	98.87	99.48	101.19
Clonazepam	2	90.08	73.18	55.30	57.97	55.51	53.07
	3	97.87	91.94	85.55	88.73	88.37	85.50
	4	99.54	98.88	99.37	98.72	100.09	101.91
	5	99.85	99.91	99.91	100.59	100.98	103.29
	6	100.41	100.32	100.43	100.34	100.59	103.14
	7	100.66	99.98	100.19	99.81	100.05	100.54
	8	99.59	99.30	99.40	96.76	96.42	91.47

*prepared in 10% ethanol

[00182] The data obtained confirmed that benzodiazepines appeared to be stable between pH 4-7 at the higher temperature over the 72 h period. Given that the duration of planned permeation studies was likely to be less than 24 hours and that the physiological pH of the nasal mucosa may vary between pH 5 to 6.5, buffer pH 6 was selected as the buffer of choice for the permeation studies.

[00183] In addition to the stability against heat degradation, the effect of drug binding or degradation in the presence of nasal sheep mucosa was also determined (Table 6).

Table 6

Percentage (%) drug recovered in the presence of nasal sheep mucosa at 37°C

Drug	% recovery					
	*Buffer pH 5		*Buffer pH 6		*Buffer pH 7	
	24 h	48 h	24 h	48 h	24 h	48 h
Lorazepam	96.92	94.90	96.78	96.96	96.19	91.68
Clonazepam	97.78	96.45	97.47	97.14	99.30	97.78
Diazepam	97.64	95.62	98.02	124.68	97.61	94.68

*prepared in 10% ethanol

[00184] The data, presented as described in Equation 2 (Materials and Methods), were such that any loss in recovery would be as a result of the effect of the presence of nasal sheep mucosa but not heat degradation. The data generally suggested that some degree of binding or degradation (<10%) was apparent in the presence of nasal sheep mucosa for drug.

[00185] Preliminary permeation studies were performed as described above in the Materials and Methods section. Permeation achieved steady state, which suggested that drug permeation was not affected by the solubility of drug in receiver fluid (10% ethanol in pH 6 buffer). The data clearly showed steady state flux of the drug over a 24 h period.

[00186] Final permeation studies were performed over a 7 hour test period. The permeation characteristics of the drug in the preliminary study appeared to be closely similar to that in the final permeation study. Figure 1 presents a graphic representation of the mean cumulative amount of the benzodiazepines permeated per unit area over a period of 7 h. The data suggested that permeation of the benzodiazepines were at steady state as demonstrated by the linear permeation rate of drug.

[00187] The HPLC methodology was shown to be "fit for purpose" with no interference peaks present at the same retention time as the drug peaks. Although the

solubility study demonstrated that sink conditions did not apply throughout both permeation studies, nevertheless permeation achieved steady state for the benzodiazepines suggesting that the solubility of drug in the receiver fluid (10% ethanol in pH 6 buffer) was not rate limiting.

[00188] The preliminary stability data presented above suggested that the benzodiazepines were stable at 37°C over 24 h in receiver fluid (10% ethanol in buffer pH 6). In addition, greater than 95% of drugs were recovered in the presence of nasal sheep mucosa at 37°C over 48 h, suggesting that only a low degree of binding or degradation occurred.

[00189] The permeation characteristics for the benzodiazepines were found to be very similar in both preliminary and final study where steady state flux was observed. In conclusion, the data demonstrated that the benzodiazepines had acceptable stability in the context of use for intranasal administration, as well as acceptable permeation characteristic through nasal mucosa.

Example 2

Solubility in Solvent Matrices

[00190] The solubility of clonazepam in a number of neat solvents was determined using standard methods. The results are presented in Tables 7A and 7B.

Table 7A

Solubility of Clonazepam in Neat Solvents

Matrix	Solubility (mg/mL)
PEG 300	37.0
PEG 200	30.3
propylene glycol	3.4
Triacetin	5.8
Glycofurol	67.3
Transcutol®	38.7
Water	<0.1

[00191] From Table 7A it can be seen that Glycofurol was a good solvent for clonazepam and may therefore be useful for achieving target solubility of, for example, 10 to 20 mg/mL. Further, the presence of Glycofurol may facilitate solubility in

formulations solvents with lower clonazepam solubility, such as triacetin or propylene glycol. Transcutol® and PEG (polyethylene glycol) matrices also demonstrated high solubility.

[00192] The solubilities of several other benzodiazepines were measured in DEGEE (diethylene glycol monoethyl ether, transcutol) by the techniques of Example 1. Initially, 10 mg of the drug was loaded in the glass vial and 130 -μL of DEGEE was added, and the samples were sonicated for 10 minutes. In the case of lorazepam and diazepam, the initial 10 mg went completely into solution, so another 10 mg was added to the vial prior to sonication again for 10 minutes. Samples were stored at -16°C and 25°C overnight, and centrifuged (5000 rpm, 2 minutes, -10°C and 23°C for the -16°C and 25°C samples, respectively). The lorazepam samples had completely dissolved at both temperatures, so the measured concentration indicates only a lower limit of solubility. Clonazepam was measured by UV at 350 nm; all others at 300 nm. The solubilities shown below in Table 7B indicate that solubility is sufficient over a wide range of temperature to achieve therapeutic dose of these benzodiazepines.

Table 7B

Solubility of Benzodiazepines in Transcutol®

	T = 25°C	T = -16°C
Clonazepam	38.9	35.3
Lorazepam	>110	>130
Diazepam	96.5	87.6

[00193] Further, the solubility of clonazepam in binary mixtures of Transcutol®(TC), triacetin (TA), glycofurol (GF) and propylene glycol (PG) was evaluated. Solubility limits of clonazepam were determined for the following formulations:

Table 8

Binary Mixture Formulations

Formulation	Composition
K	70%GF + 30% TA
R	30% GF + 60% PG + 10% citrate/TWEEN/metabisulfite
T	30% GF + 70% PG
i	30% GF + 70% TA
ii	50% TC + 50% TA
iii	50% TC + 50% PG

[00194] Excess drug (50 mg) was capped with about 500 µL of the solvent matrix in a 1.5 mL microfuge tube and the solution was mixed on a vortex shaker for several minutes. Thereafter, the solution was placed in an ultrasonic bath at 25°C for 45 minutes. The temperature was regulated with a thermometer and controlled by adding ice into the bath. After 15 minutes of standing, the solutions were centrifuged at 3,000x g for 30 minutes. Solutions were then stored for 16 hours at 25°C in an ICH cabinet protected from light.

[00195] The solubility of clonazepam in neat solvents was as shown in Table 7A. From the data in Table 7A, the theoretical solubility of clonazepam in mixtures was calculated. The results of the solubility tests and the theoretical values were as shown in Table 9.

Table 9

Solubility of Clonazepam in binary mixtures of matrices

Formulation	Measured Solubility (mg/mL)	Theoretical solubility (mg/mL)	Meas./Theor. (%)
K - 70% GF + 30% TA	49.8	48.8	102.0
R - 30% GF + 60% PG + 10% c/t/m (aq)	11.5	22.2	51.9
T - 30 GF + 70% PG	16.7	22.6	74.0
i - 30% GF + 70% TA	22.9	24.2	94.4
ii - 50% TC + 50% TA	27.6	22.2	123.9
iii - 50% TC + 50% PG	21.7	21.0	103.0

[00196] Further, the data presented in Figure 2 demonstrated a linear relationship between the solubility and composition (based on percents) of the binary mixtures of triacetin and glycofurol, as well as propylene glycol and glycofurol. From the data in the figure, it can be inferred that the solubility in the 50:50 mixture would be about 36.4

mg/mL. Based on the data the solubility of clonazepam in binary mixtures of GF and PG the relationship between solubility and composition does not appear to be as linear as it is in the mixtures of GF and TA.

[00197] These data demonstrate the usefulness of solvent solutions comprising binary solvent mixtures to solubilize clonazepam, for example, for use in formulation of intranasal pharmaceutical compositions.

[00198] The solvent systems set forth in Table 8 and Table 9 provide examples of formulations with a minimum number of solvent components in the system which helps reduce possible interactions. These solvent combinations also increase the chemical potential and system thermodynamics helping to ensure that the drug (e.g., clonazepam) prefers to cross the nasal membrane due to decreasing solubility. The solvent systems set forth in Table 8 and Table 9 also avoid components that may provide a thermodynamic sink (e.g., PEG and cyclodextrins) where clonazepam would prefer to remain in the nasal cavity with a non-penetrating excipient.

Example 3

Further Stability Studies

[00199] Eighteen 20 mg/mL clonazepam formulations were set up for accelerated stability studies: six weeks held at 60°C with exposed head-space. Samples were withdrawn at 0, 1, 2, 4 and 6 weeks and assayed for clonazepam at 20,000 fold dilution and for degradation products at 20-fold dilution. Color was assessed by visual inspection at 6 weeks. Clonazepam is subject to both oxidative (color) and hydrolytic (chemical) degradation. Oxidative degradation was scored using a relative color scale of 1 (lightest = least degradation) to 5 (darkest = most degradation). Hydrolytic degradation was evaluated by sampling and analysis of the sample using HPLC and a clonazepam reference standard. The results of these analyses are presented in Table 10.

Table 10

Stability Screen at 60°C

#	Formulations	Chemical Degradation % Clonazepam remaining					Oxidative
		0 wks	1 wk	2 wks	4 wks	6 wks	Color/ 6 wks
1	100%Glycofurol	96%	101%	96%	90%	81%	1
2	95% Glycofurol + 5% H_2O	94%	105%	99%	82%	68%	4
3	100% Transcutol®	100%	111%	103%	94%	88%	1
4	90% Transcutol® + 10% H_2O	98%	100%	94%	79%	67%	4
5	80% Glycofurol + 20% Transcutol®	84%	99%	99%	93%	82%	2
6	70% Glycofurol + 20% Transcutol® + 10% H_2O	113%	99%	93%	72%	63%	5
7	70% Glycofurol + 30% Triacetin	104%	108%	105%	91%	82%	2
8	30% GF + 70% PEG 200	105%	93%	79%	67%	60%	4
9	50% Glycofurol + 50% Transcutol®	108%	107%	97%	86%	73%	3
10	50% Transcutol® +50% PEG 200	96%	93%	79%	76%	68%	4
11	70% Transcutol® +30% Triacetin	106%	110%	101%	99%	92%	1
12	60% Transcutol + 30% Triacetin +10% H_2O	104%	108%	101%	86%	78%	3
13	60% Transcutol® +30% Triacetin +10% 10 mM citrate pH 4	107%	105%	104%	96%	91%	2
14	60% Transcutol®+30% Triacetin +10% 10 mM phosphate pH 4	102%	108%	109%	101%	92%	2
15	60% Transcutol® + 40% Propylene glycol	105%	110%	104%	95%	89%	2
16	5% GF +95% PEG200	106%	89%	74%	61%	53%	5
17	10% GF + 90% PEG200	99%	85%	77%	62%	55%	5
18	10% TC + 90% PEG200	102%	88%	77%	64%	54%	5

[00200] After a 2-week incubation at 60°C it was evident from the assay results that formulations containing PEG were the least stable formulations. These results were corroborated in the clonazepam assay (% clonazepam remaining) after four weeks and six weeks. After two weeks, the percent clonazepam had dropped below 80% in all formulations containing PEG and down to 50-60% in the formulations containing 70-95% PEG and 68% in the formulation containing 50% PEG.

[00201] Formulations containing 5-10% water also demonstrated some level of clonazepam instability. Thus, the percent clonazepam dropped to 63 – 78% in 6 weeks at 60°C. In contrast to the formulations containing 5-10% water the formulations containing 10% aqueous buffer at pH 4 demonstrated relatively high stability. Thus, the assay of those formulations was in the 90% range after 6 weeks of storage at 60°C.

[00202] Concomitant with the drop in percent clonazepam, an intense color development was seen in those formulations, as all PEG containing formulations scored 4 or 5 in color intensity at 6 weeks. Formulations that contained water without buffer also demonstrated color development and scored from 3 to 5 after 6 weeks of storage. This is clearly exemplified by formulation 1 and 2, 3 and 4, and 5 and 6. These observations suggested that the color development may be related to hydrolysis events.

[00203] Comparison of degradation product HPLC profile of the formulations containing water with forced degradation samples which were exposed to HCl, NaOH and H_2O_2 revealed that the similarity is greatest with the degradation products from incubation with HCl which further supports the theory of hydrolysis. In contrast, formulations with water that were buffered at pH 4 (#13 and 14) demonstrated only low color development and scored 2. This indicated that hydrolysis can be prevented by keeping the pH at a low level (for example, increased stability of benzodiazepines in the pH range 4.5 to 5.5, see, e.g., P.C.T. International Publication No. WO 91/16929; and Pharmazie, 1974 Oct-Nov, **29**(10-11), pages 700-707).

[00204] As can be seen from the results presented in Table 10, better stability was generally achieved in the absence of free PEG polymers. The data presented above indicated that PEGs lead to an increase in degradation of clonazepam. Similarly, water appeared to contribute to increased degradation of clonazepam as well. In view of the results presented above, an anhydrous solvent matrix for clonazepam is preferred.

Further, formulations without PEG also appeared to be preferred in order to improve clonazepam stability.

[00205] Addition of an anti-oxidant to the formulations of the present invention used for intranasal delivery of benzodiazepines may provide desirable protective benefits to such formulations. Examples of a suitable anti-oxidants include, but are not limited to, tocopherol and derivatives thereof, ascorbic acid and derivatives thereof, butylhydroxyanisole, butylhydroxytoluene, fumaric acid, malic acid, propyl gallate, sodium sulfite, metabisulfites (including sodium metabisulfite) and derivatives thereof, as well as EDTA disodium, trisodium and the tetrasodium salts. Soluble, organic anti-oxidants are preferred, for example, butylhydroxytoluene.

[00206] Further, the data indicate protective effects resulting from the inclusion of pH modifiers when an aqueous solvent was used. Microbial challenge with 5 organisms (staphylococcus aureas, pseudomonas aeruginosa, escherichia coli, candida albicans and aspergillus niger) showed a log plate count of less than 1/mL observed after a period of 28 days, indicating that the liquid formulation itself is microcidal and therefore a non-sterile product is likely acceptable.

Example 4

Screening Formulations for Nasal Irritation Potential Using a Rat Model

[00207] A number of formulations were tested in a rat irritation model. The first objective was to establish the irritation threshold of Transcutol®. Two formulations were tested containing 20% and 50% Transcutol® in PEG 200. The blood pressure signals integrated as a function of time were as shown in Figure 3.

[00208] In Figure 3, the designations were as follows: CLZ2080 -- 10 mg/mL clonazepam, 20% Transcutol® (TC), 80% Polyethylene Glycol (PEG); CLZ5050 -- 10 mg/mL clonazepam, 50% TC, 50% PEG; CLZ70G30T -- 10 mg/mL clonazepam, 70% GF, 30% TA; CLZ20T80P02T, 10 mg/mL clonazepam, 10% TC, 90% PEG 200 and 0.2% TWEEN 20; Saline (negative control); Acetic Acid (HOAc) 0.3% (positive irritation control); Acetic Acid (HOAc) 1.5% (positive irritation control); Setron (positive irritation control).

[00209] The data shown in Figure 3 demonstrated slight, transient irritation apparent in the test animals. After instillation of compositions, irritation typically lasted

less than 1.5 minutes in rats (range 0.7 to 2.2 minutes). Irritation was generally greater than saline and similar to irritation from 1.5% acetic acid. Veterinary evaluation of the data resulted in the conclusion that nasal irritation from these formulations was not significant.

[00210] Two other clonazepam formulations were tested (70% PEG and 30% GF; and 10% TC, 90% PEG 200 and 0.2% Tween 20) and similar results were obtained. Tween 20 (polyethylene glycol sorbitan monolaurate) was used as a possible irritation reducer.

[00211] One formulation, CLZ5050 appeared to produce more intense irritation than the other formulations as instillation was associated with a blood pressure drop. The drop biased the drawing of a base line and therefore the integration of the signal.

[00212] In a second rat nasal irritation experiment, eight clonazepam formulations and one formulation matrix without clonazepam (K: 30% TA, 70% GF) were tested in the irritation model and compared with irritation results obtained using 0.9% acetic acid. The formulations used in and results from the rat nasal irritation study are presented in Table 11. In the table, Iden. -- is the identifier associated with the formulation; MBP -- integrated mean blood pressure over the duration of the irritation response; T -- duration of irritation response (minutes); TC – Transcutol®; PEG -- polyethylene glyco; TA -- triacetin; GF -- glycofurol; PG -- propylene glycol; H2O -- water; Tw -- TWEEN 20; w/o clz = without clonazepam. Fifty μL of each formulation containing 20 mg/mL clonazepam was administered to each animal.

Table 11

Rat Nasal Irritation Study

Formulation									MBP		$T_{(min)}$	
Iden.	TC	PEG	TA	GF	PG	H2O	Tw	N	aver.	stdev[c]	Avg	err[c]
I	20	80						3	26	8	1.8	0.2
H	50	50						4[a]	25	4	1.9	0.2
K			30	70				3	8	3	0.7	0.1
M		70		30				3	21	9	1.7	0.1
I+Tw	20	80					0.2	3	22	11	1.2	0.2
T				30	70			2[b]	27	(8)	1.2	(0.1)
R_{wa}				30	60	10		3	42	10	1.8	0.5
R				30	60	10[d]	0.2	3	25	1	2.2	0.2
K w/o clz			30	70				3	22	4	1.3	0.2
0.9% HOAc								2	26	11	1.6	(0.3)

a = blood pressure drop must be due to intense irritation. The drop biases the drawing of a base line and therefore the integration of the signal.
b = the third animal in the group reacted very strongly to administration, received cardiac resuscitation. The results from this animal were not included in the data processing.
c = numbers in parentheses are used when $n < 3$.
d = includes citrate buffer pH4, and sodium metabisulphite.

Sodium metabisulfite and citric acid were each present at less than 1% (w/w) basis in the above formulations.

[00213] Acetic acid 0.9% has been found to be tolerated by volunteers in a human trial. The objective of this experiment was to provide a preliminary test a variety of formulations and compare them with respect to irritation. Because a slightly irritating profile would be tolerated for an intranasal formulation against seizure clusters and other acute indications such as panic attacks, the major concern was that volunteers participating in a clinical Phase I trial would not suffer unnecessary pain. The irritation scores based on measurement of blood pressure are presented in Figure 4 and Table 11. In Figure 4, the columns for saline, acetic acid solutions and a setron formulation (i.e., the right-most four columns) represented data from previous experiments and were inserted for comparison. Table 11 also present the duration of the irritation response in minutes. The results showed that all formulations tested gave a relatively short-lived irritation response, in the range from 0.7 to 2.2 minutes.

[00214] To test the irritation of Transcutol®, two formulations were tested containing 20% and 50% Transcutol® with PEG 200 as the cosolvent. Transcutol® at

20% (I) or 50% (H) demonstrated similar irritation scores suggesting that Transcutol® is no more irritating than PEG. A third formulation containing Transcutol® was the same as I but with 0.2% Tween. Comparison of I and I with Tween-20 suggested that Tween did not provide a substantial reduction of irritation in this formulation.

[00215] Formulation K (30% TA, 70% GF), which showed a good pharmacokinetic profile (see Example 5), had the lowest irritation score of the formulations tested in this experiment.

[00216] Formulation K was also tested without clonazepam to obtain information on the effects of clonazepam on irritation. Comparison of the irritation scores of K and K without clonazepam showed that clonazepam appeared to have an irritation reducing effect.

[00217] Formulations M and T contain the same amount of glycofurol but M contains 70% PEG while T contains propylene glycol as the cosolvent. The irritation score of these two does not differ significantly indicating a similar degree of irritation by PG and PEG.

[00218] Formulation R with 10% buffer (citrate/Tween/bisulphite) or with 10% water was the only water containing formulation tested. The formulation with water only appeared to be significantly more irritating than the formulation that contained buffer/Tween/bisulphite. Formulation R with buffer demonstrated similar irritation profile as did the non-aqueous formulations I, H, M and T.

[00219] Acetic acid 0.9% has been tested for irritation in a human trial and was found to be irritating but tolerable. All formulations tested except R with water demonstrate irritation equal or lower than this reference formulation (Figure 4) suggesting that they had minor irritation but were tolerable.

[00220] These nasal irritation data suggested that the clonazepam formulations of the present invention were suitable for intranasal delivery.

Example 5

Pharmacokinetics and Tolerability

[00221] Different clonazepam formulations were delivered intranasally and intravenously to rabbits. Many of the administrated formulations demonstrated intranasal

bioavailability higher than 70% that of the intravenous formulations. Those that contained Transcutol® at concentrations 20-100% demonstrating that Transcutol® was a useful absorption enhancer and solvent for clonazepam

[00222] Additionally, the intranasal clonazepam formulations containing Transcutol® in the concentration range 20-100% yielded pharmacokinetic (PK) profiles with t_{max} lower than 4 minutes. The absorption enhancing effects of Transcutol® were also demonstrated by this performance index.

[00223] Some exemplary pharmacokinetic data for clonazepam formulations is presented in Table 12A (N=1 for each formulation). In the table, Tw or tween is TWEEN20, EtOH is ethanol, Triac or TA is Triacetin, phosph is phosphate buffer, metabisulph is sodium metabisulphite, citr is citrate buffer, AUC is area under the curve T_{max} is minutes, C_{max} is in ng/ml, and F% is bioavailability of the intranasal formulation as compared to the intravenous formulation-- other abbreviations are as used herein above.

[00224]

Table 12A

Example Clonazepam Formulations and Pharmacokinetic Data

Formulation	PEG	TA	TC	GF	PG	Tw	Et OH	H2 O	Dose (mg)	T_{max}	C_{max}	*AUC*	F%
100% Transcutol®			100						0.191	1.4	26	*1048*	125%
30% Triacetin + 70% Transcutol®		30	70						0.201	1.1	50	*1039*	118%
30%Triac.+60%TC+10%H2O		30	60					10	0.190	1.1	29	*1165*	111%
40%PG+60%TC			60		40				0.195	2.9	45	*1182*	110%
30%TA+60%TC+10%citrate		30	60					10	0.187	1.9	31	*1130*	110%
30% Triacetin + 70% Transcutol®		30	70						0.201	3.0	39	*902*	102%
90% TC + 10% H2O			90					10	0.192	3.0	39	*1157*	109%
30%TA+60%TC+10%citrate		30	60					10	0.187	3.0	26	*938*	91%
30% TA + 60%TC + 0.2% tween + 10% citrate pH 4		30	60					10	0.191	1.4	23	*758*	91%
100% Transcutol®			100						0.191	1.6	39	*789*	94%
80% GF + 20% TC			20	80					0.212	2.7	29	*963*	83%
80% GF + 20% TC			20	80					0.212	3.3	34	*980*	84%
30%Triac.+60%TC+10%H2O		30	60					10	0.190	1.5	24	*978*	94%
50% PEG200+50% TC	50		50						0.196	1.6	44	*1105*	102%
40%PG+60%TC			60		40				0.195	3.3	24	*1021*	95%
30%TA+60%TC+10%phosph.		30	60					10	0.187	1.8	18	*826*	80%
100% Glycofurol				100					0.191	15.6	18	*876*	105%
50% GF + 50% TC			50	50					0.218	2.2	38	*1185*	99%
30%TA + 70% GF		30		70					0.191	3.4	20	*811*	77%
90% TC + 10% H2O			90					10	0.192	1.5	21	*826*	78%
95% GF + 5% Tween-20				95		5			0.190	1.4	26	*759*	73%
30%TA+60%TC+10%phosph.		30	60					10	0.187	1.4	23	*679*	66%
50% PEG200+50% TC	50		50						0.196	3.4	30	*839*	78%
10% GF + 0.2% tween + 90%	90			10					0.182	5.7	13	*642*	81%

Formulation	PEG	TA	TC	GF	PG	Tw	Et OH	H2 O	Dose (mg)	T_{max}	C_{max}	*AUC*	F%
PEG 200													
100% GF				100					0.212	3.1	18	*682*	58%
100% GF				100					0.212	1.6	20	*647*	55%
30%TA + 70% GF		30		70					0.191	5.4	15	*707*	67%
10% GF + 0.2% tween + 90% PEG 200	90			10					0.182	3.7	10	*414*	52%
10% TC + 0.2%tween + 90% PEG 200	90		10						0.193	9.9	18	*650*	77%
50%PG+20%TC+20%EtOH+ 10%citr/Tween/metabisulph			20		50		20	10	0.200	15.6	33	*1332*	84%
50%PG+20%TC+20%EtOH+ 10%citr/Tween/metabisulph			20		50		20	10	0.200	1.3	52	*1133*	72%
30%GF+60%PEG200+10%citr/Tween/metabisulph	60			30				10	0.200	3.0	16	*728*	46%
30%GF+60%PEG200+10%citr/Tween/metabisulph	60			30				10	0.200	3.5	42	*773*	49%
100% PEG 300	100								0.201	20.9	17	*690*	79%
100% PEG 200	100								0.195	3.3	15	*475*	56%
10% GF + 90% PEG 200	90			10					0.211	3.0	13	*589*	64%
10% GF + 90% PEG 200	90			10					0.211	5.6	16	*678*	73%
30% TA + 60%TC + 0.2% tween + 10% citrate pH 4		30	60					10	0.191	1.4	23	*482*	58%
10% TC + 0.2%tween + 90% PEG 200	90		10						0.193	46.4	13	*640*	76%
80%PEG200+20%TC	80		20						0.198	3.0	17	*750*	69%
10% GF+80%PEG+10%citr/Tween/ metabisulph	80			10				10	0.200	3.8	25	*840*	53%
30%GF+70%PG				30	70				0.200	4.7	28	*956*	60%
5% GF + 95% PEG 200	95			5					0.200	15.1	14	*622*	71%

Formulation	PEG	TA	TC	GF	PG	Tw	Et OH	H2 O	Dose (mg)	T_{max}	C_{max}	*AUC*	F%
50% GF + 50% TC			50	50					0.218	3.0	10	*298*	25%
70% GF+20% TC+10% H2O			20	70				10	0.214	5.3	20	*655*	56%
30%GF+70%PEG200	70			30					0.189	5.8	9	*445*	43%
30%GF+70%PEG200	70			30					0.189	15.0	14	*653*	63%
10%GF+50%PEG+30%PG+10%citr/Tween/metabisulph	50			10	30			10	0.200	3.4	25	*748*	47%
30%GF+70%PG				30	70				0.200	2.9	14	*585*	37%
30%GF+70%PG				30	70				0.200	3.4	15	*332*	21%
10% GF+80%PEG+10%citr/Tween/metabisulph	80			10				10	0.200	3.1	23	*459*	29%
10%GF+50%PEG+30%PG+10%citr/Tween/metabisulph	50			10	30			10	0.200	3.3	17	*588*	37%
100% PEG 200	100								0.195	21.3	9	*400*	47%
80%PEG200+20%TC	80		20						0.198	10.4	12	*593*	54%
100% PEG 300	100								0.201	30.4	9	*427*	49%
5% GF + 95% PEG 200	95			5					0.200	5.4	10	*297*	34%
95% GF + 5% Tween-20				95		5			0.190	44.8	10	*518*	50%
10% GF+80%PEG+10%citr/Tween/metabisulph	80			10				10	0.200	30.4	14	*636*	40%
70% GF+20% TC+10% H2O			20	70				10	0.214	60.0	6	*270*	23%

Sodium metabisulfite and citric acid were each present at less than 1% (w/w) basis in the above formulations.

[00225] Some clonazepam formulations without Transcutol® also provided a rapid rise in blood levels post-intranasal dosing including, for example, 95% GF, 5% Tween-20, 100% GF, 10%GF, 90% PEG, 100% PEG and 30% TA, 70% GF.

[00226] The pharmacokinetic data presented above illustrated that clonazepam compositions formulated for intranasal administration are pharmaceutically efficacious to deliver clinically relevant amounts of clonazepam into the bloodstream in a short time period -- making such intranasal formulations clinically useful, for example, for the treatment of seizure clusters. Such clonazepam compositions comprise, for example, one or more solvents selected from the group including, but not limited to, Transcutol®(diethylene glycol monoethylether) and similar alkylethers, propylene glycol, triacetin, Glycofurol (ethoxylated furanyl alcohol or tetrahydrofurfuryl alcohol polyethyleneglycol ether) and similar ethoxylated tetrahydrofurfuryl alcohols, as well as polyethylene glycol (e.g., PEG 200, PEG 300, etc.). However, as noted above, free PEG polymers lead to reduced stability of clonazepam formulations.

[00227] The data shown in Table 12 above were reanalyzed. The rabbit pilot PK experiments had been performed in two groups of ten animals, JC01 (Group 1) and JC02 (Group 2). The JC01 experiments were performed in a group of rabbits which were older and heavier than the JC02 group of rabbits. Each group of rabbits had their own set of intravenous clonazepam PK data for the calculations of bioavailability.

[00228] The intranasal formulations were 4 mg/mL. The animals were administered 25 μL of formulation to each nostril, 50 μL in all, with an Eppendorf dosing pipette. The animal was held in a supine position while being dosed and for about 10 seconds after. The intravenous formulation, Rivotril® injectable, was administered as 500μL injected over 30 seconds into the marginal ear vein on opposite site to the blood sampling ear. All rabbits received 0.2 mg clonazepam.

[00229] Five formulations were tested on each study day, where each of the formulations was administered to two rabbits. The data were analyzed before the composition of the formulations administered to the next group of animals was decided.

[00230] Due to the different body weights of the two rabbit groups, the C_{max} and the 60 minute AUC results from the two groups were not directly comparable. The relative bioavailability was corrected for weight differences between the two groups, based on results of the IV administrations to each group. The C_{max} was not directly comparable between the two groups, but was included in the table as a relative indication peak levels within each group.

Table 12B: Example Clonazepam Formulations and Pharmacokinetic Data

Group 1 Rabbits						
ID	Formulation	Rabbit no.	Dose (mg)	t-max	C-max	Relative BA
IV	Intravenous	21-25	0.214			100%
1	100% PEG 300	21	0.201	20.9	27.3	62%
		26	0.201	30.4	14.5	38%
2	100% PEG 200	22	0.195	3.3	26.0	44%
		27	0.195	21.3	14.6	37%
3	100% Glycofurol	23	0.191	-	-	-
		28	0.191	15.6	30.4	83%
4	100% Transcutol	24	0.191	1.4	44.6	99%
		29	0.191	1.6	64.9	74%
5	30% Triacetin + 70% Transcutol	25	0.201	3.0	64.6	81%
		30	0.201	1.1	81.5	93%
6	10% GF + 90% PEG 200	21	0.211	5.6	27.4	61%
		26	0.211	3.0	25.8	58%
7	5% GF + 95% PEG 200	22	0.200	5.4	20.2	32%
		27	0.200	15.1	27.1	65%
8	10% GF + 0.2% tween + 90% PEG 200	23	0.182	3.7	23.9	59%
		28	0.182	5.7	20.1	55%
9	30% TA + 60%TC + 0.2% tween + 10% citrate pH 4	24	0.191	3.0	48.5	90%
		29	0.191	1.4	43.5	53%
10	10% TC + 0.2%tween + 90% PEG 200	25	0.193	46.4	24.0	67%
		30	0.193	9.9	32.8	66%

Group 2 Rabbits						
ID	Formulation	Rabbit no.	Dose (mg)	t-max	C-max	Relative BA
A	IV	33+35	0.214			100%
B	100% GF	31	0.212	3.1	19.9	53%
		32	0.212	1.6	23.2	54%
C	80% GF + 20% TC	34	0.212	2.7	31.2	73%
		36	0.212	3.3	39.7	78%
D	50% GF + 50% TC	37	0.218	2.2	41.1	79%
		38	0.218	3.0	14.4	25%
E	70% GF+20% TC+10% H2O	39	0.214	5.3	25.2	51%
		40	0.214	3.2	9.5	20%
F	90% TC + 10% H2O	31	0.192	3.0	43.5	105%
		32	0.192	1.5	24.6	76%
G	30%Triac.+60%TC+10%H2O	33	0.190	1.5	30.5	84%
		34	0.190	1.1	31.1	103%
H	50% PEG200+50% TC	35	0.196	1.6	47.2	94%
		36	0.196	3.4	34.6	78%
I	80%PEG200+20%TC	37	0.198	3.0	17.9	59%
		38	0.198	10.4	14.1	53%
J	95% GF + 5% Tween-20	39	0.190	44.8	10.9	47%
		40	0.190	1.4	29.6	73%
K	30% Triacetin + 70% Glycofurol	31	0.191	5.4	17.0	69%
		36	0.191	3.4	24.9	84%
L	40%PG + 60%TC	32	0.195	2.9	51.3	111%
		37	0.195	3.3	24.2	85%
M	30%GF+70%PEG200	33	0.189	15.0	17.3	69%
		38	0.189	5.8	12.0	48%
N	30%TA+60%TC+10%citrate	34	0.187	1.9	33.7	105%
		39	0.187	3.0	30.9	94%
O	30%TA+60%TC+10%phosph.	35	0.187	1.8	19.8	76%
		40	0.187	1.4	27.9	72%

P	10% GF + 80% PEG200 + 10% citr/tween/metab	36	0.200	3.8	25	25%
		32	0.200	3.1	23	37%
		31	0.200	30.4	14	49%
Q	10% GF + 50% PEG200 + 30% PG + 10% citr/tween/metab	37	0.200	3.4	25	39%
		33	0.200	3.3	17	39%
R	30% GF + 60% PG + 10% citr/tween/metab	34	0.200	3.0	16	51%
		38	0.200	3.5	42	43%
T	30% GF + 70% PG	35	0.200	4.7	28	49%
		39	0.200	2.9	14	35%
		40	0.200	3.4	15	22%
U	50% PG + 20% EtOH + 20% TC + 10% citr/tween/metab	32	0.200	15.6	33	69%
			0.200	1.3	52	72%

Note: Tw or tween is TWEEN20, EtOH is ethanol, Triac or TA is Triacetin, phosph is phosphate buffer, metabisulph is sodium metabisulphite, citr is citrate buffer.

[00231] As exemplified in Tables 12A and 12B above, the composition may comprise a solvent matrix of two solvents, for example, a first solvent that provides high solublization of clonazepam (for example, TC or GF) that, after application to nasal mucosa, is absorbed by the nasal mucosa leading to clonazepam super saturation, and a second solvent (for example, TA or PG) in which clonazepam has lower solubility relative to the first solvent. In preferred embodiments, the compositions are substantially non-aqueous or anhydrous; however, the compositions may further comprise an aqueous component (for example, of less than about 10% aqueous content, preferably of less than about 5% aqueous content, more preferably of less than about 2% aqueous content, wherein the aqueous content is preferably buffered with a physiologically acceptable buffer to obtain a pH range of about pH 4 to about pH 7, preferably between about pH 4 to about pH 6.5). The benzodiazepine compositions of the present invention may comprise further components as well, for example, anti-oxidants (for example, sodium metabisulfite or butylhydroxytoluene (BHT). Preferred embodiments typically do not include polyethylene glycol polymers as a solvent but may include solvents like tetrahydrofurfuryl alcohol polyethyleneglycol ether (Glycofurol) wherein the solvent molecules contain polyethylene glycol polymers as an intrinsic part of their molecular structure, that is, polyethylene glycol polymers as substituent groups of a larger chemical

structure (also, see, for example, published P.C.T. International Patent Application Nos. WO 03/070273 and WO 03/070280).

[00232] The pharmacokinetics and tolerability of four clonazepam compositions comprising binary solvent systems were further evaluated. The four formulations were as follows in Table 13.

[00233]

Table 13

Compositions of binary solvent systems (10 mg/mL clonazepam)

Composition	Solvent System
I	50% diethyleneglycol monoethylether + 50% triacetin
II	50% diethyleneglycol monoethylether + 50% propylene glycol
III	50% glycofurol + 50% triacetin
IV	50% glycofurol + 50% propylene glycol

[00234] The pharmacokinetics of the formulations in Table 13 were evaluated by nasal administration to rabbits and compared to intravenous (i.v.) administration of clonazepam in rabbits. Sample size for each formulation was N=10 with instillation of 10 mg/mL clonazepam dose adjusted to body weight. A summary of the data is presented in Figure 5.

[00235] The data is further summarized in Table 14.

Table 14

PK Data for Selected Formulations

Formulation		Dose (mg)	T_{max}	C_{max}	AUC	Bioavail.
I	50%TC+50%TA	0.214	20.3	9.02	462	43%
II	50%TC+50%PG	0.214	3.51	24.31	704	66%
III	50%GF+50%TA	0.214	3.24	10.14	454	43%
IV	50%GF+50%PG	0.214	3.26	19.34	604	57%
Intravenous	Injected Rivotril	0.214	1.70	49.70	1061	100%

[00236] The intranasal PK profiles of the formulations presented above demonstrated a rapid absorption of clonazepam such that clinically relevant amounts of clonazepam reach the bloodstream in a short period of time. Short-term bioavailability does not necessarily

need to be high; it is of higher importance that the blood levels become high in as short a time as possible. Lower bioavailability can be balanced out, for example, with higher dose. An advantage of a higher dose and low short term bioavailability may be passage of the drug that is not absorbed intranasally into the gastro-intestinal tract resulting in the remainder of the drug undergoing classical GI absoprtion leading to a sustained release profile.

[00237] As can be seen from the PK data in rabbits, benzodiazepine compositions of the present invention formulated for intranasal delivery may be characterized, for example, by a T_{max} of benzodiazepine, after a single intranasal administration (in one or both nostrils), of 2 hours, often less than 1 hour likely less than 30 minutes or less than 15 minutes. Further, pharmaceutical compositions of benzodiazepines for intranasal delivery, as described herein, may be characterized, for example, by providing at least one of a mean maximum plasma concentration (C_{max}) of benzodiazepine of at least about 3.0 ng/mL or at least about 15% of the concentration of an intravenously delivered dose often 30% of an intravenously delivered dose or 50% or an intravenously delivered dose, and a mean plasma Area Under the Curve over 60 minutes (AUC) value of clonazepam of at least about 400 ng-hr/mL, when a single dose of the composition is administered intranasally to deliver a dose of at least about 0.2 mg of clonazepam. Further, the bioavailability of benzodiazepine compositions of the present invention, after intranasal administration, is typically greater than 30% often greater than 40% and frequently greater than 50% of that of intravenous administration.

[00238] In addition to the PK parameters discussed above, the experiments performed in support of the present invention evaluated the local tolerance in the upper and lower respiratory tract of formulations I-IV containing clonazepam as active drug. This tolerance was assessed in the rabbit as model. Treatments were performed during seven consecutive days before histopathological evaluation of selected tissues.

[00239] The rabbits used in these experiments were as follows: Breed, New Zealand White; Sex, 30 males and 30 females; Weight, Mean body weight 2.466 ± 0.093 (SD) kg for the male rabbits, 2.465 ± 0.114 (SD) kg for the female rabbits. Animals showing any concurrent disease at the time of the treatment were not included. Rabbits were obtained from Charles River Laboratories, L'Arbresle Cedex, France.

[00240] Animals were weighed during the acclimatisation period for allocation, within the 3 days prior to treatment and just before slaughter. The dose-level of 10 mg/mL (1 mg clonazepam in 100 µL solution) was selected to be comparable to an anticipated dose to be administered in humans.

[00241] The treatment groups are detailed in Table 15. Formulation 5 is a vehicle control -- 50 % glycofurol; 50 % propylene glycol (with no clonazepam). Formulation 6 is a saline control (0.9% NaCl in water).

Table 15

Allocation of treatments into groups

Group	Treatment	Number of animals	Concentration of Clonazepam (mg/mL)	Number of treatments
1	Formulation I TC/TA+	5 males 5 females	10	7
2	Formulation II TC/PG+	5 males 5 females	10	7
3	Formulation III GF/TA+	5 males 5 females	10	7
4	Formulation IV GF/PG+	5 males 5 females	10	7
5	Formulation 5 GF/PG-	5 males 5 females	0	7
6	Formulation 6 S-	5 males 5 females	0	7

[00242] The selected route of administration was the route of administration of the final product.

[00243] Whatever the formulation, 0.1 mL of the formulation was daily administered to all animals by nasal instillation during seven consecutive days.

[00244] All administrations were performed in the right nostril using a 1 mL pipette (B13, Adjustable pipettes Pipetman P200 from Gilson) fitted with a plastic cone. The required volume of item was measured with the pipette and placed just inside the nostril of the animal.

[00245] Treatment details were recorded in the raw data including dose administered, formulation identification, date and time of administration.

[00246] Six animals per group, three males and three females at Day 8, and the remaining animals at Day 15, after a seven-day recovery period, were sacrificed by ex-sanguination from abdominal aorta under isoflurane anaesthesia.

[00247] Following euthanasia, macroscopical examination of larynx, trachea, bronchi, lungs and oesophagus were performed.

[00248] The head of the animal, with the larynx and specimens of trachea, bronchi, lungs and oesophagus were taken at necropsy and fixed in formalin for histopathology.

[00249] From head, nasal mucosa, turbinates, in addition to larynx and trachea were sampled after specific preparation and examined. Any observed macroscopic abnormalities or lesions were also sampled and fixed, with a border of surrounding tissue, for histopathology.

[00250] Nasal mucosa and turbinates were examined in the nasal cavities on three head sections corresponding to nasal cavities proximal, nasal cavities turbinates and nasal cavities olfactory.

[00251] Histopathological examinations were performed and the results evaluated by a pathologist. All results were tabulated per group, means and standard deviations were calculated on each organ. Statistical comparisons were performed between group using ANOVA. There were no obvious differences in growth between groups.

[00252] Severity of the eventual modifications observed in the histological preparations were scored by the pathologist as follows: 0, no lesions; 1, slight; 2, moderate; and 3, severe.

[00253] Figure 6 summarizes the histopathology results for the nasal cavities of the animals. Severity scores in group 3 was statistically higher than scores of groups 4, 5 and 6 ($p=0.003$). Irritative modifications like erosion and fibrino-leucocytic material in turbinates lumen were observed mainly in group 3 (2/3 females and 1/3 males), also for group 1 (1/3 females) and group 5 (2/3 males) but not for other treated or control groups. These modifications were not observed in necropsy on day 15. Mild epithelial atrophy on turbinates was noted in necropsy on day 8 and also in necropsy on day 15 mainly for treated

group 1 and slighter for other treated groups. Control group 6 showed no epithelial atrophy. Blood was sometimes observed in aerian lumen for larynx and also nasal cavities both in treated and control groups and are probably of traumatic origin. The best local tolerance was observed for treated group 2 and 4. These results indicate generally good nasal tolerance for the tested formulations.

[00254] Blood or petechia were found in larynx on 15 animals (2 from group 1, 4 from group 2, 3 from group 3, 2 from group 4, 4 from group 5) during necropsy and on 6 animals (1 from group 2, 2 from group 4, 3 from group 5) at histopathology examination. Table 16 presents mean and SD severity scores in each group.

Table 16

Mean and SD severity score on larynx in each group

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Mean score	0.0	0.1	0.0	0.2	0.3	0.0
SD	0.0	0.3	0.0	0.4	0.5	0.0

Slight epithelial desquamation were observed on oesophagus from two animals from group 4. Table 17 presents mean and SD severity scores in each group.

Table 17

Mean and SD severity score on oesophagus in each group

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Mean score	0.0	0.0	0.0	0.2	0.0	0.0
SD	0.0	0.0	0.0	0.4	0.0	0.0

[00255] Petechia or blood were observed during necropsy on 17 animals (4 from group 1, 3 from group 2, 5 from group 3, 1 from group 4, 4 from group 5). No histopathological lesions were observed in bronchi and trachea.

[00256] Lung modifications were observed during necropsy on 17 animals (1 from group 1, 3 from group 2, 3 from group 3, 1 from group 6). Congestive foci were histologically recorded on two animals from group 2 at Day 15. Table 18 presents mean and SD severity scores in each group.

Table 18

Mean and SD severity score on lungs in each group

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Mean score	0.0	0.2	0.0	0.0	0.0	0.0
SD	0.0	0.4	0.0	0.0	0.0	0.0

[00257] Considering the whole respiratory tract, microscopical lesions were mainly observed in the very upper part, the nasal cavities. As no lesions were recorded in the control group, it is likely that all the lesions were related to the treatments. Petechia recorded at necropsy and presence of blood observed during histopathological examination can be due to a trauma induced by the treatment. In the majority of animals (20 out of the 26 presenting petechia or blood at necropsy), lesions recorded at necropsy were associated with histopathological findings. Irritative lesions were observed just after treatment and were not present after a one week recovery. Mild epithelial atrophy was observed after a one week recovery. Considering severity scores, formulation 3 induced significantly the most severe lesions. Local tolerances of the other formulation were nearly similar.

[00258] In conclusion, the results of necropsy and histopathological examination, including comparison of severity scores, suggested that the clonazepam compositions of the present invention comprising formulations for intranasal delivery have acceptable tolerability for pharmaceutical use.

Example 6

Sprayability and Viscosity of Solvent Matrices

[00259] Fourteen representative solvent matrices used for clonazepam formulations were tested for spray pattern and compared with water. The solvent mixtures were made up, spiked with minute amounts of Coomassie Brilliant Blue Dye and 100 µL were subsequently filled into Pfeiffer unit-dose devices (Pfeiffer of America, Princeton, NJ). To measure the spray pattern, the devices were actuated below a sheet of paper that was located 3 cm above the spray nozzle. All measurements were made at ambient room temperature (20-25°C). The smallest (D_{min}) and the largest (D_{max}) diameter of the blue pattern formed on the sheet of paper were measured and the results used to calculate the D_{max}/D_{min} ratio, the area of the

pattern and the average spray angle. The plume area at 3 cm was calculated using the equation for the area of an ellipse using the half of the two diameters as the ellipse radii. Viscosity of all formulations was measured using Brookfield DV-I viscometer (Brookfield Engineering Laboratories, Inc., Middleboro, Massachusetts). The results from the measurements are shown in Table 19. Table 19 presents data related to sprayability and viscosity of solvent mixtures used in clonazepam formulations. Viscosity, plume area at 3 cm, spray angle and D_{max}/D_{min} ratio reflecting the symmetry of the spray plume are presented.

Table 19

Sprayability and Viscosity

Composition	Avg. viscosity (cP)	Plume area at 3 cm (cm^2)	Spray angle (°)	Ratio D_{max}/D_{min}
80% Glycofurol + 20% Transcutol®	11.5	5.93	49.2	1.07
50% Glycofurol + 50% Transcutol®	7.4	8.45	57.3	1.04
95% Glycofurol + 5% H_2O	16.7	5.73	48.6	1.22
70% Glycofurol + 30% Triacetin	14.6	5.78	48.7	1.12
60% Transcutol® + 30% Triacetin + 10% H_2O	5.8	8.71	58.1	1.03
60% Transcutol® + 40% Propylene glycol	8.8	6.42	51.0	1.11
70% PEG200 + 30% H_2O	20.6	4.07	41.6	1.14
80% PEG200 + 20% H_2O	30.0	4.10	43.3	2.04
90% PEG200 + 10% H_2O	41.7	2.46	33.6	1.79
80% PEG200+10% GF+10% H_2O	42.8	3.21	39.2	2.07
50% PEG200+30% PG+10% GF+10% H_2O	35.4	4.55	44.9	1.54
60% PG+30%GF+10% H_2O	23.3	4.92	46.3	1.79
70% PG + 30% GF	31.7	4.32	43.1	1.22
Water	1.0	15.52	73.1	1.10

[00260] While water had a viscosity of 1.0 cP the solvent mixtures tested range from 5.8 (60% Transcutol® + 30% Triacetin + 10% H_2O) to 42.8 cP (80% PEG200+10% GF+10% H_2O). The viscosity of the solvent mixtures had a negative correlation with plume area and spray angle and plume asymmetry as shown in Figure 7, Figure 8 and Figure 9.

[00261] From the data shown in Table 19, Figure 7, and Figure 8 it is evident that the spray angle became smaller with increasing viscosity of solvent matrix in the standard Pfeiffer Unit-dose devices. Figure 9 shows that the plume asymmetry remained within the range 1.0 to 1.2 up to solution viscosity about 20 cP above which irregularity in the plume shape increased. Visual inspection of the appearance of the spray plume of three solutions in the viscosity range from 5.8 to 41.7 revealed that a plume was formed and none of them "squirted."

[00262] These results demonstrated that at 20-25°C all solvent matrices tested spray well from Pfeiffer unit dose devices. The results also suggested that viscosity is a good predictor of sprayability for the formulations of the present invention. As weather may dictate substantially different conditions of use, the effect of temperature on viscosity was determined. A Gilmont falling ball viscometer was filled with diethylene glycol monoethyl ether and calibrated for several hours at each temperature. At -17°C, 8°C, 23°C and 40°C the measured viscosity was 6.6 cP, 5.4 cP, 3.8 cP and 3.1 cP, respectively. Hence, with relatively low dependence of temperature on viscosity, the 100% transcutol formulation can be expected to exhibit good spray characteristic over a wide range of temperatures below 40°C and at least about -15°C to 30°C.

Example 7

Example Compositions, Formulations, and Method of Making

[00263] In one aspect the present invention relates to benzodiazepine compositions formulated for intranasal administration. Unit dosages typically have a volume of between about 25 μL to about 150 μL, preferably about 100 μL. A unit dosage of clonazepam, for example, for the treatment of seizure clusters, is between about 0.1 mg to about 5 mg,

preferably about 1 mg to about 4 mg. Table 20 presents example formulations for nasal administration dosage forms. These example formulations provide 10 mg/mL clonazepam.

Table 20

Composition of Solution Formulations (%w/w)

General Component	Specific Component	Formulation I	Formulation II	Formulation III	Formulation IV
Solvent 1 (high solubli-zation of clonaze-pam	diethylene-glycol monoethyl-ether	49.5	49.5	--	--
	glycofurol	--	--	49.5	49.5
Solvent 2 (low clonaze-pam solubility)	propylene glycol	--	49.5	--	49.5
	triacetin	49.5	--	49.5	--
Drug	Clonazepam	1.0	1.0	1.0	1.0
Total		100	100	100	100

[00264] The following methods of making example compositions of the present invention are generally presented and can be modified by one of ordinary skill in the art in view of the teachings of the present specification. Exemplary dosage forms and methods of manufacturing are generally described.

[00265] The desired amount of clonazepam was dissolved in solvent 1 at ambient temperature with stirring until the solution is clear and homogeneous. Solvent 2 was then added and the solution was stirred until homogeneous.

[00266] Exemplary formulations of the present invention include, but are not limited to, a final concentration of between about 1 w/w% to about 20 w/w% clonazepam, between about 30 w/w% to about 70 w/w% solvent 1, and between about 70 w/w% and about 30 w/w% of solvent 2. Further components may be added as discussed herein above and w/w% composition of the components modified accordingly.

[00267] A typical target dose of intranasal clonazepam is 1 to 2 mg per unit dosage. Normally, 1 mg clonazepam (Rivotril i.v.) is administered intravenously by a health care professional in acute epileptic seizure attack. This could be achieved by intranasally

administering, for example, 100 μL of a 10 mg/mL solution with 100% bioavailability, a 13.3 mg/mL solution with a 75% bioavailability, or a 20 mg/mL formulation with 50% bioavailability.

[00268] Unit or multiple doses may be dispensed into an appropriate delivery device, for example, fixed volume metered dose devices. Devices for intranasal delivery of pharmaceuticals are known in the art (for example, manufactured by Pfeiffer of America, Princeton, N.J. and Valois of America Inc., Greenwich, CN). Devices that have the ability to consistently deliver the pharmaceutical composition of the present invention are preferred. Such devices are operable by a patient or second party, for example, medical personnel. Further, these devices leave virtually no residual clonazepam in the device after use. Accordingly, the device can be easily discarded.

[00269] Intranasal delivery devices may be modified, for example, by increasing the size of the discharge orifice in the nose piece of the applicator in order to achieve appropriate spray plume and nasal penetration. For example, a discharge orifice of about 0.07 mm may be used to accommodate higher viscosity compositions. The intranasal delivery device components may also be sterilized by methods known in the art. However, as the compositions of the present invention are anhydrous, dry heat, aseptic filtering or terminal sterilization may be necessary. However, if the formulation is microcidal, sterilization or aseptic filling will likely not be needed (see Example 3 above)

[00270] Intranasal delivery devices may be filled with single or multi-dose amounts of benzodiazepines. Devices with one or more unit-dose(s) may be sterilized employing methods and technology known in the art. Intranasal delivery devices comprising the benzodiazepine compositions of the present invention may further be sealed with a tamper-proof seal. In addition, appropriate child-proofing control means may also be added to the devices.

[00271] The benzodiazepine compositions of the present invention may be packaged under nitrogen in order to reduce oxidative damage to the clonazepam or to the excipients. Similarly, the manufacturing process may also be carried out under limited oxygen conditions.

Example 8

Human Pharmacokinetic Study

[00272] The human pharmacokinetics, safety, and tolerability of the benzodiazepines compositions of the present invention formulated for intranasal delivery for therapeutic applications are evaluated using standard clinical procedures. Benzodiazepine compositions formulated for intranasal delivery are provided, for example, for application by the participants to intranasal mucosa.

[00273] A primary objective of initial studies in humans is to determine and compare pharmacokinetic profiles of three dosage forms of a benzodiazepine: oral, i.v., and intranasal, following single administration. An example of such a study in humans is a cross-over study performed in 12 healthy male volunteers. Plasma and urine level of clonazepam and 7-amino-clonazepam are determined, for example, using HPLC and UV detection. Secondary objectives of such a study include determination of safety and tolerability of the intranasal clonazepam formulations of the present invention and evaluating their pharmacodynamic effects using qEEG mapping (see, e.g., Example 9, below). Further the initial studies in humans are used to determine local tolerability of intranasal formulation using questionnaire and the Visual Analog Scale (VAS). VAS is a validated instrument that has been used in numerous studies to quantify subjective opening of the nasal passages. In addition, cognitive, sleepiness and mood effects are evaluated using questionnaires and scales (see, e.g., Example 10 below). Further, attention and vigilance may be evaluated using, for example, LEEDS Psychomotor Multiple Choice Reaction Time (MCRT) testing.

Example 9

qEEG Mapping

[00274] EEG profiles are determined for patients dosed intranasally with benzodiazepine compositions of the present invention. Vehicle controls without clonazepam may also be administered. Standard frequencies of the EEG bands are as follows: delta (0.5-305 Hz); theta (4-7.5 Hz); alpha (8-12.5 Hz); and beta (13-32 Hz). The latter two are divided into sub-bands as follows: alpha 1 (8-9.5 Hz) and alpha 2 (10-12.5 Hz); and beta 1 (13-17.5 Hz), beta 2 (18-20.5 Hz), and beta 3 (21-32 Hz)

[00275] The functional correlates of the EEG bands are as follows: delta, sedative potential; theta, cognition; alpha, vigilance/attention; and beta, arousal/anxiety. Increases in beta bands have been shown to be correlated with subjective anxiolysis (Ansseau, M., et al., "Self-reports of anxiety level and EEG changes after a single dose of benzodiazepines. Double-blind comparison of two forms of oxazepam," Neuropsychobiology 12(4):255-9 (1984).

[00276] As a control clonazepam may be administered i.v. at selected doses. Placebo is also administered i.v.

[00277] Interkinetic map (absolute energy) of EEG parameters relative to time after administration of clonazepam versus placebo are obtained.

[00278] Sedation effects may also be evaluated using, for example, the Stanford sleepiness scale.

[00279] These results are expected to support the use of clonazepam compositions formulated for intranasal administration for pharmaceutical applications, for example, for treatment of seizure clusters wherein a rapid onset of anti-convulsive effect is seen with minimal adverse effects (such as minimal increases in sedation).

Example 10

Cognitive Effects of Benzodiazepines

[00280] This example describes the pharmacodynamic effects of benzodiazepine compositions formulated for intranasal administration using neurocognitive tests. A selection of tests from a computerized assessment system of Cognitive Drug Research ("CDR," Reading, United Kingdom) is employed. The study is typically a double-blind, randomized, placebo-controlled cross-over design. As a control, the group may receive benzodiazepine intravenous (i.v.) and placebo at selected dosages.

[00281] Cognitive function is typically assessed using an attentional task battery to assess attention and a word recognition task to assess secondary memory. Following training on the cognitive test procedures at screening and on Day −1, CDR assessments are typically completed at pre-dose and 30, 60, 90, 120 and 180 minutes post-dose on Day 1 of each period. The attentional task battery and the Word Recognition task from the CDR

computerized cognitive assessment system are administered. Parallel forms of the tasks are presented at each assessment to allow for repeated assessment by presenting different, but equivalent stimuli.

[00282] Tests may be administered, for example, in the following order: Word Presentation; Simple Reaction Time; Digit Vigilance; Choice Reaction Time; and Word Recognition. Two composite scores were generated from the collected data: Power of Attention, the speed measures from the three attentional tasks all strongly load on a single factor; and Continuity of Attention, the accuracy measures from the attentional tasks Choice Reaction Time and Digit Vigilance both reflect the ability of the subject to sustain attention and avoid error. Summary statistics (n, number; mean; sem, standard error; sd, standard deviation; median; min, minimum; max, maximum; and missing) are typically calculated for each measure at each time point by dose. For each measure, pre-dose (baseline) data is subtracted from the data at each post-dosing time to derive 'difference from baseline' scores. Figures (mean ± sem) are plotted using the unadjusted scores and derived 'difference from baseline' scores.

[00283] Repeated measures analysis of covariance (ANCOVA) are conducted on the data using, for example, SAS PROC MIXED. Fixed terms are fitted to the model for sequence, dose, period, time and the dose*time interaction. A random effect of subjects within sequence are fitted to the model. Pre-dose (baseline) scores are used as a covariate. Significance is typically tested at the 0.05 level.

[00284] For the majority of measures, the selected therapeutic doses of benzodiazepines are expected to show little statistical support for significant impairments. Benzodiazepines are expected to show a pattern of dose dependent impairment of cognition (attention and secondary memory). The size and duration of the impairment will be determined with increasing dose of the benzodiazepine.

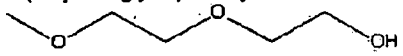
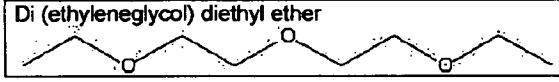
Example 11

Solubility of Clonazepam in Glycol Ethers at 25°C

[00285] A number of glycol ether solvents are believed to be acceptable for solubilizing benzodiazepines in intranasal applications. Four glycol ethers were compared, as shown in the table below.

Table 21

Glycol Ethers

#	Name	CAS	Common	Density
1	1,2-dimethyxoethane 	110-71-4	monoglyme	0.867
2	Di (ethylene glycol) methyl ether 	111-77-3	methyl carbitol	1.023
3	Diethylene glycol monoethyl ether 	111-90-0	Carbitol DEGEE	0.999
4	Di (ethyleneglycol) diethyl ether 	112-36-7	Diethyl carbitol	0.909

[00286] 10 mg of clonazepam was weighed into glass vials used in the Pfeiffer mono-dose spray system (Pfeiffer of America, Princeton, NJ). Four samples of each of four solvents were prepared as follows. 130-μL of each solvent was pipetted into the vial, which was then stoppered with a black chlorobutyl rubber stopper. The samples were then sonicated for 10 minutes and two of each was stored at 25C for at least 12h.

[00287] The vials were removed from the chamber, placed inside polyethylene centrifuge vials, and centrifuged for 2 minutes at 5000 rpm. 10 μL of liquid was then sampled from each vial, accurately weighed, and diluted with 1 mL of acetonitrile. The drug concentration was analyzed by UV using an Agilent HPLC system with no column, 10 μL injection volume, acetonitrile mobile phase, 0.3 mL/min and UV detection at 350nm. The solubilities were calculated from peak area based on calibration with blank and standard solutions, and are shown below.

Table 22

Solubilities of Clonazepam in Glycol Ethers

Solvent	Solubility at 25C, mg/mL
1,2-dimethyxoethane	39.3
Di (ethylene glycol) methyl ether	56.4
Diethylene glycol monoethyl ether (DEGEE)	41.8
Di (ethyleneglycol) diethyl ether	19.0

Example 12

Solubilities of Clonazepam in Glycol Ethers at 3 Temperatures

[00288] Samples were prepared using procedures of Example 11 (25°C solubilities, included in table below for reference). The samples were stored in the refrigerator or freezer for at least 12 hours, and precipitate had substantially settled. The vials were then centrifuged at -5°C and 5°C for the -15°C and 5°C samples, respectively, at 5000 rpm for 2 minutes. The solubilities shown below indicate very little temperature dependence on solubility between 25°C and -15°C for clonazepam in these glycol ethers. These compositions could be stored at temperatures up to 30°C and down to -15°C and retain their stability.

Table 23

Solubilities (mg/mL) of Clonazepam in Glycol Ethers

Solvent	15C	5C	25C
1,2-dimethyxoethane	35.2	35.7	39.3
Di (ethylene glycol) methyl ether	58.1	53.9	56.4
Diethylene glycol monoethyl ether	43.3	37.7	41.8
Di (ethyleneglycol) diethyl ether	19.5	18.5	19.0

Example 13

Solubilities of Clonazepam in Water-Containing Solvents

[00289] The samples from Example 11, after completing the solubility measurement in 100% solvent, were partly pipetted into another set of glass vials (Pfeiffer mono-dose vials) and mixed with varying proportions of pH6.8 buffered water to form 120μL aqueous mixtures of 20% to 80% glycol ether. All samples immediately showed precipitation. The vials were stored at 25°C for approximately 1 day. Prior to sampling, the vials were centrifuged at 5000 rpm for 2 minutes at 23°C. The results are shown below; neat solvent solubilities from Example 11 are included for reference. Increased water content decreases solubility substantially.

Table 24

Solubilities (mg/mL) of Clonazepam in Solvent/Water Solutions

%Solvent	100	80	60	40	20
Solvent %Water	0	20	40	60	80
1,2-dimethyxoethane	39.3	29.6	9.2	0.64	0.18
Di (ethylene glycol) methyl ether	56.4	18.9	2.8	1.00	0.26
Diethylene glycol monoethyl ether	41.8	21.8	4.5	0.52	0.30
Di (ethyleneglycol) diethyl ether	19.0	38.8	8.5	1.23	0.31

Example 14

Human Pharmacokinetic Study Results

[00290] A human pharmacokinetic study was carried out as described in Example 8.

[00291] 15 young, healthy male volunteers received a single dose of 1 mg clonazepam by oral, intravenous and intranasal routes in a three-period cross-over design. The intranasal formulation of clonazepam produced its median T_{max} at 0.200 hours (approximately 12 minutes) post-dose while the median T_{max} was 2 hours after oral administration and the median T_{max} following intraveneous administration was 0.10 hours.. The mean C_{max} values after administration of 1mg of clonazepam by the oral, intranasal routes were comparable (intranasal route: mean±SD, 7.12±3.81 ng/mL and oral route: mean±SD, 7.64±1.74 ng/mL; and intravenous route: mean±SD, 42.5±10.8). Accordingly, C_{max} of the intranasal route was 93% of that of the oral route and 17% of that of the intravenous route.

[00292] AUCs at 24 hours after administration of 1 mg of clonazepam were similar for the intravenous and oral routes (approximately 106 and 95 ng·h/mL, respectively), while the AUC at 24 hours after intranasal administration (approximately 58 ng·h/mL) was roughly

half that observed after intravenous administration. Accordingly AUC_{in}:AUC_{iv}=1:1.83 and AUC_{in}:AUC_{oral}=1:1.64 and the bioavailability was 55% relative to intravenous and 61% relative to oral.

[00293] Somnolence and nasal discomfort were the most common side effects reported in the study (75.6% and 26.7%, respectively). Somnolence was reported by 10 of 15 (approximately 67%) subjects after intranasal dosing and 13 of 15 (approximately 87%) subjects after oral dosing. Approximately 93% of the subjects reported somnolence or sedation (11/15 for somnolence and 3/15 for sedation) after intravenous dosing. Nasal discomfort was reported by 12 of 15 subjects (approximately 80%) after intranasal dosing. There were no clinically relevant changes in laboratory parameters,

[00294] After administration of 1 mg of clonazepam, 7-Amino-clonazepam concentrations increased continuously over the 24-hour blood sample collection period for all three routes of administration. The mean C_{max} for the intranasal route (1.17 ng/mL) was lower than values observed for the intravenous and oral routes. The mean C_{max} was similar for the intravenous and oral routes (approximately 2 ng/mL). The mean AUC_t for the intranasal route (16.9 ng·h/mL) was lower than values observed for the intravenous and oral routes. The mean AUC_t was similar for the intravenous and oral routes (approximately 30 ng·h/mL).

Example 15

qEEG Mapping Results

[00295] EEG profiles were determined as described in Example 9 for the 15 volunteers described in Example 14. Based on changes from baseline, clonazepam produced EEG changes characteristic of benzodiazepines. Effects were greatest after intravenous administration, followed by intranasal and oral routes of administration. Statistically significant differences between routes of administration occurred at different time points, indirectly demonstrating different time courses for different effects. In general, clonazepam administration by all three routes increased delta and beta activity and decreased alpha and theta activity on the EEG. This pattern of activity was noted soon after administration of clonazepam by the intranasal and intravenous routes (i.e., within the first 3 to 6 minutes after dosing) and occurred later after oral administration (at approximately 2 hours after dosing).

[00296] A post-hoc analysis focusing on the time course of effects for beta-1 relative power established that intranasal administration of clonazepam is efficient, with a magnitude of effect similar to that from oral administration and an intermediate time delay of action between the intravenous and oral routes. Together with the EEG profile in the delta, theta, and alpha bands from mapping analysis, these results are in agreement with previous pharmacodynamic changes reported with various benzodiazepine drugs.

Example 16

Cognitive Effects of Clonazepam

[00297] Psychomotor and subjective test results were obtained as described in Example 10 for the 15 volumteers described in Example 14. Intranasal clonazepam spray was shown to possess a rapid onset of action comparable to the intravenous formulation on objective tests (Leeds Psychomotor Test) and subjective tests (Bond and Lader VAS and Karolinska Sleepiness Scale). Effects with intravenous and intranasal administration were first apparent at approximately 30 minutes while effects with oral administration were first apparent at approximately 2 hours.

We claim:

1. A pharmaceutical composition for transmucosal administration to a mammal, comprising

a solvent system comprising a first solvent in which benzodiazepine is soluble, the first solvent capable of penetrating nasal mucosal tissue, and a second solvent in which clonazepam in less soluble than in the first solvent, wherein the solvent system comprises 10% (weight/weight) or less of an aqueous buffer solution with the caveat that the solvent system does not comprise free polyethylene glycol polymers; and

a therapeutically effective amount of a benzodiazepine.

2. A pharmaceutical composition for transmucosal administration to a mammal, comprising

a solvent system comprising an alkyl ether solvent in which clonazepam is soluble, the solvent capable of penetrating nasal mucosal tissue, and

a therapeutically effective amount of benzodiazepine,

wherein the composition is a single phase and homogeneous.

3. The composition of claim 1, wherein the first solvent is diethylene glycol monoethylether or tetrahydrofurfuryl alcohol polyethyleneglycol ether.

4. The composition of claim 1, wherein the first solvent is present at a weight percent of between about 30% to about 70%.

5. The composition of claim 4, wherein the second solvent is glycerol triacetate or propylene glycol.

6. The composition of claim 1 or 2, wherein the benzodiazepine is selected from the group consisting of alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flunitrazepam, flurazepam, halazepam, ketazolam,

loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, tetrazepam, and triazolam.

7. The composition of claim 6, wherein the benzodiazepine is selected from the group consisting of lorazepam and diazepam.

8. The composition of claim 1 or 2, further comprising one or more components selected from the group consisting of surfactant, anti-oxidant, pharmaceutically acceptable polymer, polyalcohol, lipid, mucosa penetration enhancing agent, colorant, flavoring agent, anesthetic agent, co-solvent, and agent to adjust osmolarity.

9. The composition of claim 1 or 2, wherein the composition is formulated to be sprayable between -15°C and 30°C.

10. The pharmaceutical composition of claim 2 wherein the alkyl ether solvent is selected from the group consisting of 1,2-dimethoxyoethane, di(ethylene glycol) methyl ether, diethylene glycol monoethylether and di(ethyleneglycol) diethyl ether.

11. The pharmaceutical composition of claim 10 wherein the alkyl ether solvent is diethylene glycol monoethylether.

12. The pharmaceutical composition of claim 8 wherein the antioxidant is butylhydroxytoluene at a concentration of 100 to 3000 ppm.

13. The composition of claim 1 or 2, wherein the composition is used at a unit therapeutic dose of between about 50 μL and 300 μL or between about 25μL.and 150μL.

14. The composition of claim 7, wherein the therapeutically effective amount of diazepam is between 2.0 mg and 40 mg per unit dose.

15. The composition of claim 7, wherein the therapeutically effective amount of lorazepam is between 0.5 mg and 10 mg per unit dose.

16. A pharmaceutical composition comprising a benzodiazepine for transmucosal administration to a mammal, characterized by (i) a T_{max} of the benzodiazepine, after a single transmucosal administration, of no more than 2 hours and (ii) a bioavailability of the benzodiazepine, after a single transmucosal administration, of no less than 30% of the bioavailability of an equivalent dose of the benzodiazepine delivered orally.

17. The composition of claim 16 wherein the T_{max} of the benzodiazepine, after a single transmucosal administration, is less than or equal to 30 minutes and the bioavailability of the benzodiazepine, after a single transmucosal administration, is greater than or equal to 55% of the bioavailability of an equivalent dose of the benzodiazepine delivered orally.

18. A pharmaceutical composition comprising a benzodiazepine for transmucosal administration to a mammal, characterized by (i) a C_{max} of the benzodiazepine, after a single transmucosal administration, of at least about 75% of the C_{max} of an equivalent dose of the benzodiazepine delivered orally, and (ii) a bioavailability of the benzodiazepine, after a single transmucosal administration, of no less than 30% of the bioavailability of an equivalent dose of clonazepam delivered orally.

19. The composition of claim 61 wherein the C_{max} of a benzodiazepine, after a single transmucosal administration, greater than or equal to 90% of the C_{max} of an equivalent dose of the benzodiazepine delivered orally, and a bioavailability of the benzodiazepine, after a single transmucosal administration, is greater than or equal to 55% of the bioavailability of an equivalent dose of the benzodiazepine delivered orally.

20. The composition of claim 16, 17, 18 or 19 wherein the transmucosal delivery is via the intranasal route.

21. A pharmaceutical composition comprising a benzodiazepine for intranasal administration to a mammal, characterized by (i) a ratio of the AUC of the benzodiazepine, after a single intranasal administration, (AUC_{in}) to the AUC of an equivalent dose of the benzodiazepine delivered orally (AUC_{oral}) of at least about AUC_{in}:AUC_{iv} = 1:1.33, wherein the AUC values are determined over the same time period.

22. A method for administering an active agent to a mammal in need thereof, the method comprising:

delivery of a benzodiazepine to the mammal's bloodstream via nasal mucosa of the mammal, wherein the benzodiazepine is delivered in a dosage form comprising a composition of claims 1 - 21.

23. The method of claim 22, wherein the mammal is suffering from seizure clusters and delivery occurs at the onset of the symptoms of seizures or wherein the mammal is suffering from anxiety states selected from the group consisting of to panic attacks, social phobia, social anxiety and performance anxiety.

24. A method of manufacturing a benzodiazepine composition, comprising

mixing the solvent system and the benzodiazepine of any of claims 1-21 to provide a single-phase, homogeneous solution suitable for intranasal administration of the benzodiazepine.

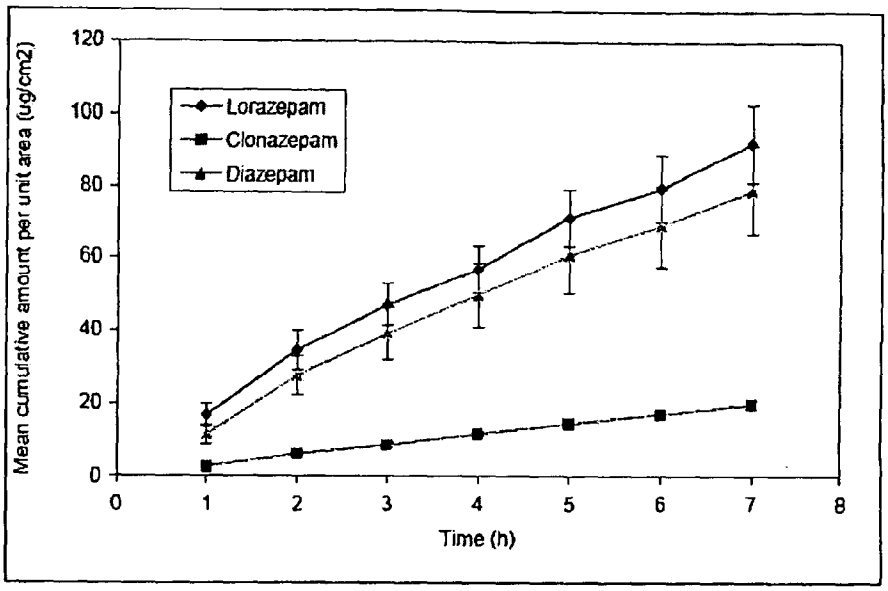


FIGURE 1

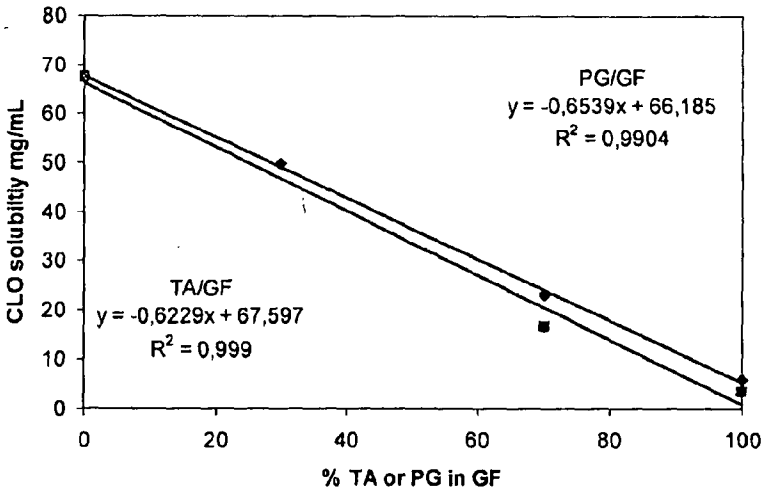


FIGURE 2

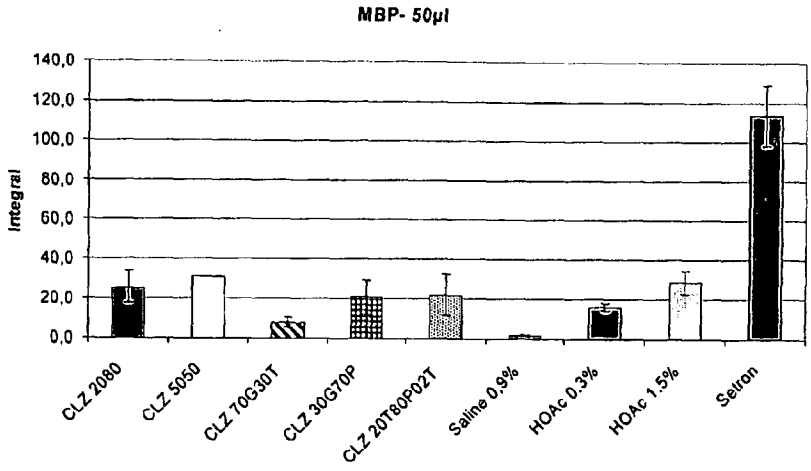
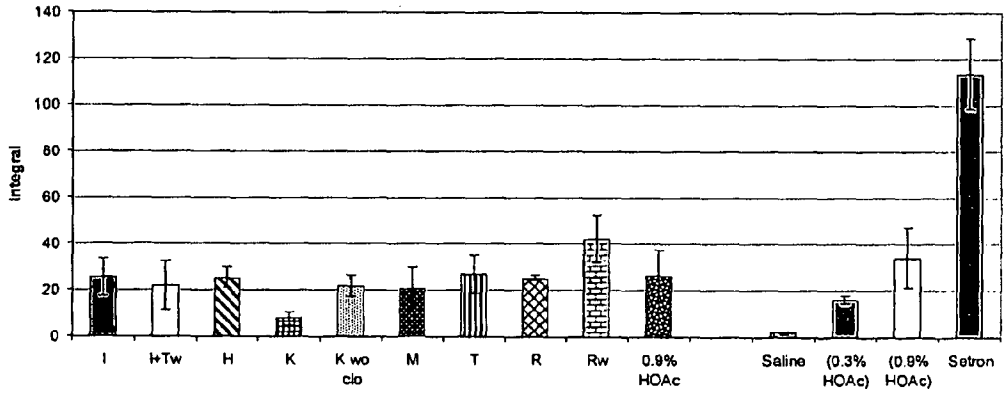


FIGURE 3



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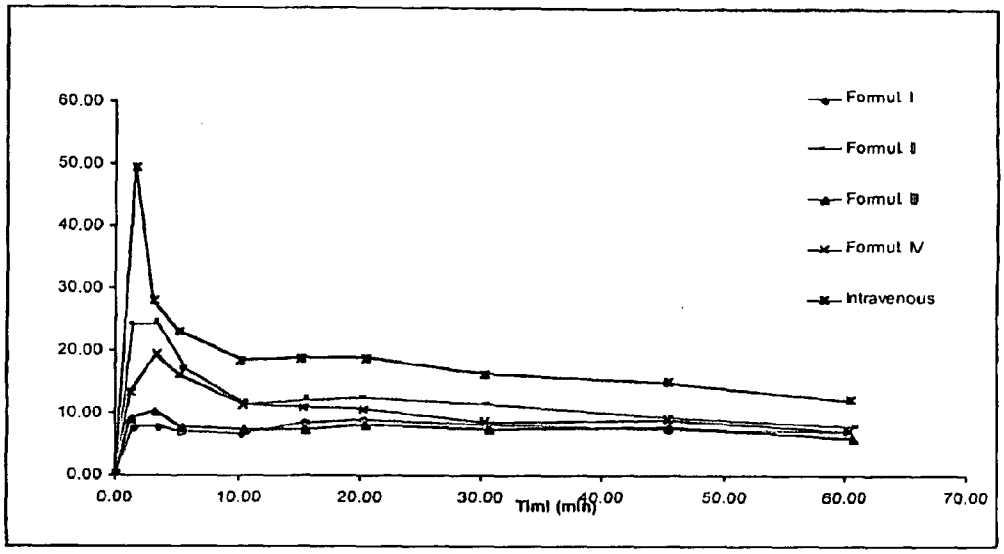
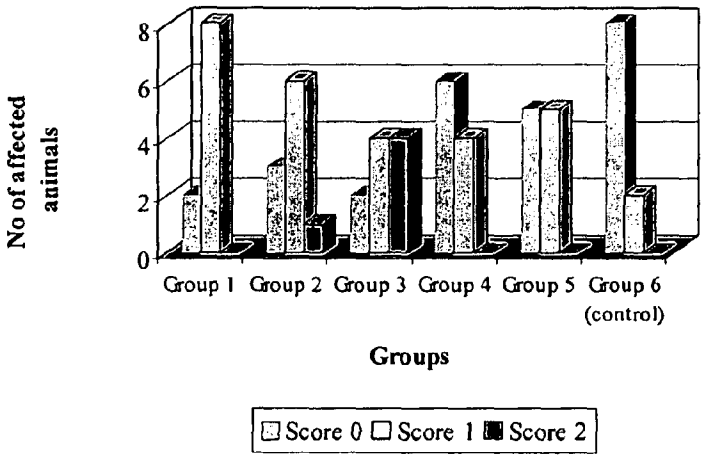


FIGURE 5



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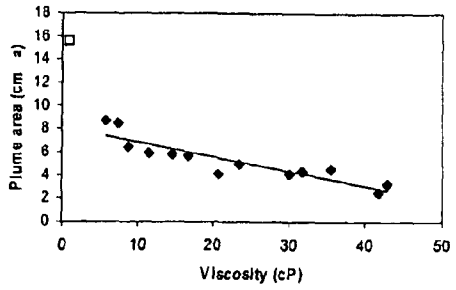

FIGURE 7

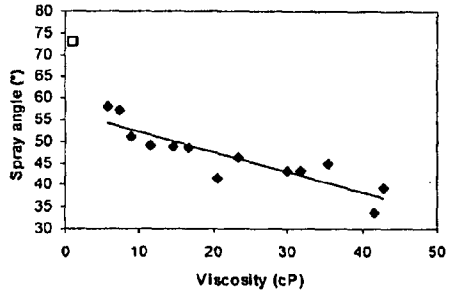

FIGURE 8

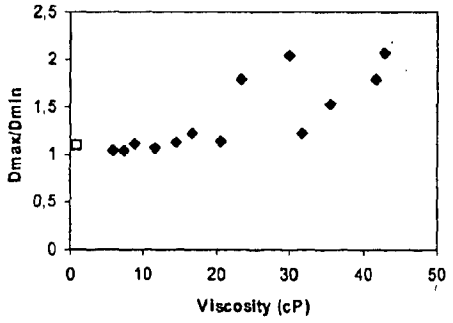

FIGURE 9

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(54) **Title**: PHARMACEUTICAL SOLUTIONS AND METHOD FOR SOLUBILIZING THERAPEUTIC AGENTS

(57) **Abstract**: Pharmaceutical solutions containing hydrophobic or lipophilic therapeutic agents and methods for producing the same are provided. Pharmaceutical solutions of the invention are produced by dissolving the therapeutic agent in one or more tocopherols or tocotrienols and one or more alcohols or glycols. These solutions are used to produce pharmaceutical compositions.

WO 2009/120933 A2

PHARMACEUTICAL SOLUTIONS AND METHOD FOR SOLUBILIZING THERAPEUTIC AGENTS

This patent application claims the benefit of priority from U.S. Application Serial No. 61/040,281, filed March 28, 2008, teachings of which are herein incorporated by reference in their entirety.

Background of the Invention

A vast number of potential therapeutic agents are discovered each year, many of which are water insoluble or poorly water soluble. For such hydrophobic compounds, direct injection may be impossible or highly dangerous, and can result in hemolysis, phlebitis, hypersensitivity, organ failure and/or death. Such compounds are termed by pharmacists as "lipophilic", "hydrophobic", or in their most insoluble form, "amphiphobic".

A few examples of therapeutic agents in these categories are ibuprofen, diazepam, griseofulvin, cyclosporin, cortisone, proleukin, etoposide and paclitaxel. (Kagkadis et al. *PDA J. Pharm. Sci. Tech.* 1996 50(5):317-323; Dardel *Anaesth. Scand.* 1976 20:221-24; Sweetana and Akers *PDA J. Pharm. Sci. Tech.* 1996 50(5):330-342).

Administration of chemotherapeutic agents is particularly problematic. Most of these agents are poorly soluble and thus are difficult to deliver in aqueous solvents and to supply at therapeutically effective levels. Further, water-soluble, chemotherapeutic agents are generally taken up by both cancer and non-cancer cells, making such agents non-specific and oftentimes unacceptably toxic.

For therapeutic agents that cannot be formulated as an aqueous solution, emulsions have oftentimes provided a cost-effective and therapeutically acceptable alternative. However, it is difficult to render emulsions sterile and/or

endotoxin free for intravenous injection. Oils typically used for pharmaceutical emulsions include saponifiable oils from the family of triglycerides, for example, soybean oil, sesame seed oil, cottonseed oil, safflower oil and the like (Hansrani, et al. *J. Parenter. Sci. Technol.* 1983 37:145-150). One or more surfactants are used to stabilize the emulsion, and excipients are added to render the emulsion more biocompatible, stable and less toxic. Lecithin from egg yolks or soybeans is a commonly used surfactant. Sterile manufacturing can be accomplished by sterilization of all the components before manufacture, followed by aseptic technique in all stages of manufacture. Improved ease of manufacture and assurance of sterility is obtained by terminal sterilization following sanitary manufacture, either by heat or by filtration. However, terminal sterilization by heat or filtration treatments is not suitable for all emulsions.

Vitamin E emulsions have been disclosed. For example, injectable vitamin E emulsions are described by Hidiroglou and Karpinski (*Brit. J. Nutrit.* 1988 59:509-518) for dietary supplementation in sheep and for research on the pharmacokinetics of vitamin E and its derivatives. An injectable form of vitamin E for mice was prepared by Kato et al. (*Chem. Pharm. Bull.* 1993 41(3):599-604). Micellar solutions were formulated with TWEEN 80, BRIJ 58 and HCO-60. Isopropanol was used as a co-solvent, and was then removed by vacuum evaporation; the residual oil glass was then taken up in water with vortexing as a micellar suspension. An emulsion was also prepared by dissolving vitamin E with soy phosphatidycholine (lecithin) and soybean oil. Water was added and the emulsion prepared with sonication. Ethanol-free emulsions of alpha-tocopherol, stabilized by biocompatible surfactants, as a vehicle or carrier for

therapeutic drugs is also disclosed in U.S. Patent Nos. 6,667,048 and 6,660,286.

E-Ferol, a vitamin E emulsion for vitamin E supplementation and therapy in neonates was also disclosed by Alade et al. (*Pediatrics* (1986) 77(4):593-597). The surfactant mixture used to emulsify the 25 mg/mL vitamin E in E-Ferol was composed of 9% TWEEN 80 and 1% TWEEN 20. However, this supplement was not safe.

An alternative means of solubilizing low solubility compounds is direct solubilization in a non-aqueous milieu, for example, alcohols (such as ethanol), dimethylsulfoxide, and/or triacetin. For example, WO 95/11039 describes the use of vitamin E (100 mg), lecithin (20 mg), ethanol (100 mg) and EUTANOL (500 mg) as an injectable formulation of the immunosuppressant molecule cyclosporine (50 mg). U.S. Patent No. 5,689,846 discloses various alcohol solutions of paclitaxel. U.S. Patent No. 5,573,781 discloses the dissolution of paclitaxel in ethanol, butanol and hexanol and an increase in the antitumor activity of paclitaxel when delivered in butanol and hexanol as compared to ethanol.

WO 95/31217 discloses that tocopherols can be used as solvents and/or emulsifiers of drugs that are substantially insoluble in water, in particular for the preparation of topical formulations. The use of vitamin E-TPGS as an emulsifier in formulations containing high levels of α-tocopherol is mentioned and formulations for topical administration composed of a lipid layer (α-tocopherol), the drug and vitamin E-TPGS as an emulsifier in quantities of less than 25% w/w of the formulation.

WO 97/03651 discloses lipid vehicle drug delivery compositions that contain at least five ingredients: a therapeutic drug, vitamin E, an oil in which the drug and vitamin E are dissolved, a stabilizer (either phospholipid,

a lecithin, or a poloxamer which is a polyoxyethylene-polyoxypropylene copolymer) and water.

Similarly, U.S. Patent No. 6,962,691 teaches topical compositions composed of at least ten ingredients: alendronate sodium, povidone, povidone vinyl acetate, vitamin E, menthol, dimethyl isosorbide, acetone, ethanol, tetrafluroroethane and, dichlorodifluoromethane.

U.S. Patent No. 4,393,073 also suggests vitamin E as an active ingredient in pharmaceutical compositions containing ethanol.

Summary of the Invention

An aspect of the present invention relates to a pharmaceutical solution comprising a therapeutic agent dissolved in one or more natural or synthetic tocopherols or tocotrienols, or any combination thereof and one or more alcohols or glycols, or any combinations thereof. In some embodiments, the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w) and the alcohol(s) and/or glycol(s) is in an amount from about 1% to about 70% (w/w).

Another aspect of the present invention relates to methods for producing these pharmaceutical solutions.

Another aspect of the present invention relates to methods of treatment of a patient with these pharmaceutical solutions.

Detailed Description of the Invention

The present invention is directed to the use of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents for solubilizing therapeutic agents, in particular hydrophobic or lipophilic therapeutic agents. Advantageously, the resulting pharmaceutical solution is not

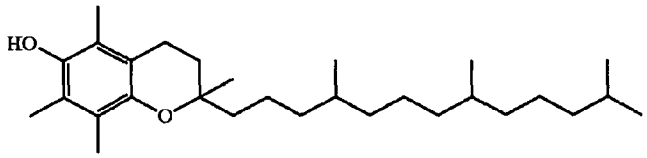
an emulsion or vesicle, and can be used directly in the production of pharmaceutical compositions. Moreover, the combination of a tocopherol and/or a tocotrienol and an alcohol and/or glycol is much less irritating to the skin and/or mucous membranes than pure alcohol solutions and generally provides higher loading of a therapeutic agent than emulsions, liposomes, encapsulations, or cyclodextrins.

A solution in the context of the present invention is a homogeneous mixture composed of three or more substances. In such a mixture, a solute is dissolved in another substance, known as a solvent. In accordance with the present invention, a pharmaceutical solution is formed by dissolving a therapeutic agent in a tocopherol and/or a tocotrienol and an alcohol and/or glycol as solvents. In one embodiment of the present invention, the therapeutic agent is dissolved completely in the tocopherol and/or a tocotrienol and the alcohol and/or glycol solvents. In another embodiment of the present invention, the therapeutic agent may not be completely solubilized and thus is partially dissolved in the tocopherol and/or a tocotrienol and the alcohol and/or glycol solvents. In this embodiment, particulates of therapeutic agent may be present in the pharmaceutical solution. The resulting pharmaceutical solutions of either embodiment can be used in a variety of pharmaceutical compositions with various modes of administration.

The combination of tocopherol and/or a tocotrienol and alcohol and/or glycol is also useful in solubilizing at least in part amphiphobic therapeutic agents. In this embodiment, the solution acts as a transport phase through partial solubilization to increase the bioavailability of the amphiphobic therapeutic agent from a finely divided suspension of the agent.

Tocopherols and/or tocotrienols for use in accordance with the present invention include a family of natural and

synthetic compounds, also known by the generic names tocols or vitamin E. Alpha-tocopherol is the most abundant and active form of this family of compounds, and it has the following chemical structure:



Other members of this family include beta-, gamma-, and delta-tocopherol, alpha-, beta-, gamma-, and delta-tocotrienols, tocopsoralen, alpha-tocopherol derivatives and/or analogs such as tocopherol acetate, phosphate, succinate, nicotinate and linoleate, as well as isomers thereof and esters thereof. Use of the phrase tocopherol(s) and/or tocotrienol(s) herein is meant to be inclusive of any member of this family alone or in combination. In one embodiment of the present invention the tocopherol(s) and/or tocotrienol(s) employed is alpha-tocopherol.

Examples of alcohol(s) for use in the present invention include, but are not limited to ethanol, propyl alcohol, butyl alcohol, pentanol, benzyl alcohol, and any isomers thereof, and any combinations thereof. Examples of glycols for use in the present invention include, but are not limited to ethylene glycol, propylene glycol, butylene glycol, pentylene glycol, and any isomers thereof, and any combinations thereof. In one embodiment of the present invention the alcohol is ethanol (ethyl alcohol). Preferred is use of an ethanol that is biocompatible in the sense that it is not toxic and does not cause any physiological or pharmacological effects. In this regard, the ethanol is desirably 180 to 200 proof ethanol, *i.e.*, in the range of 90-100% ethanol. Advantageously, diluting a tocopherol or tocotrienol with an alcohol or glycol dramatically reduces

the inherent viscosity of the tocopherol or tocotrienol thereby allowing for generation of sprayable formulations.

In accordance with the present invention, solutions of one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols are used in the solubilization of hydrophobic or lipophilic therapeutic agents thereby providing increased bioavailability of the therapeutic agent. In some embodiments, the tocopherol(s) and/or tocotrienol(s) is in an amount from about 30% to about 99% (w/w) and the alcohol(s) and/or glycol(s) is in an amount about 1% to about 70% (w/w).

As a non-limiting example, the solubility of Diazepam at room temperature is less than or equal to 6.67% in 190 proof ethanol. However, combining tocopherol and ethanol has been found to provide solubility of the Diazepam approaching the 10% level. By way of illustration, at 70% tocopherol:30% ethanol (200 proof), Diazepam is soluble to greater than or equal to 8% and at 95% tocopherol:5% ethanol (200 proof), Diazepam is soluble at greater than or equal to 9%.

Accordingly, preferred for some embodiments is that alpha-tocopherol and ethanol constitute 60% to 99% and 1% to 40%, respectively, of the pharmaceutical solution. In other embodiments, the alpha-tocopherol and ethanol constitute approximately 70% to 90% and 10% to 30%, respectively, of the pharmaceutical solution. In still other embodiments, the tocopherol and ethanol are used at ratios of approximately 95:5, 90:10, 85:15, 80-20, 75:25, 70:30, 65:35, or 60:40, respectively.

Pharmaceutical solutions of the present invention can be produced by dissolving any difficult to solubilize therapeutic agent (*i.e.*, hydrophobic or lipophilic therapeutic agents) in one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols as pharmaceutically acceptable solvents. By therapeutic agents

it is meant to be inclusive of, but is not limited to, small organic molecules, therapeutic peptides, non-peptides and nucleotides. Hydrophobic derivatives of water-soluble molecules such as lipid conjugates/prodrugs are also within the scope of therapeutic agents.

Exemplary hydrophobic or lipophilic therapeutic agents which can be solubilized in accordance with the present invention include, but are in no way limited to, steroids such as Dexamethasone, 17-beta-Estradiol; benzodiazepenes such as Diazepam, alpraxolam, bromazepam, chlordiazepoxidem, clonazepam, estazolam, flunitrazepam, flurazepam, lorazepam, lormetazepam, mexazolam, nitrazepam, oxazepam, temazepam, and triazolam; Rapamycin and analogues; Taxol (paclitaxel) and analogues; Actinomycin D; Prostaglandins (PGE1); Vitamin A; Probucol; Batimastat; Statins (HMG-CoA Reductase Inhibitors; Trapidil (and other anti-proliferative Growth Factor Inhibitors); Cytochalasin B; and microtubule binding agents such as epothilones, elutherobin and discodermolide. Pharmaceutical solutions and compositions formulated from the solutions may comprise one or more therapeutic agents in solution. Further, pharmaceutical compositions formulated from the pharmaceutical solutions of the present invention may further comprise one or more additional therapeutic agents in encapsulated or micronized (not dissolved) forms.

The present invention also provides for use of a combination of tocopherol and/or a tocotrienol and alcohol and/or glycol to solubilize at least in part amphiphobic therapeutic agents. In this embodiment, the solution acts as a transport phase through partial solubilization to increase the bioavailability of the amphiphobic therapeutic agent from a finely divided suspension of the agent.

Pharmaceutical solutions of the invention can be formulated into pharmaceutical compositions for administration to animals, preferably humans, via

intravascular, oral, intramuscular, cutaneous and subcutaneous routes. Specifically, pharmaceutical compositions of the present invention can be administered by any of the following nonlimiting exemplary routes, intraabdominal, intraarterial, intraarticular, intracapsular, intracervical, intracranial, intraductal, intradural, intralesional, intralocular, intralumbar, intramural, intranasal, intraocular, intraoperative, intraparietal, intraperitoneal, intrapleural, intrapulmonary, intraspinal, intrathoracic, intratracheal, intratympanic, intrauterine, and intraventricular. The pharmaceutical compositions of the present invention can be nebulized using mechanical nebulizers or suitable aerosol propellants which are known in the art for pulmonary delivery of lipophilic compounds. The most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular therapeutic agent which is being used.

Pharmaceutical solutions of the instant invention are particularly useful in formulations to be administered to mucosal membranes, i.e. the nasal mucosa or lungs of a subject by any suitable means. For many therapeutic agents, administration via the nasal route provides for faster attainment of therapeutic levels of the therapeutic agent systemically. However, many therapeutic agents are so slightly soluble in water that a therapeutically effective amount cannot be dissolved in a volume of aqueous solvent that is amenable to application to a mucosal membrane. Use of a pharmaceutical solution of the present invention, however, provides for improved ability to dissolve hydrophilic and lipophilic therapeutic agents, thus providing a useful delivery system for administration of such agents to one or more mucosal membranes, including the nasal mucosal membranes. Such solutions can be administered

via, for example, a metered dose inhaler or nebulizer, or in a mist sprayer.

The instant pharmaceutical solutions comprising a therapeutic agent, one or more tocopherols and/or tocotrienols and one or more alcohols and/or glycols can also be formulated into a pharmaceutical composition for injection by combining the instant pharmaceutical solution with, *e.g.*, saline solution or water and a Vitamin E solubilizing agent such as Cremophor. Such pharmaceutical compositions may further contain other pharmaceutically acceptable additives such as, but not limited to, acidifying, alkalizing, buffering, chelating, complexing and solubilizing agents, antioxidants and antimicrobial preservatives, penetration enhancers, humectants, suspending and/or viscosity modifying agents, tonicity and wetting or other biocompatible materials.

For oral therapeutic administration, the instant pharmaceutical solutions can be combined with one or more carriers and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, foods and the like. Such compositions and preparations should contain at least 0.1% of active compound. Tablets, troches, pills, capsules, and the like can also contain one or more of the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. The above listing is merely representative and one skilled in the art could envision other binders, excipients, sweetening agents and the like. When the unit dosage form is a capsule, it can

contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials can be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules can be coated with gelatin, wax, shellac or sugar and the like.

A syrup or elixir can contain the instant pharmaceutical solution, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be substantially non-toxic in the amounts employed.

In addition, the instant pharmaceutical solution can be formulated into sustained-release preparations and devices including, but not limited to, those relying on osmotic pressures to obtain a desired release profile.

Formulations suitable for parenteral administration can be aqueous or non-aqueous injection solutions, which are generally isotonic with the blood of the intended recipient. These preparations can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions can include suspending agents and thickening agents. The formulations can be presented in unit\dose or multi-dose containers, for example sealed ampoules and vials.

Formulations suitable for topical application to the skin can take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, oil or other pharmaceutical formulation which accomplishes direct contact between the therapeutic agent and the skin. Topical formulations can also be prepared which are suitable for occlusive therapy.

Formulations in the forms of ointments, creams, lotions and pastes can generally have carriers in the forms of

oleaginous bases (*e.g.*, White Petrolatum and White Ointment); absorption bases formed by adding a water-in-oil emulsifying agent to an oleaginous base (*e.g.*, Hydrophilic Petrolatum, AQUABASE, and AQUAPHOR); water-in-oil emulsion bases, prepared by adding water to an absorption base (*e.g.*, HYDROCREAM, EUCERIN, NIVEA, and Cold Cream); oil-in-water emulsion bases (*e.g.*, DERMABASE, UNIBASE, VELVACHOL, and hydrophilic ointment); and water soluble bases (*e.g.*, polyethylene glycol ointment such as PEG 400-600 G or PEG 3350-400 G). Suitable carriers to produce a spray, gel, or aerosol are well-known in the art.

A carrier for topical application can also contain additional ingredients such as other carriers, moisturizers, penetration enhancers, humectants, emollients, dispersants, radiation blocking compounds, cleansing agents, anti-infective agents (*e.g.*, antibiotics, fungicides, scabicides, or pediculicides), anti-inflammatory agents (*e.g.*, corticosteroids), keratolytics (agents that soften, loosen, and facilitate exfoliation of the squamous cells of the epidermis), as well as other suitable materials that do not have a significant adverse effect on the activity of the topical composition. Additional ingredients can include, for example a sodium acid phosphate moisturizer, witch hazel extract, glycerine humectant, apricot kernal oil emollient, or corn oil dispersant. Other materials which can optionally be included in a topical composition include inositol or B-complex vitamins.

Formulations suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration can also be delivered by iontophoresis (*see*, for example, *Pharmaceutical Research* 3 (6):318 (1986)) and typically take the form of an optionally

buffered aqueous solution. Formulations of the present invention are also suitable for delivery via microneedle delivery technology for cutaneous administration.

What is claimed is:

1. A pharmaceutical solution comprising one or more therapeutic agents dissolved in one or more tocopherols or tocotrienols and one or more alcohols or glycols.

2. The pharmaceutical solution of claim 1 wherein the one or more tocopherol or tocotrienol is 30% to 99% and the one or more alcohol or glycol is 1% to 70% of the volume of the pharmaceutical solution.

3. The pharmaceutical solution of claim 1 wherein the one or more tocopherols or tocotrienols is alpha-tocopherol.

4. The pharmaceutical solution of claim 1 wherein the one or more alcohols or glycols is ethanol.

5. A pharmaceutical solution consisting of a therapeutic agent dissolved in alpha-tocopherol and ethanol.

6. A pharmaceutical composition comprising the pharmaceutical solution of any of claims 1 through 5.

7. The pharmaceutical composition of claim 6 further comprising one or more additional therapeutic agents in encapsulated or micronized forms.

8. The pharmaceutical solution of any of claims 1 through 5 wherein the one or more therapeutic agents is partially dissolved in one or more tocopherols or tocotrienols and one or more alcohols or glycols.

9. A method for solubilizing a therapeutic agent comprising dissolving a therapeutic agent in one or more

tocopherols or tocotrienols and one or more alcohols or glycols to form a pharmaceutical solution.

10. The method of claim 9, wherein the one or more tocopherol or tocotrienol is 30% to 99% and the one or more alcohol or glycol is 1% to 70% of the volume of the pharmaceutical solution.

11. The method of claim 9 wherein the one or more tocopherols or tocotrienols is alpha-tocopherol.

12. The method of claim 9 wherein the one or more alcohols or glycols is ethanol.

13. The method of any of claims 9 through 12 wherein the therapeutic agent is partially dissolved in one or more tocopherols or tocotrienols and one or more alcohols or glycols.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
AEGIS1210-13WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2011/056735	**18 OCTOBER 2011 (18.10.2011)**	18 OCTOBER 2010 (18.10.2010)

Applicant

AEGIS THERAPEUTICS, LLC et al

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of :
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☒ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figure is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/056735

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-18
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 11-18 pertain to methods for treatment of the human by therapy and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

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

3. ☐ 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 and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/056735

A. CLASSIFICATION OF SUBJECT MATTER

A61K 38/08(2006.01)i, A61K 38/04(2006.01)i, C07K 7/06(2006.01)i, C07K 1/04(2006.01)i, A61K 47/42(2006.01)i, A61K 47/48(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 38/08; A61K 31/70; A61K 31/5513; A61K 38/28; A61K 38/02; A61K 31/722; A61K 38/21

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

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), PubMed, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008-0299079 A1 (ELIAS MEEZAN et al.) 04 December 2008 See abstract; paragraphs [0010], [0053], [0054], [0058], [0060], [0065], [0069], [0072], [0109].	1-10
X A	US 2010-0209485 A1 (EDWARD T. MAGGIO) 19 August 2010 See abstract; paragraphs [0038], [0039], [0044], [0099], [0110] and claims.	1-6,9,10 7,8
A	US 2009-0258865 A1 (STEVE CARTT et al.) 15 October 2009 See abstract; paragraph [0138].	1-10
A	US 2010-0203119 A1 (MICHAEL LEANE et al.) 12 August 2010 See paragraphs [0060], [0061]; claims 1, 10.	1-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent 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 citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 JUNE 2012 (19.06.2012)	**20 JUNE 2012 (20.06.2012)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
PARK, JEONG UNG
Telephone No. 82-42-481-8131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008-0299079 A1	04.12.2008	US 2006-045869 A1	02.03.2006
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		US 2011-0020435 A1	27.01.2011
		US 7425542 B2	16.09.2008
		US 7998927 B2	16.08.2011
		US 8076290 B2	13.12.2011
		US 8084022 B2	27.12.2011
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		US 2006-0115525 A1	01.06.2006
		WO 2004-100941 A1	25.11.2004

Electronic Acknowledgement Receipt

EFS ID:	17255197
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Heather Glasson
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.201
Receipt Date:	29-OCT-2013
Filing Date:	27-MAR-2009
Time Stamp:	14:39:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	35401_716_201_trans_102913.pdf	35692 b7d87974ea248a12700b8db0e69d21e0e2e06947	no	4

Warnings:

Information:

2	Information Disclosure Statement (IDS) Form (SB08)	35401_716_201_SB08_102913.pdf	151156 3a4d18c8f6c9c85c4482d752812243d6fd522aae	no	9
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3	Foreign Reference	EP0396777A1.pdf	873011 e2f535a7bb3ea352e44aca0c6b7e7f244db37fbc	no	15
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4	Foreign Reference	EP1417972A1.pdf	774989 59fc260877276d1763a836d5e1b8b9771ef118eb	no	13
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5	Foreign Reference	JP01_151528.pdf	517069 330960b2469e006c48e9691d7de3e44a9e29028d	no	9
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6	Foreign Reference	WO1991_19481.pdf	2850242 0bb49ff01434e0f6e9fa1a18e6cf63f1b121dba7	no	34
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7	Foreign Reference	WO1994_05262A1.pdf	2689740 f46c701d7198537f7f1e244e00b0a56f964b9d0c	no	39
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8	Foreign Reference	WO1995_000151A1.pdf	2327882 8f391fc4f9e73aca72d7664324f7c48bf53a7a7e	no	28
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9	Foreign Reference	WO1995_31217A1.pdf	2202508 aa5ef696d60c5829cbb84d382adfc72dcf63ad02	no	40
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10	Foreign Reference	WO2000_001390A1.pdf	1197779 ac8ab9276ed630bed4bc9dcceba84b106c19bae2	no	18

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11	Foreign Reference	WO2003_055464A1.pdf	2720932 49d8ee9d6ae4535d3e2c8206b167898ed8721c60	no	32
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12	Foreign Reference	WO2005_018565A2.pdf	7063693 28cf77de737b60765a206f1fa94dc8b39c164c91	no	77
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13	Foreign Reference	WO2008_027395.pdf	7491199 bfdfd7ede94206a36c21b9a43a31649d13fa3ff6	no	90
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14	Foreign Reference	WO2009_120933A2.pdf	935952 0fdd7185bfc368e43863aef6a5ae09e105e71cbc	no	16
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15	Non Patent Literature	Ahsan_2003_Effects_of_the_permeability_.pdf	1535343 5d16a5fa21a63adb21d5f5adadd8f8130668e404	no	8
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16	Non Patent Literature	Ahsan_2003_Sucrose_cocoate_a_component_.pdf	1362904 6d9a241cb45417f8f7a1e59fcd386df428f04f11	no	9
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17	Non Patent Literature	Albert_1975_Pharmacokinetics_of_diphenhydramine_.pdf	1209170 77257c5f837bbd28b55bc500526c4986bfcf5cf9	no	12
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18	Non Patent Literature	Arnold_2004_Correlation_of_tetradecylmaltoside_.pdf	1727509 3e39cb0bbed13729689c3f15680bd413c6c00457	no	9
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19	Non Patent Literature	AU2009228093_OA_19JUL2013.pdf	519659 [illegible]c4a6	no	2

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20	Non Patent Literature	Beam_1977_Blood_Brain_Cerebrospinal_Fluid_Concentrations.pdf	2259141 a3b479b98a93cdb985854969b594871c4e3fe76b	no	7
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21	Non Patent Literature	Bhairi_2001_A_guide_to_the_properties_.pdf	2015393 b406602bf75e3a58dd93f78db60c2524ea9bd0ca	no	43
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22	Non Patent Literature	Birkett_1991_Bioavailability_and_First_Pass_Clearance.pdf	609661 4f6ed2846f2aae3bd554bd82d9246d2a672dfc5b	no	3
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23	Non Patent Literature	Birkett_1990_How_Drugs_are_Cleared_by_the_Liver.pdf	279116 4336e122ade80f801d3e5a1a5bec2330ef524310	no	2
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24	Non Patent Literature	Castro_2005_Ecologically_safe_alkyl_.pdf	1914785 9bca51dd2683c52f685dc92dedf5e58ceb5192d7	no	15
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25	Non Patent Literature	Chavanpatil_2005_Nasal_Drug_Delivery_of_Sumatriptan_Succinate.pdf	366815 bd3e67dc254f8a6364699da76296548b10e3820a	no	3
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26	Non Patent Literature	Chen_2005_Peptide_Drug_Permeation.pdf	788307 7b90690e6f05f512ae7ca08083ce152216e2d3e8	no	5
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27	Non Patent Literature	Chen_Quay_2009_Identification_of_tight_junction_Document_.pdf	2356198 9160ce58454bf530803a13e90230208a6f0eded7	no	14
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28	Non Patent Literature	Chiou_1989_Improvement_of_Systemic_Absorption_of_Insulin.pdf	3054624 [illegible]3f0b	no	4

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29	Non Patent Literature	Chiou_1989_Systemic_Delivery_of_Insulin_Through_Eyes.pdf	4898377 eb6cca4b8c8bb6bf099bc342d0be6950d4e87225	no	13
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30	Non Patent Literature	Communication_from_CN_Pat_Office_AO_.pdf	296944 0750d813ac6a386f4740ac95ee02a7ab083dff0c	no	3
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31	Non Patent Literature	Davis_2003_Absorption_Enhancers_for_Nasal_Drug_Delivery.pdf	3814193 bef397ce163fc3b7fc1b1efa939bc44a47c38ce8	no	22
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33	Non Patent Literature	Definition_of_encephalin_2012-09-13_at_the_medical-dictionary_thefreedictionary_.pdf	156482 7d55a3ba8de6b89b96ded49242eb65277911be31	no	1
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34	Non Patent Literature	Definition_of_pilus_2013_.pdf	203899 5f6af85616b6ea13362cff6e447283bc2793189d	no	2
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35	Non Patent Literature	Definition_of_villus_2013_.pdf	301150 e8ea88a821be822e292b132a22702c96709b0dfc	no	2
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36	Non Patent Literature	Drewe_1993_Enteral_absorption_of_octreotide.pdf	999024 49487f200a45375ea539b8094c05e5bc6e3ea1a3	no	6
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42	Non Patent Literature	Fricker_1996_Permeation_enhancement_of_octreotide_.pdf	2640153 a3635c6911c8f61fc57bebeb211280bd4040afeb	no	7
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50	Non Patent Literature	Katzung_1998_Basic_and_Clinical_Pharmacology_7th_Edition.pdf	2862877 4e361efe938493c47b31772eae64b49d59c591d6	no	18
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51	Non Patent Literature	Lacy_1999_Drug_Information_Handbook_7th_Edition.pdf	1230625 be208ada19d8b12c08c8b24d13bea6fc305ef7f5	no	6
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52	Non Patent Literature	Lahat_1998_Intranasal_midazolam_for_childhood_.pdf	228935 e877e17f3c649d607af1440902bd2a5bb6373ca3	no	1
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53	Non Patent Literature	Lehninger_1982_Principles_of_Biochemistry_with_an_Extended_Discussion.pdf	1001727 fbcbb5b237aefcb619238f1e9f9198558d0406da	no	4
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59	Non Patent Literature	Murakami_1992_Assessment_of_Enhancing_Ability_of_Medium-Chain.pdf	3431343 86086d9c5ba3e65105b68ea692c78bf1c7dd0209	no	11
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Information:					
		Total Files Size (in bytes):	106492478		

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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Steve Cartt *et al.*	Group Art Unit: 1612
Serial Number: 12/413,439	Examiner: Milligan, Adam C.
Filing Date: March 27, 2009	**CONFIRMATION NO: 9049**
Title: ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS	

FILED ELECTRONICALLY ON: October 29, 2013

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

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Madam:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

A. ☒ *37 CFR §1.97(b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☒ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

B. ☐ *37 CFR §1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97(e) provided concurrently herewith;

-- OR --

☐ a fee of $180.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR §1.97(d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in §1.97(e);

-- AND --

ii. a fee of $180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97(e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e)(1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98(a)(2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☒ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☒ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner, for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 35401-716.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: October 25, 2013

By: /Matthew V. Grumbling/
Matthew V. Grumbling
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Customer No. 021971

Electronic Acknowledgement Receipt

EFS ID:	17255648
Application Number:	12413439
International Application Number:	
Confirmation Number:	9049
Title of Invention:	ADMINISTRATION OF BENZODIAZEPINE COMPOSITIONS
First Named Inventor/Applicant Name:	Steve Cartt
Customer Number:	21971
Filer:	Matthew Virgil Grumbling/Heather Glasson
Filer Authorized By:	Matthew Virgil Grumbling
Attorney Docket Number:	35401-716.201
Receipt Date:	29-OCT-2013
Filing Date:	27-MAR-2009
Time Stamp:	14:55:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Olesen_2005_The_headaches_.pdf	101788 4591cde660de920ed5f8898adaa8f8d0cacd46c4	no	1

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2	Non Patent Literature	Paulsson_2001_Controlled_Drug_Release_from_Gels.pdf	1286706 1330cef474c9a60a9e9d5e4c63590d4809b36f86	no	7
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3	Non Patent Literature	Phillips_2001_The_challenge_of_gene_.pdf	932670 82bfd5f4b0e48da7c9e29358c056cc9428cd227a	no	6
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4	Non Patent Literature	Pillion_2002_Synthetic_long_chain_.pdf	1254954 398ddc1c00f87d724d5054656de9d03f87114f30	no	7
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5	Non Patent Literature	Pillion_1991_Systemic_Absorption_of_Insulin_Delivered_Topically.pdf	6618981 9f6d28a2bab26cdd4bf6816e32433680b5cfb64b	no	7
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8	Non Patent Literature	Salzman_1985_Intranasal_Aerosolized_Insulin.pdf	5558987 dcd80fc72ce3e328242f72a45067bb3764ae848e	no	7
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9	Non Patent Literature	Sanders_1986_Pharmacokinetics_of_ergotamine_.pdf	718184 334c50f2be8bc2c4bf2b9b14db4cf9b215db9ad0	no	4
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10	Non Patent Literature	Shim_1993_Administration_Route_Dependent_.pdf	2088442 98582d18d2db3b79db2a3f9772e597b795cc3106	no	17
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Information:					