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SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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TÍTULO SOLICITADO: COMPOSICIONES PARA LA TRANSMISIÓN
TRANSMUCOSA ORAL DE LA METFORMINA

PUBLICACIÓN: Gaceta 591 de 30 de Abril de 2008, número de
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SOLICITANTE: GENEREX PHARMACEUTICALS INC.

PRIORIDAD: US 60/666,475 de 30/03/2005

APODERADO: DILIA MARÍA RODRÍGUEZ D'ALEMÁN

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito ratificar los argumentos que permitirán demostrar que la solicitud de la referencia, que reivindica una composición de absorción transmucosal oral que consiste en un agente farmacéutico que corresponde a Metformina y un acelerador de absorción, en forma de tabletas de goma de mascar, cápsulas o pastillas, incumple los requisitos de patentabilidad

establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario:

- ❖ La publicación internacional WO 99/42086 "ORALLY ADMINISTRABLE IMMEDIATE-RELEASE AND PROLONGED-RELEASE GALENIC FORM COMPRISING AN ABSORPTION-PROMOTING AGENT AND USE OF THIS ABSORPTION-PROMOTING AGENT" revela formulaciones de administración oral que contienen metformina, específicamente hidrocloreto de metformina en combinación con diversos compuestos del mismo tipo que los mencionados por la solicitud colombiana en trámite y que a su vez tienen la misma funcionalidad de "mejoradores o aceleradores de la absorción" (como por ejemplo monolaurato, mono-oleato, ácidos grasos con 18 átomos de carbono, entre otros) que permiten la mejorada absorción por vía transmembrana o paracelular de dicho activo, demostrando la ausencia de novedad de la reivindicación 1 y de nivel inventivo del resto de reivindicaciones de la solicitud en trámite.
- ❖ La publicación internacional WO 99/47125 "CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE" revela explícitamente formulaciones en tabletas de liberación controlada con un núcleo que comprende un agente antihiper glucémico como hidrocloreto metformina, en combinación con diversos compuestos que tienen la funcionalidad de "mejoradores o aceleradores de la absorción" como el laurilsulfato de sodio; así mismo, es importante resaltar que el intervalo de cantidades de principio activo (metformina) en esta anterioridad, comprende a los intervalos mencionados por la solicitud colombiana, lo que demuestra la ausencia de novedad de la reivindicación 1 y de nivel inventivo del resto de reivindicaciones de la solicitud en trámite.
- ❖ La publicación internacional WO 02/36100 "CONTROLLED RELEASE METFORMIN COMPOSITIONS" revela también formulaciones sólidas orales de liberación controlada que contienen metformina o su sal clorhidrato en cantidades entre 50-98%, junto con otros excipientes del mismo tipo que los mencionados por la solicitud colombiana en trámite y que a su vez tienen la misma funcionalidad de "mejoradores o aceleradores de la absorción" (sales biliares, ácido oléico, o lauril sulfato de sodio), nuevamente demostrando la

ausencia de novedad de la reivindicación 1 y de nivel inventivo del resto de reivindicaciones de la solicitud en trámite.

- ❖ Finalmente la publicación internacional WO 91/01132 "CHEWING GUM COMPOSITION WITH ACCELERATED, CONTROLLED RELEASE OF ACTIVE AGENTS" revela formulaciones masticables tipo goma de mascar, que son formulaciones utilizadas con anterioridad para la absorción del principio activo a través de la mucosa bucal, en donde el éxito de dicha formulación depende de la adición de agentes "mejoradores o aceleradores de la absorción" tal y como lo expone la solicitud colombiana en trámite. Además, ésta anterioridad menciona que este tipo de formulaciones son ideales para compuestos del tipo guanidas o biguanidas, a la que corresponde precisamente la metformina, principio activo utilizado en la formulación de la solicitud colombiana en trámite. En otras palabras esta anterioridad demuestra que este tipo de formulaciones son convencionales, y la inclusión de cualquier principio activo en éstas, se resume a aplicar los ensayos de preformulación y formulación pertinentes para asegurar la calidad, seguridad, eficiencia y eficacia de este tipo de medicamentos.

II. COMPLEMENTO DE INFORMACION.

En relación con los argumentos expuestos anteriormente, existen otras publicaciones que evidencian el uso de "mejoradores de la absorción" en formulaciones del mismo tipo que las reivindicadas por la solicitud colombiana en trámite, veamos:

- La patente Americana US 6,432,383 publicada el 13 de Agosto de 2002 y titulada "METHOD FOR ADMINISTERING INSULIN" revela una formulación micelar que comprende insulina y al menos un mejorador de la absorción como por ejemplo lecitina, ácido glicólico, ácido hialurónico, ácido láctico, extracto de manzanilla, ácido oléico, glicerina, poliglicerina, lisina, entre muchos otros, en concentración entre 1 y 10% w/w y cuya formulación podría ser una forma masticable apropiada para liberarse a través de la membrana de la mucosa oral :

FIELD OF THE INVENTION

The present invention relates to an improved delivery system for the administration of large-molecule pharmaceuticals, e.g. peptidic drugs, vaccines and hormones. In particular it relates to pharmaceuticals which may be administered through the oral and nasal membranes. (...)

formulation, a pharmaceutically acceptable edetate in a concentration of from 1 to 10 wt./wt. % of the total formulation, at least one alkali metal salicylate in a concentration of from 1 to 10 wt./wt. % of the total formulation, and at least one micelle forming compound selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening of primrose oil, trihydroxy oxo cholanylglycine, glycerin, polyglycerin, lysine, polylysine. (...)

5. The method of claim 3, wherein said formulation comprises: insulin, an alkali metal lauryl sulfate, a pharmaceutically acceptable edetate, at least one alkali metal salicylate, and at least one micelle forming compound selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening of primrose oil, trihydroxy oxo cholanylglycine, glycerin, polyglycerin, lysine, polylysine, triolein and mixtures thereof, wherein each of said sulfate, (...)

9. The method of claim 5, wherein said micelle forming compound is lecithin, lecithin in combination with hyaluronic acid, evening of primrose oil or borage oil.

- La publicación internacional WO 98/02187 publicada el 22 de Junio de 1998 y titulada "PHARMACEUTICAL COMPOSITION CONTAINING ACID ADDITION SALT OF BASIC DRUG" revela:

- 1 A pharmaceutical composition formulated for transdermal or transmucosal delivery comprises as an active ingredient a compound of the formula I:



wherein B^+ is a cation of a basic drug and $RCOO^-$ is an anion of (a) an unsaturated or saturated C_8-C_{18} monocarboxylic fatty acid or (b) a bile acid, together with one or more excipients for transdermal or transmucosal delivery. (...)

7 A pharmaceutical composition according to any one of claims 1 to 6 selected from the group consisting of a sublingual tablet, a nasal spray, a buccal tablet and a suppository.

➤ La publicación internacional WO 02/067903 publicada el 06 de Septiembre de 2002 y titulada "COMPOSITIONS AND METHODS OF MANUFACTURE ORAL DISSOLVABLE DOSAGE FORMS" revela:

1. A dissolvable drug-containing dosage-form for use in the transmucosal delivery of a drug to a patient, comprising:

1) a binding agent that is formed into a solid matrix dissolvable in the mouth of a patient;

2) a pharmacologically effective dose of a potent central nervous system affecting drug that can be absorbed through mucosal tissues of the mouth, pharynx, and esophagus, the drug dispersed throughout the solid matrix; and

3) a buffer dispersed throughout the solid matrix, the buffer capable of controlling the pH of the mouth, pharynx, and esophagus to optimize permeation of the drug in order to facilitate transmucosal absorption of the drug;

wherein when the solid matrix dissolves in the mouth of the patient, the pharmacologically effective dose of the drug is released for absorption through mucosal tissues of the mouth, pharynx, and esophagus of the patient.

(...)

40. The drug-containing dosage-form of claim 1, further comprising a permeation enhancer dispersed throughout the solid matrix, the permeation enhancer capable of modifying the permeability of the drug in the mucosal tissue in order to facilitate transmucosal absorption of the drug.

(...)

61. The drug-containing dosage-form of claim 41, further comprising a permeation enhancer held within the drug containment matrix, the permeation enhancer capable of modifying the permeability of the mucosal tissues of the mouth, pharynx, and esophagus towards the drug in order to facilitate transmucosal absorption of the drug.

62. The drug-containing dosage-form of claim 41, wherein the permeation enhancer is selected from the group consisting of a bile salt, a bile salt analog, a bile salt derivative, and mixtures thereof.

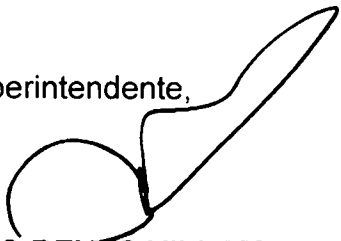
Ahora, si dichos "mejoradores de la absorción" no se mencionan en todos los casos para los mismos tipos de formulaciones o no se encuentran formulados junto a los mismos fármacos reivindicados por la solicitud colombiana en trámite; se puede apreciar con claridad que el uso de dichos "mejoradores de la absorción" son una herramienta versátil y ampliamente utilizada con anterioridad en el estado de la técnica como estrategia tecnológica para facilitar la absorción de cualquier tipo de fármaco a través de mucosas como la mucosa oral, cuando esto sea necesario. Por lo tanto la inclusión de dichos "mejoradores de la absorción", en una formulación para administración oral que contiene metformina para su absorción a través de la mucosa oral, carece por completo de nivel inventivo, puesto que simplemente aplica esta estrategia farmacotécnica reconocida y eficientemente empleada, para solucionar una evidente necesidad de aumentar o mejorar la absorción de metformina en la mucosa oral.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS.

- La patente Americana US 6,432,383 publicada el 13 de Agosto de 2002 y titulada "METHOD FOR ADMINISTERING INSULIN" columnas 1, 3 y capítulo reivindicatorio.
- La publicación internacional WO 98/02187 publicada el 22 de Junio de 1998 y titulada "PHARMACEUTICAL COMPOSITION CONTAINING ACID ADDITION SALT OF BASIC DRUG" capítulo reivindicatorio.
- La publicación internacional WO 02/067903 publicada el 06 de Septiembre de 2002 y titulada "COMPOSITIONS AND METHODS OF MANUFACTURE ORAL DISSOLVABLE DOSAGE FORMS" capítulo reivindicatorio.

Señor Superintendente,



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(12) **United States Patent**
Modi

(10) **Patent No.:** **US 6,432,383 B1**

(45) **Date of Patent:** ***Aug. 13, 2002**

(54) **METHOD FOR ADMINISTERING INSULIN**

WO WO00/47203 8/2000

(75) **Inventor:** **Pankaj Modi, Ancaster (CA)**

OTHER PUBLICATIONS

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(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(52) **U.S. Cl.** **424/43; 424/45; 424/46; 424/434; 424/435; 424/455; 503/303; 503/304; 514/3; 514/4; 514/866; 514/946; 514/947**

(58) **Field of Search** **424/43, 45, 46, 424/434, 435, 455; 514/4, 3, 866, 946, 947; 530/303, 304**

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(57) **ABSTRACT**

A mixed micellar pharmaceutical formulation includes a micellar proteinic pharmaceutical agent, an alkali metal lauryl sulphate, alkali metal salicylate, a pharmaceutically acceptable edetate and at least one absorption enhancing compounds. The absorption enhancing compounds are selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening of primrose oil, trihydroxy oxo cholanyl glycine, glycerin, polyglycerin, lysine, polylysine, triolein and mixtures thereof. The amount of each absorption enhancing compound is present in a concentration of from 1 to 10 wt./wt. % of the total formulation, and the total concentration of absorption enhancing compounds are less than 50 wt./wt. % of the formulation. A method for administering insulin to the buccal mucosa using a metered dose inhaler is also disclosed.

11 Claims, No Drawings

METHOD FOR ADMINISTERING INSULIN

FIELD OF THE INVENTION

The present invention relates to an improved delivery system for the administration of large-molecule pharmaceuticals, e.g. peptidic drugs, vaccines and hormones. In particular it relates to pharmaceuticals which may be administered through the oral and nasal membranes.

BACKGROUND OF THE INVENTION

In spite of significant efforts in academic and commercial laboratories, major breakthroughs in oral peptide and protein formulation have not been achieved. Relatively little progress has been made in reaching the target of safe and effective oral formulations for peptides and proteins. The major barriers to developing oral formulations for proteins and peptides include poor intrinsic permeability, luminal and cellular enzymatic degradation, rapid clearance, and chemical stability in the gastrointestinal (GI) tract. Pharmaceutical approaches to address these barriers, which have been successful with traditional small, organic drug molecules, have not readily translated into effective peptide and protein formulations. Although the challenges are significant, the potential therapeutic benefits remain high especially in the field of diabetes treatment using insulin.

Scientists have explored various administration routes other than the injection for proteins and peptides. These routes include oral, intranasal, rectal, vaginal cavities for the effective delivery of large molecules. Out of the above four mentioned routes oral and nasal cavities have been of greatest interest to scientists. Both the oral and nasal membranes offer advantages over other routes of administration. For example, drugs administered through these membranes have a rapid onset of action, provide therapeutic plasma levels, avoid first pass effect of hepatic metabolism, and avoid exposure of the drug to hostile GI environment. Additional advantages include easy access to the membrane sites so that the drug can be applied, localized and removed easily. Further, there is a good potential for prolonged delivery of large molecules through these membranes.

The oral routes have received far more attention than has the other routes. The sublingual mucosa includes the membrane of ventral surface of the tongue and the floor of the mouth whereas the buccal mucosa constitutes the lining of the cheek. The sublingual mucosa is relatively permeable thus giving rapid absorption and acceptable bioavailability of many drugs. Further, the sublingual mucosa is convenient, acceptable and easily accessible. This route has been investigated clinically for the delivery of a substantial number of drugs. The ability of molecules to permeate through the oral mucosa appears to be related to molecular size, lipid solubility and peptide protein ionization. Small molecules, less than 1000 daltons appear to cross mucosa rapidly. As molecular size increases, the permeability decreases rapidly. Lipid soluble compounds are more permeable than non-lipid soluble molecules. Maximum absorption occurs when molecules are un-ionized or neutral in electrical charges. Therefore charged molecules present the biggest challenges to absorption through the oral mucosae.

Most proteinic drug molecules are extremely large molecules with molecular weight exceeding 6000 daltons. These large molecules have very poor lipid solubility and are practically impermeable. Substances that facilitate the absorption or transport of large molecules (>2000 daltons) across biological membranes are known as the enhancers, (Lee et al., Critical Reviews in Therapeutic drug Carrier

Systems, 8, 91, 1991; Lee et al., Critical Reviews in Therapeutic drug Carrier Systems, 8, 115, 1991, 1992). Enhancers may be characterized as chelators, bile salts, fatty acids, synthetic hydrophillic and hydrophobic compounds, and biodegradable polymeric compounds.

Various mechanisms of action of enhancers have been proposed. These mechanisms of action, at least for protein and peptidic drugs include (1) reducing viscosity and/or elasticity of mucous layer, (2) facilitating transcellular transport by increasing the fluidity of the lipid bilayer of membranes, and (3) increasing the thermodynamic activity of drugs (Critical Rev, 117-125, 1991, 1992).

Many enhancers have been tested so far and some have found to be effective in facilitating mucosal administration of large molecule drugs. However, hardly any penetration enhancing products have reached the market place. Reasons for this include lack of a satisfactory safety profile respecting irritation, lowering of the barrier function, and impairment of the mucociliary clearance protective mechanism. The main factor to be considered in the use of enhancers especially related to bile salts, and some protein solubilizing agents is extremely bitter and unpleasant taste. This makes their use almost impossible for human consumption on a daily basis. Several approaches were utilized to improve the taste of the bile salts based delivery systems, but none of them are commercially acceptable for human consumption to date. Among the approaches utilized includes patch for buccal mucosa, bilayer tablets, controlled release tablets, use of protease inhibitors, buccally administered film patch devices, and various polymer matrices.

The basic problem associated with the above technologies is the use of large quantities of bile acids and their salts to promote the transport of the large molecules through membranes in the form of localized delivery system using patches or tablets. In spite of using protease inhibitors and polymer coatings the technologies failed to deliver proteinic drugs in the required therapeutic concentrations. Further, the problem is compounded because of the localized site effect of the patch which resulted in severe tissue damage in the mouth. Most attempts were made to deliver large molecules via the oral, nasal, rectal, and vaginal routes using single bile acids or enhancing agents in combination with protease inhibitors and biodegradable polymeric materials. However, it is extremely difficult to achieve therapeutic levels of proteinic drugs using these formulations. As single enhancing agents fails to loosen tight cellular junctions in the oral, nasal, rectal and vaginal cavities for a required period of time to allow passage of large molecules through the mucosal membranes without further degradation. This problem makes it impractical to use the above mentioned systems for a commercial purpose. In order to overcome the above mentioned problem of the bitter taste, irritation and the penetration of large molecules through the sublingual, buccal and GI tract mucosal lining, a system has now been designed where protein drug was encapsulated in mixed micelles made up of combination of enhancers, e.g. yolk proteins (lecithins). This system allows opening of the paracellular junctions (tight junctions) in oral as well as in GI tract by GI motility movement with high degree of protease activity preserved and protecting molecules from premature degradation in the hostile acidic and proteolytic GI environment.

It is believed that the mixed micelles encapsulate molecules with high degree of efficiency (>90% encapsulation). These mixed micelles are extremely small in the size (1 nm to 10 nm), and are smaller than the pores of the membranes in the oral cavity or the GI tract. It is therefore believed that

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the extremely small size of mixed micelles helps encapsulated molecules penetrate efficiently through the mucosal membranes of the oral cavity.

The absorption of proteins and peptides is believed to be enhanced by the diffusion of large molecules entrapped in the mixed micellar form through the aqueous pores and the cell structure perturbation of the tight paracellular junctions.

The amount of physiologically peptide or protein in the compositions of this invention is typically a quantity that provides an effective amount of the drug to produce the physiological activity (therapeutic plasma level) for which peptide or protein is being administered. In consideration of the fact that the bioavailability of any active substance can never be 100%, that is to say the administered dose of the active drug is not completely absorbed, it is preferable to incorporate slightly larger amount than the desired dosage. Where the dosage form is a spray (aerosol) or the like which is repeatedly dispensed from the same container, it is recommendably so arranged that the unit dose will be slightly greater than the desired dose. It should be understood that dosage should vary with species of warm blood animals such as man, domestic animals, and their body weights. Although the composition of this invention is prepared as the microfine droplets (1 to 10 nm or less) by the virtue of its preparation methods used and suitable combinations of enhancer compound characteristics. The utilization of atomizer or aerosol spray devices (metered dose inhalers or nebulizers) may be useful to further a sufficient reduction of particle size for effective inhalation from the nasal or oral cavity so the drug may successfully absorbed or reach to the specific site.

The therapeutic composition of the present invention can be stored at room temperature or at cold temperature. Storage of proteinic drugs is preferable at the cold temperature to prevent the degradation of the drugs and to extend their shelf life. While the mixed micellar therapeutic composition of the invention is applied to the mucosal membranes, the sites of administration may the same as those used for the usual mucosal therapeutic preparation. Generally, oral, transdermal and nasal are the favourite sites of the administration but the composition can be applied to the rectal and vaginal mucosa. According to the physiologically active peptide or protein used, the dosage form and the site of administration, a specific administration method can be selected.

As used herein, the term "edetate" is used herein to refer to pharmaceutically acceptable salts of ethylenediaminetetraacetic acid.

SUMMARY OF THE INVENTION

Accordingly the present invention provides a mixed micellar pharmaceutical formulation, having a pH of between 6.0 and 7.0 comprising a proteinic pharmaceutical agent in micellar form, water, an alkali metal lauryl sulphate in a concentration of from 1 to 10 wt./wt. % of the total formulation, a pharmaceutically acceptable edetate in a concentration of from 1 to 10 wt./wt. % of the total formulation, at least one alkali metal salicylate in a concentration of from 1 to 10 wt./wt. % of the total formulation, and at least one micelle forming compound selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxy polyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening of primrose oil, trihydroxy oxo cholanylglycine, glycerin, polyglycerin, lysine, polylysine,

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trioclein and mixtures thereof, wherein the amount of each absorption enhancing compound is present in a concentration of from 1 to 10 wt./wt. % of the total formulation, and the total concentration of absorption enhancing compounds are less than 50 wt./wt. % of the formulation.

In an embodiment, the alkali metal lauryl sulphate, the edetate and the alkali metal salicylate are each in a concentration of from 2 to 5 wt./wt. % of the total formulation.

In one embodiment, the edetate is an alkali metal edetate. Preferably the alkali metal edetate is selected from the group consisting of disodium edetate, dipotassium edetate, and combinations thereof. In another embodiment, the alkali metal lauryl sulphate is sodium lauryl sulphate.

In a further embodiment, the alkali metal salicylate is sodium salicylate.

In another embodiment, the lecithin is selected from the group consisting of Phospholipon-H (trade mark) saturated phospholipid, Phospholipon-G (trade mark) unsaturated phospholipid, phosphatidylcholine, phosphatidyl serine, sphingomyelin, phosphatidylethanolamine, cephalin, and lysolecithin.

In one embodiment, one of the absorption enhancing compounds is selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid and mixtures thereof, the concentration such micelle forming compound being from about 1 to about 5 wt./wt. %.

In another embodiment, suitable for delivery through nasal passages, mixed micellar pharmaceutical formulation is suitably diluted to avoid irritation of the nasal passages.

For insulin-containing and some other compositions, the composition may also contains at least one inorganic salt which opens channels in the gastrointestinal tract and may provide additional stimulation to release insulin. Non-limiting examples of inorganic salts are sodium, potassium, calcium and zinc salts, especially sodium chloride, potassium chloride, calcium chloride, zinc chloride and sodium bicarbonate.

It will be recognized by those skilled in the art that for many pharmaceutical compositions it is usual to add at least one antioxidant to prevent degradation and oxidation of the pharmaceutically active ingredients. It will also be understood by those skilled in the art that colorants, flavouring agents and non-therapeutic amounts of other compounds may be included in the formulation. Typical flavouring agents are menthol and sorbitol.

In one embodiment the antioxidant is selected from the group consisting of tocopherol, dextroxime mesylate, methyl paraben, ethyl paraben and ascorbic acid and mixtures thereof. A preferred antioxidant is tocopherol.

In a preferred embodiment at least one protease inhibitor is added to the formulation to inhibit degradation of the pharmaceutical agent by the action of proteolytic enzymes. Of the known protease inhibitors, most are effective at concentrations of from 1 to 3 wt./wt. % of the formulation.

Non-limiting examples of effective protease inhibitors are bacitracin, soyabean trypsin, aprotinin and bacitracin derivatives, e.g. bacitracin methylene disalicylate. Bacitracin is the most effective of those named when used in concentrations of from 1.5 to 2 wt./wt. %. Soyabean trypsin and aprotinin two may be used in concentrations of about 1 to 2 wt./wt. % of the formulation.

The formulation suitable for delivery through oral mucosal membranes may be in chewable form, in which case it will be necessary to add ingredients suitable for such form. Such ingredients include guar gum, powdered acacia, carrageenin, beeswax and xanthan gum.

TABLE XIII-continued

Time (minutes)	Blood glucose levels (mmol/L)	
	Oral Dose (30 units)	Injection (10 units)
120	12.8	11.0
135	12.2	10.2
150	11.6	9.6
165	11.0	9.5
180	10.6	9.1
195	10.0	8.7
210	9.5	8.2
225	8.8	8.0
240	8.2	7.5

EXAMPLE 14

Another experiment, within the scope of the present invention, was performed. In this example, the formulation was for oral administration.

A buffer solution was prepared using 0.5 g sodium lauryl sulphate, 0.5 g sodium salicylate and 0.25 g disodium edetate dissolved in 10 mL of water. The solution was added to 8 mg (200 units) insulin and mixed, to form micellar insulin.

To this micellar solution were added 0.2 g bacitracin and 0.5 g evening of primrose oil and the solution was mixed vigorously to form a mixed micellar insulin solution (about 20 units/mL).

Six human volunteers were studied. The volunteers fasted from midnight prior to the test, with no food being taken during the 4 hour study.

On the first day, the volunteers received 10 units insulin by injection (regular fast acting insulin, available from Eli Lilly). On the second day, the volunteers received 20 units of the above-prepared oral insulin (twice the injection dose). In both tests, blood glucose levels were monitored at intervals by Bayer's Glucometer Elite.

The results, showing the average for the six volunteers, were as follows:

TABLE XIV

Time (minutes)	Blood glucose levels (mmol/L)	
	Oral Dose (20 units)	Injection (10 units)
0	8.8	7.9
15	8.4	7.9
30	8.1	8.2
45	7.4	8.3
60	6.3	7.6
90	5.1	6.2
120	5.0	5.2
150	4.8	4.6
180	5.1	3.9
210	5.3	4.4
240	5.6	5.2

The results show that the oral insulin formulation of the present invention, at a dosage of twice the injected level, is comparable to the injected insulin.

EXAMPLE 15

A further experiment was performed to show another method of making the mixed micellar formulation of the present invention.

In a 250 mL round bottom flask was added 100 mg of saturated lecithin powder (Phospholipon-90H) purchased from the American Lecithin Co. To this powder was added 5 mL of absolute ethanol (USP grade). The flask was then attached to a rotary evaporator equipped with the vacuum pump and nitrogen inlet for inert atmosphere condition to minimize oxidation of the lecithin. The flask was rotated at 100-150 rpm under vacuum. The solution in the flask was heated to 60° C. by means of water bath to dissolve the powder completely. After complete dissolution of the powder, heating was stopped and the rotation speed was increased to 300 rpm, under vacuum in nitrogen atmosphere until the alcohol evaporated completely, leaving a uniform film on the side of the flask. The rotation was continued for at least 30 minutes to ensure uniform coating of film on the wall and complete solvent removal. After 30 minutes the rotation was stopped and the vacuum was released.

To this flask was added micellar insulin solution which had been prepared from an aqueous solution of insulin, sodium lauryl sulphate, sodium salicylate and disodium edetate. The flask was shaken with the help of shaker plate. Shaking was continued for at least 30 minutes and then the solution was sonicated with a high frequency sonicating probe for another 60 minutes in order to form small uniform mixed micelles. The mixed micelles so obtained were analyzed by Malvern Zeta (trade mark) particle size distribution measurement equipment equipped with the laser light scattering device. The mixed micelles particle size distribution obtained by this method was between 2 and 9 nm. To this solution was added 1 mL of 2% menthol solution and 50 mg sodium hyaluronate. The semi-clear, translucent, light blue colour solution (final volume 10 mL) was stored in a clean glass bottle and refrigerated. The solution had a pH of 6.5.

EXAMPLE 16

Another experiment, within the scope of the present invention, was performed.

A buffer solution was prepared using 0.5 g sodium lauryl sulphate, 0.5 g sodium salicylate and 0.25 g disodium edetate dissolved in 10 mL of water. The solution was added to 8 mg (200 units) insulin and mixed, to form micellar insulin.

To this micellar solution were added 0.5 g borage oil and the solution was mixed vigorously to form a mixed micellar insulin solution (about 20 units/mL).

What is claimed is:

1. A method for administering insulin to the buccal mucosa comprising spraying an effective amount of said insulin to the buccal mucosa, using a metered dose inhaler.

2. The method of claim 1, wherein said insulin is administered in solution.

3. The method of claim 1, wherein said insulin is in a mixed micelle formulation.

4. The method of claim 3, wherein said micelles are 1 to 10 nm in size.

5. The method of claim 3, wherein said formulation comprises: insulin, an alkali metal lauryl sulfate, a pharmaceutically acceptable edetate, at least one alkali metal salicylate, and at least one micelle forming compound selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening of primrose oil, trihydroxy oxo cholanylglycine, glycerin, polyglycerin, lysine, polylysine, triolein and mixtures thereof; wherein each of said sulfate,

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edetate and salicylate is present in a concentration of from 1 to 10 wt./wt. % of the total formulation, and wherein each micelle forming compound is present in a concentration of from 1 to 10 wt./wt. % of the total formulation, and the total concentration of sulfate, edetate, salicylate and micelle forming compounds is less than 50 wt./wt. % of the formulation.

6. The method of claim 5, wherein said alkali metal lauryl sulfate is sodium lauryl sulfate.

7. The method of claim 5, wherein said edetate is an alkali metal edetate.

8. The method of claim 5, wherein said alkali metal salicylate is sodium salicylate.

9. The method of claim 5, wherein said micelle forming compound is lecithin, lecithin in combination with hyaluronic acid, evening of primrose oil or borage oil.

10. The method of claim 5, wherein said formulation comprises a combination selected from the group consisting

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of: i) sodium lauryl sulphate, sodium salicylate, disodium edetate, saturated phospholipid, and sodium hyaluronate; ii) sodium lauryl sulphate, sodium salicylate, disodium edetate, lecithin, and sodium hyaluronate; iii) sodium lauryl sulphate, sodium salicylate, disodium edetate, sodium hyaluronate, and evening of primrose oil; iv) sodium lauryl sulphate, sodium salicylate, disodium edetate, saturated phospholipid, and bacitracin, v) sodium lauryl sulphate, sodium salicylate, disodium edetate, saturated phospholipid, sodium hyaluronate and bacitracin; and vi) sodium lauryl sulphate, sodium salicylate, disodium edetate, sodium hyaluronate, oleic acid and gamma linoleic acid.

11. The method of claim 5, wherein said mixed micelle formulation further comprises water.

* * * * *

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(21) International Application Number: PCT/GB97/01873 (22) International Filing Date: 11 July 1997 (11.07.97) (30) Priority Data: 96/5889 11 July 1996 (11.07.96) ZA (71) Applicant (for all designated States except IS US): FARMARC NEDERLAND B.V. [NL/NL]; Citco Trust International Management (T.I.M) B.V., World Trade Centre, Tower B, 17th floor, Strawinskylaan 1725, NL-1007 JE Amsterdam (NL). (71) Applicant (for IS only): DYER, Alison, Margaret [GB/ZA]; 10 Veldtuin Place, Morningside, Sandton 2057 (ZA). (72) Inventors; and (75) Inventors/Applicants (for US only): PENKLER, Lawrence, John [ZA/ZA]; 4 Verdun Road, Lorraine, Port Elizabeth 6070 (ZA). DE KOCK, Lueta-Ann [ZA/ZA]; The Barn, Kragga Kamma Road, Port Elizabeth 6055 (ZA). WHIT- TAKER, Darryl, Vanstone [ZA/ZA]; 504 Twin Palms Beach Road, Humewood, Port Elizabeth 6001 (ZA).	(74) Agents: WAIN, Christopher, Paul et al.; A.A. Thornton & Co., Northumberland House, 303-306 High Holborn, London WC1V 7LE (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING ACID ADDITION SALT OF BASIC DRUG (57) Abstract A pharmaceutical composition contains an acid addition salt of a basic drug and a fatty acid or bile acid. The acid addition salts thus formed exhibit enhanced transmucosal and transdermal penetration of the basic drug. The acid addition salts, an inclusion complex containing said salts and a use of said salts are also disclosed.		

CLAIMS

- 1 A pharmaceutical composition formulated for transdermal or transmucosal delivery comprises as an active ingredient a compound of the formula I:
$$B^+ RCOO^-$$
wherein B^+ is a cation of a basic drug and $RCOO^-$ is an anion of (a) an unsaturated or saturated C_8-C_{18} monocarboxylic fatty acid or (b) a bile acid, together with one or more excipients for transdermal or transmucosal delivery.
- 2 A pharmaceutical composition according to claim 1 wherein B^+ is a cation of a basic drug selected from the group consisting of codeine, morphine, fenetanyl, naratriptan, zolmitriptan, rizatriptan, verapamil, nicardipine, captopril, enalapril, ramipril, metoclopramide, cyclizine, diphenoxylate, salmeterol, fenoterol, terbutaline, bupivacaine, lidocaine, procaine and dinorphan.
- 3 A pharmaceutical composition according to claim 1 wherein B^+ is a cation of a basic drug selected from the group consisting of sumatriptan, salbutamol, codeine, and loperamide.
- 4 A pharmaceutical composition according to any one of claims 1 to 3 wherein $RCOO^-$ is an anion selected from the group consisting of caprate, laurate and glycodeoxycholate.
- 5 A pharmaceutical composition according to any one of claims 1 to 4 wherein the active ingredient is utilised in the form of a cyclodextrin complex.

- 6 A pharmaceutical composition according to any one of claims 1 to 3 wherein the active ingredient is selected from the group consisting of sumatriptan caprate, sumatriptan laurate, sumatriptan glycodeoxycholate, salbutamol laurate, salbutamol caprate, salbutamol glycodeoxycholate, codeine caprate, codeine laurate, loperamide glycodeoxycholate, sumatriptan caprate cyclodextrin complex, salbutamol caprate cyclodextrin complex, and salbutamol glycodeoxycholate cyclodextrin complex.
- 7 A pharmaceutical composition according to any one of claims 1 to 6 selected from the group consisting of a sublingual tablet, a nasal spray, a buccal tablet and a suppository.
- 8 A pharmaceutical composition according to any one of claims 1 to 6 selected from the group consisting of a transdermal patch and a topical gel.
- 9 A compound of the formula I:
- $$B^+ RCOO^-$$
- wherein B^+ is a cation of a basic drug and $RCOO^-$ is an anion of (a) an unsaturated or saturated C_8 - C_{18} monocarboxylic fatty acid or (b) a bile acid, with the proviso that the compound is not propranolol laurate or salbutamol stearate.
- 10 A compound according to claim 9 wherein B^+ is a cation of a basic drug selected from the group consisting of codeine, morphine, fenetanyl, naratriptan, zolmitriptan, rizatriptan, verapamil, nicardipine, captopril, enalapril, ramipril, metoclopramide, cyclizine, diphenoxylate, salmeterol, fenoterol,

terbutaline, bupivacaine, lidocaine, procaine and dinorphin.

- 11 A compound according to claim 9 wherein B^+ is a cation of a basic drug selected from the group consisting of sumatriptan, salbutamol, codeine, and loperamide.
- 12 A compound according to any one of claims 9 to 11 wherein $RCOO^-$ is an anion selected from the group consisting of caprate, laurate and glycodeoxycholate.
- 13 A compound according to any one of claims 9 to 12 which is selected from the group consisting of sumatriptan caprate, sumatriptan laurate, sumatriptan glycodeoxycholate, salbutamol caprate, salbutamol laurate, salbutamol glycodeoxycholate, codeine caprate, codeine laurate and loperamide glycodeoxycholate,
- 14 A cyclodextrin inclusion complex comprises a compound of the formula I:
- $$B^+ RCOO^-$$
- wherein B^+ is a cation of a basic drug and $RCOO^-$ is an anion of (a) an unsaturated or saturated C_8 - C_{18} monocarboxylic fatty acid or (b) a bile acid, and an unsubstituted or substituted α , β or γ -cyclodextrin.
- 15 The use of a compound of the formula I
- $$B^+ RCOO^-$$
- wherein B^+ is a cation of a basic drug and $RCOO^-$ is an anion of (a) an unsaturated or saturated C_8 - C_{18} monocarboxylic fatty

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acid or (b) a bile acid, in the manufacture of a medicament for transmucosal or transdermal delivery.

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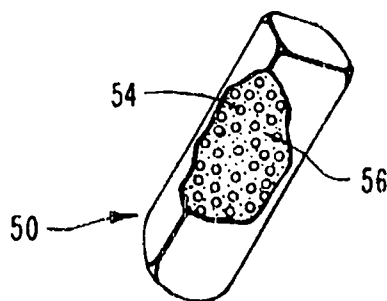
--- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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(54) Title: COMPOSITIONS AND METHODS OF MANUFACTURE FOR ORAL DISSOLVABLE DOSAGE FORMS



(57) Abstract: Compositions and methods of manufacture for dissolvable and nondissolvable drug-containing dosage-forms for non-invasive administration of medicaments through mucosal tissues of the mouth, pharynx, and esophagus of a patient. The dosage-forms are particularly useful in the transmucosal delivery of central nervous system affecting drugs in a dose-to-effect manner such that a sufficient dose is administered to produce a desired effect. A dissolvable drug-containing dosage-form includes a binding agent that is formed into a solid matrix dissolvable in the mouth of the patient, and a pharmacologically effective dose of a central nervous system affecting drug dispersed throughout the matrix. A nondissolvable drug-containing dosage-form includes a drug containment matrix that is nondissolvable in the mouth of the patient, and a central nervous system affecting

drug incorporated into the nondissolvable matrix. The dissolvable and nondissolvable drug-containing dosage-forms may include permeation enhancers capable of modifying the permeability of the mucosal tissues of the mouth, pharynx, and esophagus in order to facilitate transmucosal absorption of the drug.

CLAIMS:

What is claimed is:

1. A dissolvable drug-containing dosage-form for use in the transmucosal delivery of a drug to a patient, comprising:

5 1) a binding agent that is formed into a solid matrix dissolvable in the mouth of a patient;

 2) a pharmacologically effective dose of a potent central nervous system affecting drug that can be absorbed through mucosal tissues of the mouth, pharynx, and esophagus, the drug dispersed throughout the solid matrix; and

10 3) a buffer dispersed throughout the solid matrix, the buffer capable of controlling the pH of the mouth, pharynx, and esophagus to optimize permeation of the drug in order to facilitate transmucosal absorption of the drug;

15 wherein when the solid matrix dissolves in the mouth of the patient, the pharmacologically effective dose of the drug is released for absorption through mucosal tissues of the mouth, pharynx, and esophagus of the patient.

2. The drug-containing dosage-form of claim 1, wherein the binding agent comprises a carbohydrate that is dissolvable in the mouth of the patient.

20 3. The drug-containing dosage-form of claim 2, wherein the carbohydrate is selected from the group consisting of a cellulose, a starch, a sugar, derivatives thereof, and mixtures thereof.

4. The drug-containing dosage-form of claim 1, wherein the binding agent comprises a fat that is dissolvable in the mouth of the patient.

25 5. The drug-containing dosage-form of claim 1, wherein the binding agent comprises a protein that is dissolvable in the mouth of the patient.

6. The drug-containing dosage-form of claim 5, wherein the protein comprises a gelatin.
7. The drug-containing dosage-form of claim 1, wherein the binding agent comprises a hydrocarbon that is dissolvable in the mouth of the patient.
- 5 8. The drug-containing dosage-form of claim 1, wherein the binding agent comprises a wax.
9. The drug-containing dosage-form of claim 1, wherein the binding agent comprises a hydrogel.
- 10 10. The drug-containing dosage-form of claim 1, wherein the solid matrix is a compressed powder.
11. The drug-containing dosage-form of claim 1, wherein the drug is microencapsulated.
12. The drug-containing dosage-form of claim 1, wherein the drug is contained within a sponge-like material that is biologically inert and capable of
15 entrapping a drug and then releasing the drug over time.
13. The drug-containing dosage-form of claim 1, wherein the drug is dispersed substantially uniformly throughout the binding agent.
14. The drug-containing dosage-form of claim 1, wherein the drug is contained within the binding agent.
- 20 15. The drug-containing dosage-form of claim 1, wherein the drug adheres to the binding agent.

16. The drug-containing dosage-form of claim 1, wherein the drug is an analgesic.
17. The drug-containing dosage-form of claim 1, wherein the drug is an anesthetic.
- 5 18. The drug-containing dosage form of claim 1, wherein the drug is an anxiolytic.
19. The drug-containing dosage-form of claim 1, wherein the drug is a sedative.
20. The drug-containing dosage-form of claim 1, wherein the drug has
10 opioid agonist effects on the patient.
21. The drug-containing dosage-form of claim 1, wherein the drug has opioid antagonist effects on the patient.
22. The drug-containing dosage-form of claim 1, wherein the drug is selected from the group consisting of fentanyl, sufentanil, lofentanil, carfentanil,
15 alfentanil, or mixtures thereof.
23. The drug-containing dosage-form of claim 1, wherein the drug is selected from the group consisting of codeine, morphine, or mixtures thereof.
24. The drug-containing dosage-form of claim 1, wherein the drug is a benzodiazepine.
- 20 25. The drug-containing dosage-form of claim 1, wherein the drug is selected from the group consisting of midazolam, triazolam, oxazolam, diazepam, oxazepam, lorazepam, or mixtures thereof.

26. The drug-containing dosage-form of claim 1, wherein the drug is selected from the group consisting of phencyclidine, ketamine, propanidid, propofol, thiamylal, or mixtures thereof.

27. The drug-containing dosage-form of claim 1, wherein the drug is a
5 barbiturate.

28. The drug-containing dosage-form of claim 1, wherein the drug is selected from the group consisting of thiopental, methohexital, pentobarbital, hexobarbital, and mixtures thereof.

29. The drug-containing dosage form of claim 1, wherein the drug is a
10 cannabinoid.

30. The drug-containing form of claim 1, wherein the drug is selected from the group consisting of Δ^9 THC, CP 55,940, WIN 55,212 and levonantradol, and mixtures thereof.

31. The drug-containing dosage-form of claim 1, wherein the drug is
15 substantially ionizable and nonlipophilic.

32. The drug-containing dosage-form of claim 1, wherein the buffer comprises a citrate buffer system.

33. The drug-containing dosage-form of claim 1, wherein the buffer comprises a phosphate buffer system.

20 34. The drug-containing dosage-form of claim 1, wherein the solid matrix further comprises a lubricating agent.

35. The drug-containing dosage-form of claim 1, wherein the solid matrix further comprises a surfactant.

36. The drug-containing dosage-form of claim 1, wherein the solid matrix further comprises maltodextrin in order to aid in dissipating any unpleasant flavors of the drug in the solid matrix.

37. The drug-containing dosage-form of claim 1, wherein the solid matrix
5 further comprises a hydrophobic agent in order to slow the dissolution of the solid matrix in the mouth of the patient.

38. The drug-containing dosage-form of claim 1, wherein the solid matrix further comprises at least one flavoring.

39. The drug-containing dosage-form of claim 1, wherein the solid matrix
10 further comprises at least one sweetener.

40. The drug-containing dosage-form of claim 1, further comprising a permeation enhancer dispersed throughout the solid matrix, the permeation enhancer capable of modifying the permeability of the drug in the mucosal tissue in order to facilitate transmucosal absorption of the drug.

41. A nondissolvable drug-containing dosage form for use in transmucosal
15 delivery of a drug to a patient, comprising:

1) a drug containment matrix that is nondissolvable in the mouth of the patient; and

2) a pharmacologically effective dose of a central nervous system
20 affecting drug that can be absorbed through mucosal tissues of the mouth, pharynx, and esophagus, the drug being incorporated into the nondissolvable drug containment matrix which is configured to release the drug within the mouth of the patient for absorption through mucosal tissues of the mouth, pharynx, and esophagus.

42. The drug-containing dosage-form of claim 41, wherein the
25 nondissolvable drug containment matrix includes a chamber defined by a permeable

barrier having a pore size sufficiently large to permit passage of drug molecules there through under appropriate conditions.

43. The drug-containing dosage-form of claim 41, wherein the drug is microencapsulated.

5 44. The drug-containing dosage-form of claim 41, wherein the drug is contained within a sponge-like matrix which entraps the drug and releases the drug within the mouth of the patient over time in response to pressure exerted on the sponge-like matrix by the mouth of the patient.

10 45. The drug-containing dosage-form of claim 41, further comprising a biocompatible material to adhere together a plurality of microencapsulated drug particles into a preselected shape.

46. The drug-containing dosage-form of claim 41, wherein the drug is selected from the group consisting of fentanyl, sufentanil, lofentanil, carfentanil, alfentanil, or mixtures thereof.

15 47. The drug-containing dosage-form of claim 41, wherein the drug is selected from the group consisting of codeine, morphine, or mixtures thereof.

48. The drug-containing dosage-form of claim 41, wherein the drug is a benzodiazepine.

20 49. The drug-containing dosage-form of claim 41, wherein the drug is selected from the group consisting of midazolam, triazolam, oxazolam, diazepam, oxazepam, lorazepam, or mixtures thereof.

50. The drug-containing dosage-form of claim 41, wherein the drug is selected from the group consisting of phencyclidine, ketamine, propanidid, propofol, thiamylal, or mixtures thereof.

51. The drug-containing dosage-form of claim 41, wherein the drug is a barbiturate.
52. The drug-containing dosage-form of claim 41, wherein the drug is selected from the group consisting of thiopental, methohexital, pentobarbital,
5 hexobarbital, or mixtures thereof.
53. The drug containing dosage form of Claim 41, wherein the drug is a cannabinoid.
54. The drug-containing form of claim 41, wherein the drug is selected from the group consisting of Δ^9 THC, CP 55,940, WIN 55,212 and levonantradol, and
10 mixtures thereof.
55. The drug-containing dosage-form of claim 41, wherein the drug is a lipophilic drug.
56. The drug-containing dosage-form of claim 41, wherein the drug is a nonlipophilic drug.
- 15 57. The drug-containing dosage-form of claim 41, further comprising a buffer held within the drug containment matrix, the buffer capable of modifying the salival pH when dissolved in saliva such that a majority of the drug remains unionized in order to facilitate transmucosal absorption of the drug.
58. The drug-containing dosage-form of claim 41, wherein the buffer
20 comprises a citrate buffer system.
59. The drug-containing dosage-form of claim 41, wherein the buffer comprises a phosphate buffer system.

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60. The drug-containing dosage-form of claim 41, further comprising a biocompatible adhesive for placing the dosage-form in a preselected position within the mouth of the patient.

61. The drug-containing dosage-form of claim 41, further comprising a
5 permeation enhancer held within the drug containment matrix, the permeation enhancer capable of modifying the permeability of the mucosal tissues of the mouth, pharynx, and esophagus towards the drug in order to facilitate transmucosal absorption of the drug.

62. The drug-containing dosage-form of claim 41, wherein the permeation
10 enhancer is selected from the group consisting of a bile salt, a bile salt analog, a bile salt derivative, and mixtures thereof.

63. A method of making a dissolvable drug-containing dosage-form for use
in transmucosal delivery of a drug to a patient, the method comprising the steps of:

- 15 1) selecting a binding agent that is dissolvable in the mouth of a patient;
- 2) adding to the binding agent a pharmacologically effective dose of a potent central nervous system affecting drug, which can be absorbed through mucosal tissues of the mouth, pharynx, and esophagus of the patient;
- 20 3) adding a buffer to the binding agent, the buffer capable of controlling the pH of the mouth, pharynx, and esophagus to optimize permeation of the drug in order to facilitate transmucosal absorption of the drug;
- 25 4) mixing the binding agent, drug, and buffer into a moldable mixture in which the drug and enhancer are dispersed throughout the binding agent; and
- 5) forming a solid matrix from the moldable mixture that is dissolvable in the mouth of the patient such that the drug is released for absorption through mucosal tissues of the mouth, pharynx, and esophagus of the patient.

64. A dissolvable drug-containing dosage form for use in transmucosal delivery of a drug to a patient, comprising:

- 1) a binding agent that is formed into a solid matrix is dissolvable in the mouth of the patient;
- 5 2) a potent dose of a central nervous system effecting drug that can be absorbed through mucosal tissues of the mouth, pharynx and esophagus, the drug disbursed throughout the solid matrix; and
- 3) a buffer disbursed throughout the solid matrix, the buffer capable of controlling the pH of the mouth, pharynx and esophagus to
10 optimized permeation of the drug in order to facilitate transmucosal absorption of the drug; wherein when the solid matrix dissolves in the mouth of the patient, the potent dose of the drug is controllably released for absorption through mucosal tissues of the mouth, pharynx and esophagus of the patient.

65. A drug-containing dosage form of claim 64, wherein the potent drug
15 when compared to the weight of the solid matrix has a relatively low dose to matrix weight ratio.

66. The drug-containing dosage form of claim 64, wherein the potent drug accounts for less than about 5% of the dosage form weight.

67. The drug-containing dosage form of claim 64, wherein the potent drug
20 accounts for less than about 3% of the dosage form weight.

68. The drug containing dosage form of claim 64, wherein the potent drug accounts for less than about 1% of the dosage form weight.

69. The drug-containing dosage form of claim 64, herein the potent drug accounts for less than about 0.5% of the dosage form weight.

25 70. The drug containing dosage form of claim 64, wherein the potent drug accounts for less than about 0.1% of the dosage form weight.

71. The drug containing dosage form of claim 64, wherein the potent drug accounts for less than about 0.05% of the dosage form weight.

72. The drug containing dosage form of claim 64, wherein the potent drug accounts for less than about 0.01% of the dosage form weight.

5 73. The drug containing dosage form of claim 64, wherein the potent drug is capable of being released slowly, over an extended period of time, to control absorption through mucosal tissue.

74. A dissolvable drug-containing dosage-form for use in the transmucosal delivery of a drug to a patient, comprising:

10 1) a binding agent that is formed into a solid carbohydrate matrix dissolvable in the mouth of a patient,

2) a pharmacologically effective dose of a potent central nervous system affecting drug that can be absorbed through mucosal tissues of the mouth, pharynx, and esophagus, the drug dispersed throughout the solid matrix; and

15 3) a buffer dispersed throughout the solid matrix, the buffer capable of controlling the pH of the mouth, pharynx, and esophagus to optimize permeation of the drug in order to facilitate transmucosal absorption of the drug;

20 wherein when the solid matrix dissolves in the mouth of the patient, the pharmacologically effective dose of the drug is released for absorption through mucosal tissues of the mouth, pharynx, and esophagus.

75. The dissolvable drug-containing dosage-form of claim 74 wherein the carbohydrate binding agent is selected from the group of cellulose derivatives, water-dispersible starch derivatives, and compressible sugars.

76. A dissolvable drug-containing dosage-form for use in the transmucosal delivery of a drug to a patient, comprising:

- 1) a binding agent that is formed into a solid carbohydrate matrix dissolvable in the mouth of a patient, said carbohydrate being selected from the group of microcrystalline cellulose and carboxymethyl cellulose,
 - 5 2) a pharmacologically effective dose of a potent central nervous system affecting drug that can be absorbed through mucosal tissues of the mouth, pharynx, and esophagus, the drug dispersed throughout the solid matrix; and
 - 10 3) a buffer dispersed throughout the solid matrix, the buffer capable of controlling the pH of the mouth, pharynx, and esophagus to optimize permeation of the drug in order to facilitate transmucosal absorption of the drug;
- wherein when the solid matrix dissolves in the mouth of the patient, the pharmacologically effective dose of the drug is released for absorption through mucosal tissues of the mouth, pharynx, and esophagus.