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Industria y Comercio

SUPERINTENDENCIA

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SOLICITUD

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

PATENTE DE INVENCION

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54. TÍTULO Composiciones para la Transmisión
Transmucosa Oral de la Metformina

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A61P 3/04

71. SOLICITANTE Generax Pharmaceuticals, Inc

DOMICILIO Toronto, Ontario, Canadá

74. APODERADO Dilcia Rodriguez D'Alema

22. BOGOTÁ, D. C., Agosto 27



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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
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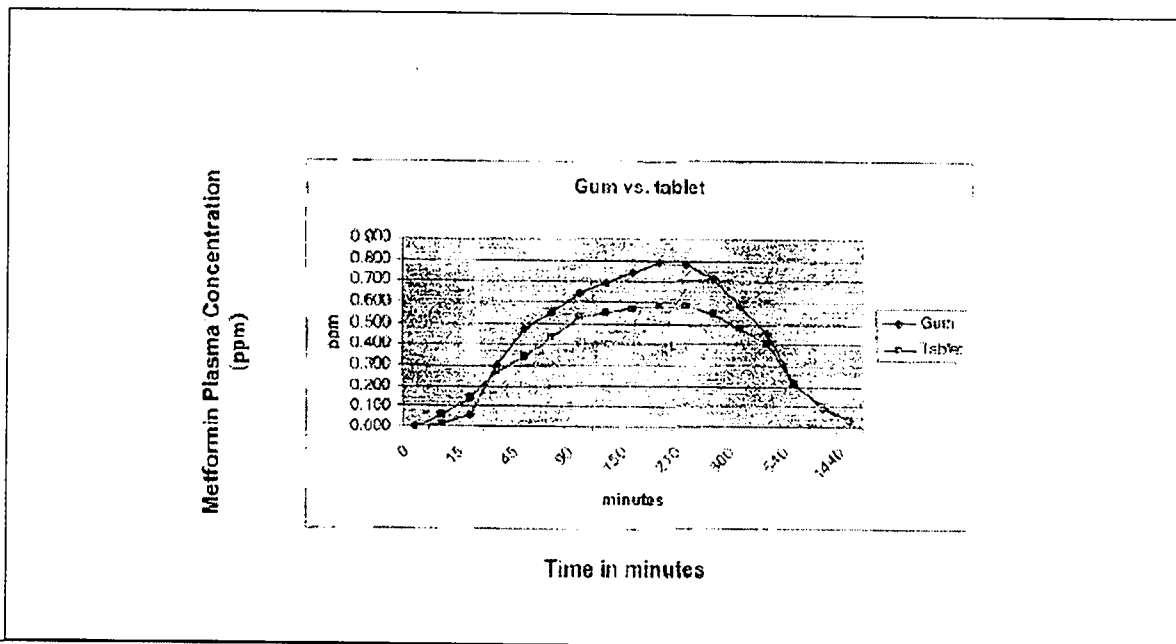
1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☒ Capitulo I.		☐ Capitulo II.	
2) SOLICITANTE (71)	Nombre: GENEREX PHARMACEUTICALS, INC Dirección: 33 Harbour Square, Suite 202, Toronto ,Ontario M5J 2G2 Nacionalidad o domicilio: Toronto,Ontario CANADA Lugar de constitución: CANADA		IDENTIFICACIÓN C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ Cual _____ NÚMERO _____
	Teléfono: _____ Fax: _____ E. Mail: _____		
3) REPRESENTANTE O APODERADO	Nombre: DILIA MARÍA RODRÍGUEZ D'ALEMAN Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C. Teléfono: 6181088 Fax: 6350824 E. Mail: info@clarkemodet.com.co		IDENTIFICACIÓN C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ
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Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina			

10)

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros:
 1. Request
 2. IB/304

11) FIGURA CARACTERÍSTICA:



12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA:

C.C. 41.654.882 de Bogotá TP 20824 CSJ

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***** CONCEPTO *****

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		1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))

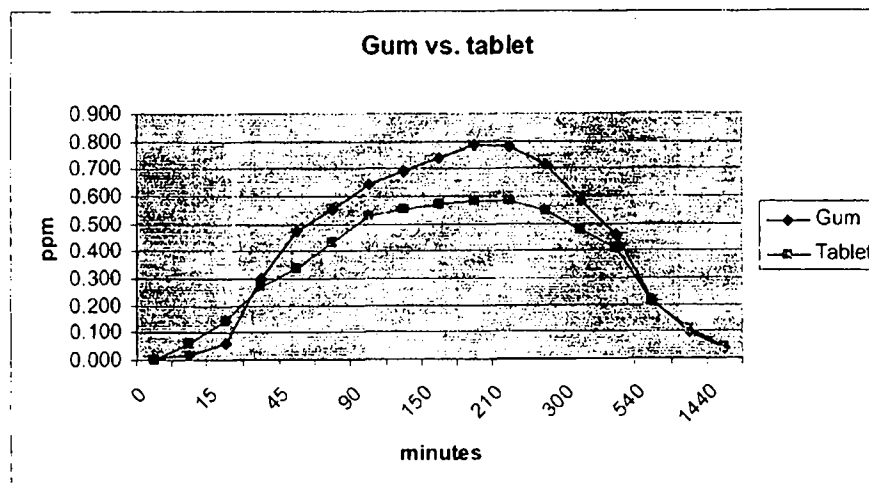
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS FOR ORAL TRANSMUCOSAL DELIVERY OF METFORMIN

Metformin Plasma Concentration
(ppm)



Time in minutes

(57) Abstract: The invention relates to oral transmucosal pharmaceutical compositions comprising metformin or a pharmaceutically acceptable salt thereof, methods of using the compositions to treat various conditions, including diabetes, methods of preparing the compositions, and preparations for use in making the compositions.

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COMPOSITIONS FOR ORAL TRANSMUCOSAL DELIVERY OF METFORMIN

BACKGROUND OF THE INVENTION

Metformin and pharmaceutically acceptable salts thereof (e.g. metformin hydrochloride, *N,N*-dimethylimidodicarbonimidic diamide hydrochloride) have been used to treat a number of conditions, including diabetes, pre-diabetes, polycystic ovary disease and obesity. Metformin's mechanisms of action include decreasing plasma glucose levels (particularly, postprandial glucose levels), decreasing hepatic glucose production, decreasing lipid levels, increasing sensitivity to insulin, and/or decreasing intestinal absorption. Furthermore, metformin acts without causing hypoglycemia.

Oral formulations (tablets) of metformin (e.g. GLUCOPHAGE, Bristol Meyers Squibb Co.) are currently in use. Administration of oral formulations of metformin may result in a number of side effects. Adverse events associated with oral formulations of metformin use are often gastrointestinal in nature (e.g. anorexia, nausea, bloating, vomiting and occasionally diarrhea, etc.). Furthermore, oral formulations of metformin may give rise to a bitter aftertaste, which may lead to loss of appetite. These side effects often result in the failure of patients to comply with taking the medication, i.e. "compliance issues". Compliance issues are prevalent in individuals of all ages, including children, who typically do not want to take medicines that taste bad.

Therefore, there is an important need for formulations of metformin that, at least, mitigate one or more of these problems to help with compliance.

SUMMARY OF THE INVENTION

In accordance with a first aspect, the invention provides an oral transmucosal metformin composition comprising a pharmaceutically acceptable carrier and an effective amount of a pharmaceutical agent consisting of metformin or a pharmaceutically acceptable salt thereof contained in said carrier, said carrier being capable of delivering a pharmaceutically effective amount of said pharmaceutical agent to an oral mucosal membrane for absorption.

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In accordance with a second aspect, there is provided a process for making the oral transmucosal metformin composition comprising mixing an effective amount of a pharmaceutical agent consisting of metformin or a pharmaceutically acceptable salt thereof with an effective amount of at least one absorption enhancer chosen from an alkali metal alkyl sulfate, glycerin, a bile acid or bile salt, lecithin, hyaluronic acid, 5 octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening primrose oil, polyglycerin, lysine, polylysine, triolein, monoolein, monooleates, monolaurates, menthol, polidocanol alkyl ethers, chenodeoxycholate, deoxycholate and pharmaceutically acceptable salts and 10 analogues thereof to form a preparation. The preparation is combined with a suitable pharmaceutically acceptable carrier to make the present composition.

In accordance with a further aspect, the invention provides a method of using, and a use of, the composition to treat various conditions chosen from diabetes, pre-diabetes, obesity and polycystic ovary syndrome. The present composition can be useful to 15 decrease plasma glucose levels, decrease hepatic glucose production, decrease lipid levels, increase sensitivity to insulin, decrease intestinal absorption of glucose, decrease hypoglycemia and reduce appetite. The method involves administering to a subject a composition according to the first aspect in order to treat such conditions. The invention also provides a use of the composition in the manufacture of a medicament for treating 20 the same conditions. The composition can be maintained in the mouth for at least 1, 20 or 30 minutes. As well, the composition can be maintained in the mouth from 1 to 30, 1 to 20 or 1 to 9 minutes.

In accordance with yet a further aspect, the invention provides a preparation for use in making a composition according to the first aspect. The preparation comprises a 25 pharmaceutical agent consisting of metformin or a pharmaceutically acceptable salt thereof, and an effective amount of at least one absorption enhancer chosen from an alkali metal alkyl sulfate, glycerin, a bile acid or bile salt, lecithin, hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening primrose oil, polyglycerin, lysine, 30 polylysine, triolein, monoolein, monooleates, monolaurates, menthol, polidocanol alkyl ethers, chenodeoxycholate, deoxycholate and pharmaceutically acceptable salts and

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analogues thereof, wherein the pharmaceutical agent is present in a concentration of from about 5 to 90, 10 to 80, 20 to 80 or 20 to 50 w/w %, , and the total concentration of the absorption enhancers is less than about 30, 20, 10, 7, 5, 2, 1, 0.5, or 0.01 w/w % all based on the total weight of the preparation.

5 The present invention has a number of advantages. By by-passing the gastrointestinal (GI) tract, gastrointestinal complications and side effects of oral formulations of metformin and its salts can be avoided. In known formulations that are ingested, a higher amount of pharmaceutical agent is required per dose due to the problem of degradation in the GI tract. The present compositions which deliver the
10 pharmaceutical agent through oral mucosal membranes can be formulated with less active ingredient. This leads to cost savings and helps to improve the taste profile.

BRIEF DESCRIPTION OF THE DRAWINGS

 The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the
15 invention, and the accompanying drawings.

 Figure 1 is a graph showing metformin plasma concentrations (ng/ml) over time. Series 1 depicts the metformin plasma concentration in an individual given an 850 mg metformin hydrochloride tablet to ingest. Series 2 and 3 represent the metformin plasma concentrations in two individuals who chewed three chiclets of chewing gum, each
20 containing 212.5 mg of metformin.

 Figure 2 is a graph showing the amount of metformin released from chewing gum compositions according to the present invention over time.

 Figure 3 is a graph comparing metformin plasma concentrations (ppm) over time in individuals given a 429 mg metformin tablet to ingest with individuals who chewed
25 gum containing 429 mg of metformin.

DETAILED DESCRIPTION OF THE INVENTION

A description of preferred embodiments of the invention follows.

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Pharmaceutical Compositions

In one embodiment, the invention is an oral transmucosal metformin composition comprising:

an effective amount of a pharmaceutical agent consisting of metformin or a
5 pharmaceutically acceptable salt thereof,

an effective amount of at least one absorption enhancer chosen from an alkali metal alkyl sulfate, glycerin, a bile acid or bile salt, lecithin, hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening primrose oil, polyglycerin, lysine,
10 polylysine, triolein, monoolein, monooleates, monolaurates, menthol, polidocanol alkyl ethers, chenodeoxycholate, deoxycholate and pharmaceutically acceptable salts and analogues thereof, and

a pharmaceutically acceptable carrier, said carrier being capable of delivering a pharmaceutically effective amount of said pharmaceutical agent to an oral mucosal
15 membrane for absorption.

The pharmaceutically acceptable salt of metformin can be metformin hydrochloride.

In one embodiment, the pharmaceutical composition is in the form of chewing gum comprising metformin hydrochloride in a concentration of from about 10 to 50 w/w
20 %, sodium lauryl sulfate in a concentration of from about 0.01 to 2 or 0.01 to 0.5 w/w %, sodium glycocholate in a concentration of from about 0.01 to 2 or 0.01 to 0.5 w/w %, glycerin in a concentration of from about 2 to 10 or 2 to 7 w/w %, and a chewing gum base in a concentration of from about 10 to 90 , 30 to 75, or 60 to 75 w/w %, all based on the total weight of the composition. In another embodiment, the composition is in the
25 form of a hard candy or lozenge.

In another embodiment, the invention is a process for making an oral transmucosal metformin composition comprising:

mixing (a) an effective amount of a pharmaceutical agent consisting of metformin or a pharmaceutically acceptable salt thereof with (b) an effective amount of at least one
5 absorption enhancer chosen from an alkali metal alkyl sulfate, glycerin, a bile acid or bile salt, lecithin, hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening primrose oil, polyglycerin, lysine, polylysine, triolein, monoolein, monooleates, monolaurates, menthol, polidocanol alkyl ethers, chenodeoxycholate, deoxycholate and
10 pharmaceutically acceptable salts and analogues thereof, to form a paste;

mixing the paste with a gum base; and

forming the resultant mixture into chewing gum tablets, capsules, caplets or chiclets.

Pharmaceutically acceptable salts and analogues of any of the disclosed
15 absorption enhancers are also within the present scope as are mixtures or combinations of any of these compounds.

The absorption enhancers are those that facilitate delivery of the pharmaceutical agent across oral mucosal membranes. As used herein, "facilitate" refers to increasing the rate and/or amount of pharmaceutical agent delivered across an oral mucosal
20 membrane (e.g. by at least about 5%, 10%, 20%, 25%, 30%, 35%, 40%, 50%, 60%, or 75%) compared to a pharmaceutical composition in which the absorption enhancer is absent.

Each absorption enhancer can be present in a concentration of up to about 30, 20, 15, 10, 5, 2, 1, 0.5, or 0.01 w/w % based on the total weight of the composition. The total
25 amount of absorption enhancers is less than about 30, preferably less than about 20, and more preferably less than about 10 or 7 w/w % based on the total weight of the composition.

The absorption enhancers are micelle forming compounds which serve to encapsulate the pharmaceutical agent and facilitate its delivery across oral mucosal membranes when the composition is formed into a solution in the oral cavity.

As will be appreciated by those skilled in the art, a micelle is a colloidal aggregate
5 of amphipathic molecules in which the polar hydrophilic portions of the molecule extend outwardly while the non-polar hydrophobic portions extend inwardly. It is believed that the presence of the micelles significantly aids in the absorption of the pharmaceutical agent both because of their enhanced absorption ability, and also because of their size. In addition, encapsulating pharmaceutical agents in micelles protects the agents from rapid
10 degradation.

It will be understood that each micelle can contain the pharmaceutical agent and one or more absorption enhancers (i.e. micelle forming compounds). Preferably, at least two micelle forming compounds are used to form mixed micelles. As used herein the term "mixed micelles" refers to at least two different types of micelles each of which has
15 been formed using a different micelle forming compound. For example, the present compositions can comprise a mix of at least two different types of micelles: micelles formed between the pharmaceutical agent and one of the micelle forming compounds (e.g. alkali metal alkyl sulfate), and micelles formed between the pharmaceutical agent and at least one additional micelle forming compound (e.g. sodium glycocholate). It will
20 be understood that each individual micelle can be formed from more than one micelle-forming compound as well.

The size of the micelles is preferably greater than 6 microns but can be smaller, such as from about 1 to about 10 nanometers, or from about 1 to about 5 nanometers. The shape of the micelle can vary and can be, for example, prolate, oblate or spherical;
25 spherical micelles are most typical. It is believed that the extremely small size of the micelles helps the encapsulated pharmaceutical agent penetrate efficiently through the oral mucosae. Thus, the present compositions offer increased bioavailability of active drug, particularly across oral mucosae, when compared with pharmaceutical preparations known in the art.

Any alkali metal alkyl sulfate can be used in the present compositions, provided compatibility problems do not arise. Preferably, the alkyl is a C8 to C22 alkyl, more preferably lauryl (C12). Any alkali metal can be utilized, with sodium being preferred. While the alkali metal alkyl sulfate is generally present in a concentration of up to about
5 30 w/w %, a concentration up to about 5 w/w % of the total composition is preferred. Even more preferred is a concentration of up to about 1, 0.5 or 0.01 w/w % of the total composition.

As used herein, the term "bile acid" includes, but is not limited to, cholic acid derivatives such as cholic, glycocholic, chenodeoxycholic, taurocholic, glycodeoxycholic
10 and taurodeoxycholic acids. Any bile acids, or salt thereof, can be used in compositions of the present invention. Preferred is sodium glycocholate. Because the present invention uses relatively low concentrations of bile salts, problems of toxicity associated with the use of these salts is minimized, if not avoided.

The lecithin can be saturated or unsaturated, and is preferably chosen from
15 phosphatidylcholine, phosphatidylserine, sphingomyelin, phosphatidylethanolamine, cephalin, and lysolecithin.

Preferred salts of hyaluronic acid are alkali metal hyaluronates, especially sodium hyaluronate, alkaline earth hyaluronates, and aluminum hyaluronate. When using hyaluronic acid or pharmaceutically acceptable salts thereof in the present compositions,
20 a concentration of between about 1 and 5 w/w % of the total composition is preferred, more preferably between about 1.5 and 3.5 w/w %.

The composition can further comprise an isotonic agent in a concentration of up to about 30, 20, 15, 10 or 6 w/w % of the total composition. Suitable isotonic agents include, but are not limited to, saccharides such as sorbitol and mannitol, and polyhydric
25 alcohols such as glycerin, polyglycerin, propylene glycol and the like, and dibasic sodium phosphate. Preferred is glycerin. The isotonic agent serves to keep the micelles in solution. Glycerin can function both as a micelle forming compound and an isotonic agent; when dibasic sodium phosphate is used it will also serve to inhibit bacterial growth.

Optionally, the pharmaceutical composition can comprise one or more additional therapeutic agents (e.g. sulfonureas). As used herein, the term "therapeutic agent" refers to an agent that ameliorates a disease or symptoms associated with a disease, including preventing or delaying the onset of the disease symptoms, and/or lessening their severity or frequency. In one embodiment, the therapeutic agent is used to treat diabetes, pre-diabetes, obesity or polycystic ovary syndrome.

An effective amount of the pharmaceutical agent should be included in the present composition. As used herein, the term "effective amount" refers to that amount of the pharmaceutical agent needed to bring about the desired result, such as obtaining the intended therapeutic treatment or prevention of a disorder in a patient, or regulating a physiological condition in a patient. Such an amount will therefore be understood as having a therapeutic and/or prophylactic effect in a patient. It will be appreciated that the effective amount will vary depending on the particular agent used, the parameters determined for the agent, the nature and severity of the disorder being treated, the patient being treated, and the characteristics of the carrier used.

An "effective amount" can also be the amount required such that peak metformin plasma concentrations are approximately equal to the peak metformin plasma concentrations in a subject administered an oral metformin hydrochloride tablet (for example, a metformin hydrochloride tablet containing about 50, 100, 250, 500, 750, 800 or 1000 mg of metformin hydrochloride). As used herein, "approximately equal" means that the peak plasma concentration of metformin after administration of the pharmaceutical composition of the invention (assessed using standard bioavailability measurements) is within 10% of the peak metformin plasma concentration after administration of an oral tablet formulation of metformin.

It will be understood that any decrease in plasma glucose levels, hepatic glucose production, lipid levels, intestinal absorption or weight loss can be therapeutic and/or prophylactic as can be any increase in sensitivity to insulin. The precise dosage level should be determined by the attending physician or other health care provider and will depend upon well-known factors, including the age, body weight, sex and general health of the individual, and the use (or not) of concomitant therapies. Of course, the skilled

person will realize that divided and partial doses are also within the scope of the invention. The determination of what constitutes an effective amount is well within the skill of one practicing in the art.

Pharmaceutically effective doses may be extrapolated from dose-response curves
5 derived from in vitro or animal model test systems. They may also be determined by measuring the bioavailability of known oral formulations of metformin hydrochloride. The pharmaceutical composition of the invention can then be formulated in a dose having a bioavailability that approximates the bioavailability of known oral formulations.

The amount of the pharmaceutical agent can be from about 50 to 850 milligrams.

10 Typically, the present compositions will contain about 50 to 500 milligrams per dose. Depending on the dosing regimen, each dose can contain 50, 112.5, 250 milligrams or 500 milligrams. It will be appreciated that the amount will vary depending on, amongst other things, the release characteristics of the carrier employed. The amount of active ingredient will be adjusted so that the amount of pharmaceutical agent released will
15 have the intended therapeutic and/or prophylactic effect.

Each dose can contain from about 5 to 90, more preferably from about 10 to 80 w/w %, and even more preferably from about 20 to 80 or 20 to 50 w/w % of pharmaceutical agent based on the total weight of the composition, depending upon the amount of the carrier present.

20 The present compositions optionally contain a stabilizer and/or a preservative. Phenolic compounds are particularly suited for this purpose as they not only stabilize the composition, but they also protect against bacterial growth and help absorption of the composition. A phenolic compound will be understood as referring to a compound having one or more hydroxy groups attached directly to a benzene ring. Preferred
25 phenolic compounds according to the present invention include phenol and methyl phenol (also known as m-cresol), and mixtures thereof.

The compositions of the present invention can further comprise one or more of the following: inorganic salts; antioxidants and protease inhibitors. The amount of any of

these optional ingredients to use in the present compositions can be determined by one skilled in the art.

The inorganic salt or salts should be ones which can 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.

The antioxidant is used to prevent degradation and oxidation of the pharmaceutically active ingredients. The antioxidant can be chosen from tocopherol, deteroxime mesylate, methyl paraben, ethyl paraben, ascorbic acid and mixtures thereof, as well as other antioxidants known in the pharmaceutical arts. A preferred antioxidant is tocopherol. The parabens will also provide preservation to the composition.

Protease inhibitors serve to inhibit degradation of the pharmaceutical agent by the action of proteolytic enzymes. When used, protease inhibitors are preferably in a concentration of between about 1 and 3 w/w % of the composition. Any material that can inhibit proteolytic activity can be used, absent compatibility problems. Examples include but are not limited to bacitracin and bacitracin derivatives such as bacitracin methylene disalicylates, soybean trypsin, and aprotinin. Bacitracin and its derivatives are preferably used in a concentration of between about 1.5 and 2 w/w % of the total composition, while soyabean trypsin and aprotinin are preferably used in a concentration of between about 1 and 2 w/w % of the total composition.

It will be understood by those skilled in the art that colorants, flavoring agents and non-therapeutic amounts of other compounds may also be included in the composition. When menthol is used as one of the micelle-forming compounds, it will also impart flavor to the composition.

Flavoring agents can be essential oils, essences, extracts, powders, acids and other substances capable of affecting the taste profile. Flavors which can be used include, but are not limited to, coconut, coffee, cola, chocolate, vanilla, grape fruit, menthol, licorice, anise, apricot, caramel, honey, pineapple, strawberry, raspberry, tropical fruits, cherries,

cinnamon, peppermint, wintergreen, spearmint, eucalyptus and mint flavors. In one embodiment, the flavors are chosen from menthol, caramel, coffee, and cola.

Colorants that can be used are of natural or synthetic origin and must be approvable for use in foods or medicines.

- 5 The carrier can be formulated into various shapes such as animal shapes or stars to appeal further to children.

The compositions of the present invention can be stored at room temperature or at cold temperature.

- 10 The pharmaceutical agent is to be administered through oral mucosal membranes or "oral mucosae". These include membranes of the mouth, throat, larynx, and esophagus. Membranes of the mouth are preferred, in particular, the buccal and sublingual mucosa. The sublingual mucosa includes the membrane of the ventral surface of the tongue and the floor of the mouth, and the buccal mucosa is the lining of the cheeks. The sublingual and buccal mucosae are relatively permeable, allowing for the
- 15 rapid absorption and acceptable bioavailability of many drugs. Further, the buccal and sublingual mucosae are convenient, non-evasive and easily accessible. In comparison to the GI tract and other organs, the buccal environment has lower enzymatic activity and a neutral pH that allows for a longer effective life of the drug in vivo.

- 20 The carrier is designed to release a sufficient amount of pharmaceutical agent and reside in the mouth for a sufficient period of time for absorption of the agent, so as to produce a therapeutic and/or prophylactic effect in a patient. For improved absorption, the carrier is preferably one that can be moved around the mouth so as to contact an increased surface area of the oral mucosal membranes. In preferred embodiments, the carrier is formulated as a masticatable candy (e.g. chewing gum or taffey) or as a hard
- 25 candy or lozenge that can be chewed or sucked on for a sufficient period of time while the candy is moved over oral mucosal membranes. The amount of pharmaceutical agent released is over about 50, 60, 70, 80, or 90% during the period of time in which the carrier resides in the mouth. This period of time is from about 1 to 30, preferably from about 1 to 20, and more preferably from about 1 to 10 minutes. When released in the

mouth and dissolved in saliva, the pharmaceutical agent will be present in micellar form as it will be encapsulated by the micellar forming absorption enhancers used herein. The person skilled in the art would readily understand how to make suitable carriers based on the teachings herein and common knowledge in the art.

5 Process for Making the Composition

 The present invention also provides a process for making the pharmaceutical composition of the present invention. The present compositions can be prepared by mixing an effective amount of a pharmaceutical agent consisting of metformin or a pharmaceutically acceptable salt thereof with an effective amount of at least one
10 absorption enhancer chosen from an alkali metal alkyl sulfate, glycerin, a bile acid or bile salt, lecithin, hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening primrose oil, polyglycerin, lysine, polylysine, triolein, monoolein, monooleates, monolaurates, menthol, polidocanol alkyl ethers, chenodeoxycholate, deoxycholate, and
15 pharmaceutically acceptable salts and analogues thereof to form a preparation to be combined with a pharmaceutically acceptable carrier.

 The process can comprise the step of adding one or more ingredients chosen from isotonic agents, stabilizers, preservatives, antioxidants, protease inhibitors and inorganic salts.

20 The mixing can be effected by use of a high speed stirrer such as a KitchenAid brand professional HD Series Mixer for laboratory use or the like.

 To make a chewing gum composition, the process can further comprise the steps of:

 mixing the preparation with a gum base; and

25 forming the resulting mixture into chewing gum tablets, capsules, caplets or chiclets.

The specific amounts of ingredients can be determined by one skilled in the art based upon the general guidelines provided herein.

Method of Treatment

The invention provides a method of treating conditions chosen from diabetes, pre-diabetes, obesity, and polycystic ovary syndrome, comprising administering to the subject
5 a composition in accordance with the first aspect of the invention. The present compositions can be useful in decreasing the plasma glucose level in a subject (e.g. postprandial glucose level), decreasing hepatic glucose production, decreasing lipid levels, increasing sensitivity to insulin, decreasing intestinal absorption of glucose,
10 decreasing hypoglycemia, decreasing body weight, and/or reducing appetite.

Where the composition is in the form of a masticatable candy or hard candy or lozenge, the method includes chewing and/or sucking the candy for a sufficient period of time for release and absorption of the pharmaceutical agent in micellar form, so as to produce a therapeutic and/or prophylactic effect in a patient.

15 The pharmaceutical composition can be provided in one dose (e.g. one piece or gum or candy) or may be provided in multiple doses which are administered serially. The frequency of administration and amount of metformin or its salt taken per dose will be determined by doctor's prescription based on the nature and severity of the condition to be treated and other factors, including without limitation, the sex, weight, health and age
20 of the subject.

The method can also include the steps of administering one or more other therapeutic agents to treat diabetes, pre-diabetes, obesity, and/or polycystic ovary syndrome and/or produce weight loss. Therapeutic agents for the above conditions are known in the art, and the dosing of a combination therapy can be determined by a
25 physician or health practitioner. For example, a pharmaceutical composition of the invention can be administered at the same time as the other therapeutic agent(s), or alternatively at different times of the day. In particular, the pharmaceutical composition of the invention can be administered in combination with insulin for treating diabetes.

When the pharmaceutical compositions of the invention are used in combination with insulin, the amount of insulin required for control of diabetes can be decreased.

As used herein, "diabetes" or "diabetes mellitus" refers to a condition characterized by hyperglycemia. The hyperglycemia can be a result of absolute or
5 relative impairment in insulin secretion and/or insulin action. Methods for detecting hyperglycemia are known in the art, and generally involve measuring plasma glucose levels. In asymptomatic patients, diabetes can be diagnosed when the diagnostic criterion for fasting hyperglycemia is met: a plasma (or serum) glucose level of ≥ 140 mg/dL (≥ 7.77 mmol/L) (recommended by the National Diabetes Data Group (NDDG)) after
10 overnight fast on two occasions in an adult or child; or when a subject has fasting plasma glucose levels of > 126 mg/dL (> 6.99 mmol/L) (recommended by the American Diabetes Association). Diabetes includes type 1 diabetes (insulin dependent diabetes mellitus), in which the subject produces little or no insulin, and type 2 diabetes (non-insulin dependent diabetes mellitus), in which hyperglycemia results from both an
15 impaired insulin secretory response to glucose and/or decreased insulin effectiveness in stimulating glucose uptake by skeletal muscle and in restraining hepatic glucose production (insulin resistance).

As used herein, "pre-diabetes" (also referred to as impaired glucose tolerance, i.e. IGT) refers to a condition that occurs when a subject's post-prandial plasma glucose level
20 is ~~s-are~~ higher than normal but not high enough for a diagnosis of type 2 diabetes. Methods for measuring plasma glucose levels are known in the art.

As used herein, "polycystic ovary syndrome" or "hyperandrogenic chronic anovulation" is a condition that may cause amenorrhea, but is usually characterized by irregular menses, mild obesity, and hirsutism, typically beginning in the pubertal years
25 and worsening with time. Most patients have abundant cervical mucus on examination and elevated free estrogens. Levels of most circulating androgens tend to be mildly elevated. The ovaries may be enlarged with smooth, thickened capsules or may be normal in size. Typically, the ovaries contain many 2- to 6-mm follicular cysts, and thecal hyperplasia surrounds the granulosa cells. Large cysts containing atretic cells may
30 be present.

As used herein, "obesity" refers to having a body weight more than about 30% greater than ideal body weight, as determined by a medical professional, and/or having a body mass index greater than about 27 as determined by a medical professional.

The terms "therapeutic," "treatment," and "treat" and as used herein, refer to
5 ameliorating a disease or symptoms associated with a disease, including preventing or delaying the onset of the disease symptoms, and/or lessening the severity or frequency of symptoms of the disease.

Symptoms of diabetes and pre-diabetes include, but are not limited to
10 dyslipidemia, obesity, arterial hypertension, and microvascular and macrovascular complications, for example, atherosclerosis, retinopathies, nephropathies and neuropathies. Symptoms of obesity include, but are not limited to diabetes (e.g. type 2 diabetes), coronary artery disease, peripheral arterial occlusive disease, myocardial infarction, peripheral arterial occlusive disease, dyslipidemias (e.g. hyperlipidemia), stroke, chronic venous abnormalities, orthopedic problems, sleep apnea disorders,
15 esophageal reflux disease, hypertension, arthritis, infertility, miscarriages and cancer (e.g. colorectal cancer, breast cancer).

EXAMPLES

Making of Paste Preparation

A preparation for use in making a composition according to the present invention
20 was made as follows.

Example 1

Powdered metformin hydrochloride (available from Spectrum Chemicals),
powdered sodium glycocholate (available from NutriScience Innovations, LLC), and
powdered sodium lauryl sulfate (available from Charles Tennant and Bioshop) were put
25 through a 100 mesh screen and the particles that passed through the screen were used to make the preparation.

At room temperature and a relative humidity of from 25 to 65%, 123.51 grams of liquid glycerin (available from Canada Colors and Chemicals Ltd.) was poured slowly into a high speed mixing machine and stirred for approximately two to three minutes. To this was added 4.83 grams of the powdered sodium glycholate and the two ingredients
5 were mixed for a further two to three minutes. 4.82 grams of the powdered sodium lauryl sulfate was then added and the mixture was mixed for two to three minutes more to produce an opaque solution. 1000 grams of the powdered metformin hydrochloride was then added with mixing continuing for another 15 to 20 minutes to form a homogeneous paste having a doughy texture.

10 The paste thus formed is according to the present invention and contained metformin hydrochloride in a concentration of 88.25 w/w %, glycerin in a concentration of 10.90 w/w %, sodium glycocholate in a concentration of 0.43 w/w % and sodium lauryl sulfate in a concentration of 0.43 w/w %, all based on the total weight of the paste preparation.

15 ***Example 2***

The protocol of Example 1 was repeated again with slightly differing amounts of the starting ingredients to produce a paste according to the present invention having metformin hydrochloride in a concentration of 76.98 w/w %, glycerin in a concentration of 22.28 w/w %, sodium glycocholate in a concentration of 0.37 w/w % and sodium
20 lauryl sulfate in a concentration of 0.37 w/w %, all based on the total weight of the paste preparation.

In Examples 1 and 2, the amount of glycerin used to make the paste can be reduced so as to produce a paste having as little as 10 w/w % of glycerin based on the total weight of the paste. The paste preparation can be combined with a suitable
25 pharmaceutically acceptable carrier to produce a composition according to the present invention.

Preparation of Chewing Gum Composition

Example 3

The paste according to Example 2 above was made into a chewing gum composition (chiclets) according to another aspect of the invention. Each chiclet
5 contained metformin hydrochloride in a concentration of 212.5 w/w %, glycerin in a concentration of 6.15 w/w %, sodium glycocholate in a concentration of 0.10 w/w %, and sodium lauryl sulfate in a concentration of 0.10 w/w %, all based on the total weight of the chiclet composition. The balance of each chiclet consisted of gum base.

While the chewing gum of this example contained glycerin in a concentration of
10 6.15 w/w %, the starting amount of glycerin used to make the paste may be adjusted downwardly to produce a chewing gum having as little as 3 w/w % of glycerin based on the total weight of the gum.

Example 4

The amount of ingredients used in Example 3 to make the paste were adjusted so
15 as to produce a gum composition comprising 850 mg of metformin hydrochloride, 246 mg of glycerin, 4 mg of sodium glycocholate and 4 mg of sodium lauryl sulfate.

In both Examples 3 and 4, the chewing gum was prepared in accordance with a known method as follows. A matrix material consisting of elastomers, emulsifiers and waxes was ground and placed in a traditional chewing gum mixer. Additional ingredients
20 (sweeteners, flavorings, and coloring agents) were then added to form a palatable gum base. The paste was then added to the gum base in a ratio of about 276 parts of paste to 1000 parts of gum base and all of the ingredients were mixed to form a homogenous chewing gum mass. The warm gum mass was then removed from the mixer and formed into chewing gum pieces using conventional systems and machines. The gum pieces
25 were left to harden and coated with an optional dragée coating, which contained additional coloring and flavoring agents.

Chewing gum compositions according to the present invention may be made using other known methods such as those described in U.S. Patent Nos. 5,487,902, 6,344,222, 6,432,383 and 5,470,566, the teachings of which are incorporated herein by reference.

Preparation of Candies and Lozenges

5 For example, the paste can be formed into candies and lozenges using known methods such as those disclosed in U.S. Patent No. 5,470,566, for example, the teachings of which are incorporated herein by reference.

It can also be used to make chewable capsules as described, for example, in U.S. Patent Application Publication No. U.S. 2003/0095925 A1, the teachings of which are
10 incorporated herein by reference.

Tests Involving the Administration of Metformin Gum

The chewing gum of Example 3 described above containing 212.5 mg of metformin hydrochloride per chiclet was administered to two subjects, individuals A and B. The subjects fasted overnight and the following morning were given one chiclet at
15 time = 0 which they chewed for 30 minutes and then spit out. After waiting 10 minutes, the subjects were given another chiclet to chew for another 30 minutes. The subjects then waited four hours and chewed a third chiclet before the first meal of the day for about 30 to 40 minutes. The concentration of metformin in the plasma of the individuals A and B (in ng/ml) was measured starting at time 0 and is plotted in Figure 1. Series 2 represents
20 the metformin plasma concentration for individual A. Series 3 represents the metformin plasma concentration for individual B.

A week before, individual B was given an 850 mg tablet of metformin hydrochloride sold in association with the trademark, GLUCOPHAGE, by Bristol-Meyers Squibb Co. The tablet was ingested in the morning at time = 0 after fasting
25 overnight. The concentration of metformin in the plasma of individual B (in ng/ml) was measured starting at time 0 and plotted in Figure 1 (see Series 1).

Peak plasma concentrations of metformin occurred after approximately 300 minutes in the control subject administered with GLUCOPHAGE and in one of the

subjects administered with the metformin gum. Peak plasma concentration of metformin in the second subject administered with the metformin gum occurred at approximately 360 minutes. In one of the individuals given the gum, the peak plasma concentration was over 2000 ng/ml as compared to a peak of under 1500 ng/ml in the subject given the
5 GLUCOPHAGE tablet. These results indicate that the gum is as or more effective than the tablets in delivering metformin hydrochloride to the bloodstream of human subjects, despite having far lower concentrations of metformin hydrochloride per three-chiclet dose.

Release of Metformin Hydrochloride from Chewing Gum

10 The paste preparation of Example 2 was made into three different chewing gum compositions using the known method described above. Flavored gum bases were used. The serial numbers used to identify each gum base and the chewing gum composition produced using each base are identified below.

Chewing gum composition 5475-01-1 made using cola flavored gum base 25084;

15 Chewing gum composition 5475-04-1 made using caramel flavored gum base 25046; and

Chewing gum composition 5475-05-1 made using coffee-caramel flavored gum base 25046.

20 The chewing gum compositions were in the form of one gram chiclets. The chiclets contained about 210, 217 and 214 mg of metformin hydrochloride respectively. It should be understood that the actual amount of metformin hydrochloride can vary in either direction by up to 5 %.

Each chiclet was put in a chewing machine containing a buffer solution. The chiclet was chewed at a rate of 60 chews per minute for 20 minutes. The amount of
25 metformin hydrochloride released into the buffer solution was measured using high performance liquid chromatography ("HPLC") at time = 2, 5, 10 and 20 minutes as was the percentage of metformin hydrochloride released. The results are summarised in Table 1 below and the percentage of drug released was plotted (see Figure 2).

Table 1

Sample	Assay mg/g	Release %			
		Chewing time			
		2 min.	5 min.	10 min.	20 min.
5475-01-1	210	57	91	89	95
5475-04-1	217	78	93	90	98
5475-05-1	224	78	91	93	94

Analytical data material to be found from ad hoc 9/04 43.06.

The initial release rate for gum composition 5475-01-1 is slower than for the other compositions due to the use of a slower release gum base.

5 The overall results show that metformin hydrochloride release is quite fast in all the compositions, with at least 90% of the pharmaceutical agent being released after just five minutes of chewing.

Example 5

Tests Comparing Metformin Gum with Metformin Tablets at the Same Dose Level

10 Chewing gum having the same composition as the composition of Example 3, except that the amount of metformin hydrochloride is 214.5 mg per chiclet (as opposed to 212.5 mg) was administered to a group of ten healthy volunteers (6 males, 4 females), with a mean age of 30 and 29.8 years respectively and a mean BMI of 23.9 and 21.49 respectively. At time = 0, each subject was given two chiclets to chew for a total dose of 429 mg metformin hydrochloride.

15 As a control, on another day, the same group of subjects was each given one 429 mg tablet of metformin hydrochloride sold in association with the trademark, GLUCOPHAGE, by Bristol-Meyers Squib Co.

Plasma samples (300 microlitres) obtained from the subjects were submitted to solid phase extraction (spe) with weak cation exchange prior to analysis with HPLC.

24

The concentration of metformin in the plasma of the subjects (in ppm) was measured starting at time = 0 minutes, and additional sampling occurred at 5, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 540, 720, 1440 minutes (24 hours). The volumes were plotted in Figure 3.

- 5 A Corresponding Areas under the Curve (AUC) analysis by ANOVA (f-test) and a pairwise t-test indicated that there was no significant difference in plasma concentrations of subjects given the gum as compared to subjects given the GLUCOPHAGE tablet, although the plasma concentrations with the gum tended to be higher. Peak plasma concentrations of metformin occurred at approximately 200 minutes
- 10 in both groups of subjects, with the peak plasma concentration almost 0.8 ppm in subjects given the gum versus almost 0.6 ppm in subjects given the GLUCOPHAGE tablet.

These results indicate that the gum is at least as effective as the tablets in delivering metformin hydrochloride to the bloodstream of human subjects.

- 15 While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

1. A preparation for use in making an oral transmucosal metformin composition, the preparation comprising:

a pharmaceutical agent consisting of metformin or a pharmaceutically acceptable salt thereof, and

an effective amount of at least one absorption enhancer chosen from an alkali metal alkyl sulfate, glycerin, a bile acid or bile salt, lecithin, hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening primrose oil, polyglycerin, lysine, polylysine, triolein, monoolein, monooleates, monolaurates, menthol, polidocanol alkyl ethers, chenodeoxycholate, deoxycholate and pharmaceutically acceptable salts and analogues thereof,

wherein the pharmaceutical agent is present in a concentration of from about 5 to 90 w/w % based on the total weight of the preparation.

2. An oral transmucosal metformin composition comprising:

an effective amount of a pharmaceutical agent consisting of metformin or a pharmaceutically acceptable salt thereof,

an effective amount of at least one absorption enhancer chosen from an alkali metal alkyl sulfate, glycerin, a bile acid or bile salt, lecithin, hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening primrose oil, polyglycerin, lysine, polylysine, triolein, monoolein, monooleates, monolaurates, menthol, polidocanol alkyl ethers, chenodeoxycholate, deoxycholate and pharmaceutically acceptable salts and analogues thereof, and

a pharmaceutically acceptable carrier, said carrier being capable of delivering a pharmaceutically effective amount of said pharmaceutical agent to an oral mucosal membrane for absorption.

3. The composition of claim 2, wherein each absorption enhancer is present in a concentration of up to about 30 w/w % of the total composition and the total concentration of the absorption enhancers is less than about 30 w/w % of the total composition.
4. The composition of claim 3, wherein each absorption enhancer is present in a concentration of less than about 7 w/w % of the total composition.
5. The composition of any one of claims 2 to 4, wherein the alkali metal alkyl sulfate is an alkali metal C8 to C22 alkyl sulfate.
6. The composition of claim 5, wherein the alkali metal C8 to C22 alkyl sulfate is sodium lauryl sulfate.
7. The composition of any one of claims 2 to 6, further comprising an isotonic agent, present in a concentration of up to about 30 w/w % of the total formulation.
8. The composition of claim 7, wherein said isotonic agent is glycerin.
9. The composition of any one of claims 2 to 8, further comprising a bile acid salt.
10. The composition of claim 9, wherein said bile salt is sodium glycocholate.
11. The composition of any one of claims 2 to 10, wherein said absorption enhancer is a micelle forming compound capable of forming micelles to encapsulate the pharmaceutical agent when the composition is formed into a solution in the oral cavity.
12. The composition of any one of claims 2 to 11, wherein the pharmaceutically acceptable salt of metformin is metformin hydrochloride.
13. The composition of any one of claims 2 to 12, wherein the amount of the pharmaceutical agent is from about 100 to 850 milligrams per dose.
14. The composition of claim 13, wherein the amount of the pharmaceutical agent is from about 100 to 500 milligrams per dose.

15. The composition of claim 14, wherein the amount of the pharmaceutical agent is about 250 to 500 milligrams per dose.
16. The pharmaceutical composition of any one of claims 2 to 15, in the form of chewing gum comprising metformin hydrochloride in a concentration of from about 10 to 50 w/w %, sodium lauryl sulfate in a concentration from about 0.01 to 2 w/w %, sodium glycocholate in a concentration of from about 0.01 to 2 w/w %, glycerin in a concentration of from about 2 to 10 w/w %, and a chewing gum base in a concentration of from about 10 to 90 w/w %, all based on the total weight of the composition.
17. The composition of any one of claims 2 to 15, wherein said carrier is a hard candy or lozenge.
18. The composition of any one of claims 1 to 17, wherein the membrane is the buccal membrane.
19. A process for making an oral transmucosal metformin composition comprising:
- mixing (a) an effective amount of a pharmaceutical agent consisting of metformin or a pharmaceutically acceptable salt thereof with (b) an effective amount of at least one absorption enhancer chosen from an alkali metal alkyl sulfate, glycerin, a bile acid or bile salt, lecithin, hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening primrose oil, polyglycerin, lysine, polylysine, triolein, monoolein, monooleates, monolaurates, menthol, polidocanol alkyl ethers, chenodeoxycholate, deoxycholate and pharmaceutically acceptable salts and analogues thereof, to form a paste;
- mixing the paste with a gum base; and
- forming the resultant mixture into chewing gum tablets, capsules, caplets or chiclets.
20. The composition of any one of claims 2 to 18 for use in treating diabetes in a subject.

21. Use of the composition of any one of claims 2 to 18 in the treatment of diabetes in a subject.
22. Use of the composition of any one of claim 2 to 18 in the manufacture of a medicament for the treatment of diabetes.
23. A method of treating diabetes comprising administering to the subject the composition of any one of claims 2 to 18.
24. The method of claim 23, wherein the composition is maintained in the mouth for at least 1 minute.
25. The method of claim 24, wherein the composition is maintained in the mouth for 1 minute to 30 minutes.
26. The method of claim 25, wherein the composition is maintained in the mouth for 1 minute to 20 minutes.
27. The method of claim 26, wherein the composition is maintained in the mouth for 1 minute to 9 minutes.
28. The method of claim 24, wherein the composition is maintained in the mouth for at least 30 minutes.
29. The method of claim 24, wherein the composition is maintained in the mouth for at least 20 minutes.
30. A method of increasing sensitivity to insulin in a subject, comprising administering to the subject the composition of any one of claims 2 to 18.
31. A method of decreasing intestinal absorption of glucose in a subject, comprising administering to the subject the composition of any one of claims 2 to 18.
32. A method of decreasing hypoglycemia in a subject, comprising administering to the subject the composition of any one of claims 2 to 18.

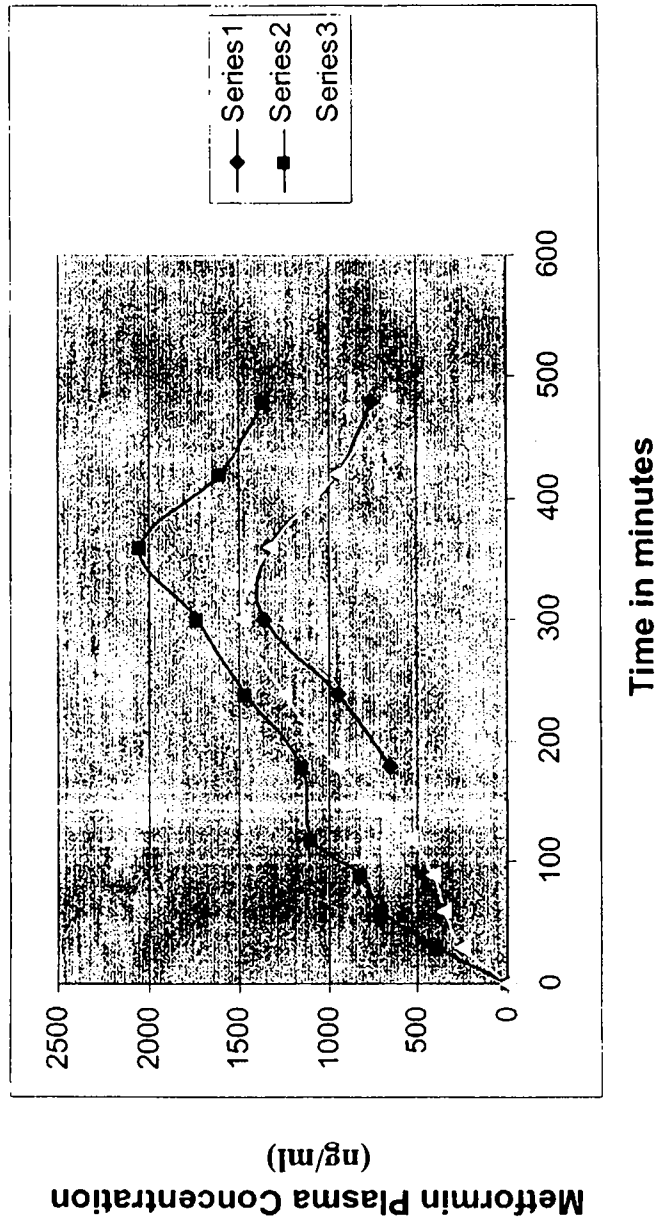
33. A method of decreasing the body weight of a subject, comprising administering to the subject the composition of any one of claims 2 to 18.

34. A method of reducing a subject's appetite, comprising administering to the subject the composition of any one of claims 2 to 18.

35. A method of treating obesity in a subject, comprising administering to the subject the composition of any one of claims 2 to 18.

36. A method of treating polycystic ovary syndrome in a subject, comprising administering to the subject the composition of any one of claims 2 to 18.

FIGURE 1



2/3

FIGURE 2

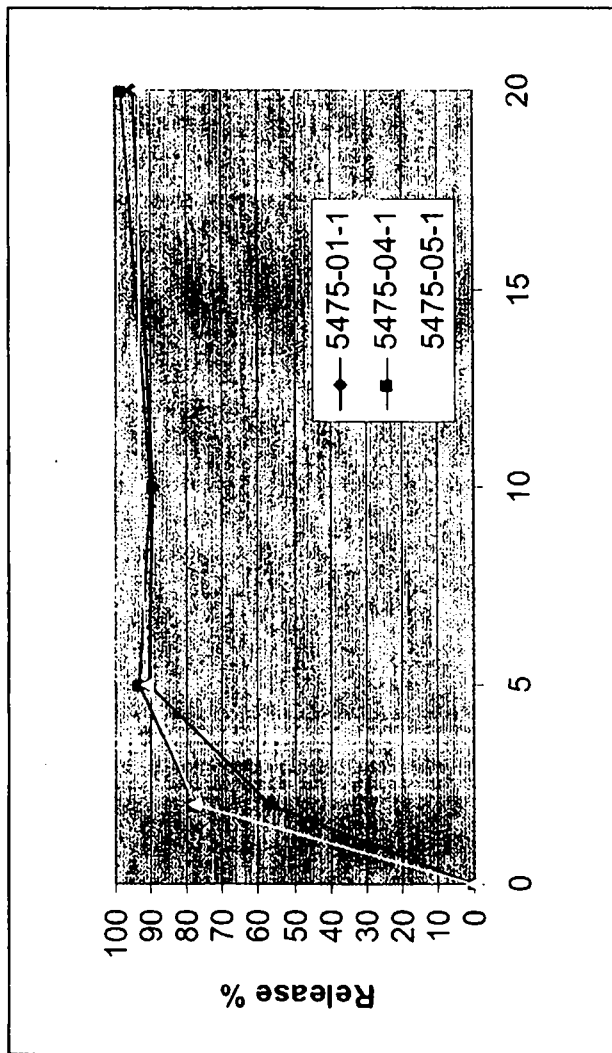
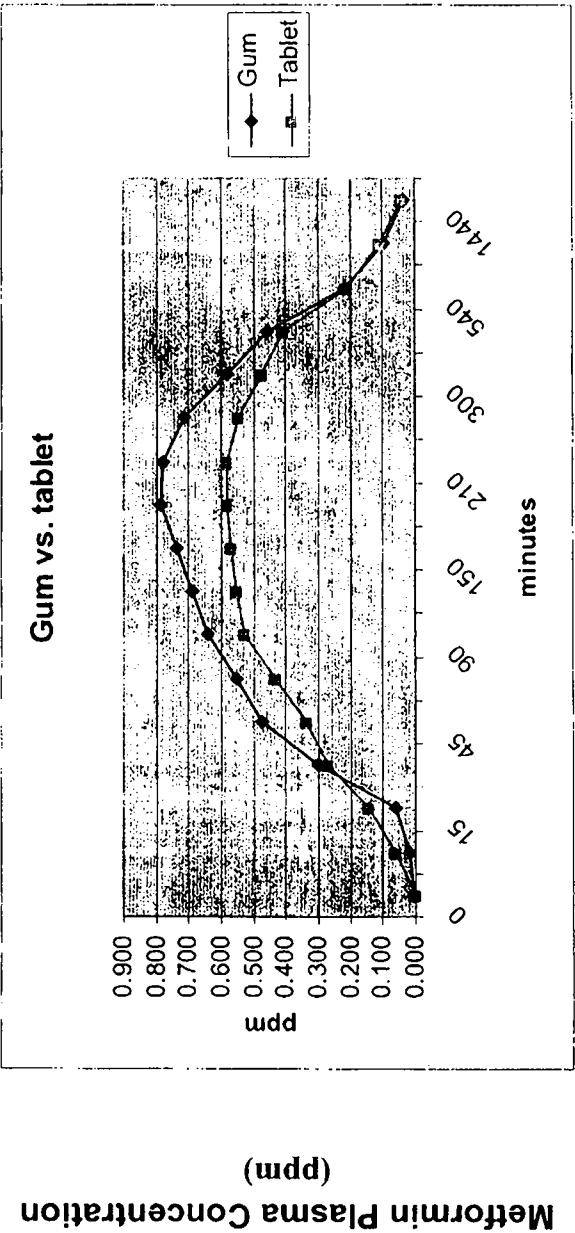


FIGURE 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000472

A. CLASSIFICATION OF SUBJECT MATTER IPC: A61K 31/155 (2006.01), A61P 3/10 (2006.01), A61P 3/04 (2006.01), A61K 47/00 (2006.01) 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 (2006.01); A61P (2006.01)		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) DWPI/Delphion; Canadian Patent database- full text plus bibliography; STN-structure and keywords, Scopus, PubMed, Google™; metformin, biguanide, oral, transmucosal, absorption enhancer or promoter		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2005/041923 A1 (ALZA CORPORATION) 12 May 2005 (12-05-2005) see abstract; page 3, paragraph [007]; page 12, paragraphs [0075]-[0076]; page 29, paragraph [0132]; page 31, paragraph [0139]; examples, and claims 1-8, 12, 16-17.	1-6, 12-13, 20-23 and 31-35
X Y	WO 99/42086 A1 (MERCK PATENT GMBH) 26 August 1999 (26-08-1999) see abstract; page 3, lines 29-35; page 4, lines 16-17; page 6, lines 24-34; page 7, line 5; page 11, line 35-page 12, line 2; page 13, lines 1-2 & 7-10, and claim 12.	1 2-10 and 12-36
X Y	WO 99/47125 A1 (ANDRX PHARMACEUTICALS, INC.) 23 September 1999 (23-09-1999) see page 3, lines 27-30; page 5, lines 1-15; page 9, lines 5-10;	1 2-10 and 12-36
☒ 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 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	"I" 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 "E" document member of the same patent family	
Date of the actual completion of the international search 24 May 2006 (24-05-2006)	Date of mailing of the international search report 13 July 2006 (13-07-2006)	
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage 1, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Connic Kuang (819) 934-3597	

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000472

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 02/036100 A1 (ANDRX CORPORATION) 10 May 2002 (10-05-2002) see abstract; page 2, pages 3-4; page 14; page 15; page 18; Example 1 and claim 29.	1 2-10 and 12-36
Y	WO 91/01132 (FERTIN LABORATORIES LTD) 07 February 1991 (07-02-1991) see abstract; page 3, lines 8-11; page 6, lines 13-14; page 11, lines 9 & 14, and page 17, lines 28-29.	2-10 and 12-36
Y	US 6,432,383 B1 (GENEREX PHARMACEUTICALS INC.) 13 August 2002 (13-08-2002) see abstract; column 4, lines 63-66, and Example 13.	2-36
A	MATHIOWITZ, E. Encyclopedia of Controlled Drug Delivery. New York: John Wiley & Sons, 1999, Volumes 1 & 2, ISBN 0-471-14828-8, page 738.	

35

INTERNATIONAL SEARCH REPORT

International application No
PCT/CA2006/000472**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. ☒ Claim Nos. : 23-36
because they relate to subject matter not required to be searched by this Authority, namely :

Claims 23-36, directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search (PCT Rule 39.1 (iv)). Regardless, this Authority has carried out a search based on the alleged effect(s) or purpose(s)/use(s) of the product defined.
2. ☐ Claim 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. ☐ Claim Nos. :
because they are dependant 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 additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
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 claim 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 claim 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.

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Information on patent family members

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COMPOSICIONES PARA LA TRANSMISION TRANSMUCOSA ORAL DE LA METFORMINA

ANTECEDENTES DE LA INVENCION

La Metformina y las sales farmacéuticamente aceptables de las mismas (e.j. 5 hidrocloruro de metformina, *N,N*-dimetilimidodicarbonimidica diamida hidrocloruro) han sido utilizados para tratar gran número de enfermedades, incluyendo la diabetes, pre-diabetes, la enfermedad del ovario policístico y la obesidad. Los mecanismos de acción de la Metformina incluyen niveles de glucosa del plasma disminuido (particularmente, niveles de glucosa posprandial), producción disminuida de la glucosa hepática, niveles 10 disminuidos de lípidos, sensibilidad aumentada a la insulina, y/o absorción intestinal disminuida. Asimismo, la metformina actúa sin causar hipoglicemia.

Las formulaciones orales (tabletas) de la metformina (e.j. GLUCOPHAGE, Bristol Meyers Squibb Co.) son las que se utilizan actualmente. La administración de las formulaciones orales de metformina pueden resultar en una gran cantidad de efectos 15 secundarios. Los efectos Adversos relacionados con el uso de las formulaciones orales de metformina son generalmente de naturaleza gastrointestinal (ej. anorexia, nausea, hinchazón, vómitos y en ocasiones, diarrea, etc.). Asimismo, las formulaciones orales de la metformina pueden dar lugar a un retrogusto amargo, que puede llevar a la pérdida del apetito. Los efectos secundarios resultan generalmente en el incumplimiento de los 20 pacientes de tomar la medicación, es decir, "cuestiones de cumplimiento". Las cuestiones de cumplimiento prevalecen en los individuos de todas las edades, incluyendo los niños, que en general, no quieren tomar medicamentos que tienen mal gusto.

Por lo tanto, existe la necesidad importante de las formulaciones de metformina que, por lo menos, mitigan uno de estos problemas para ayudar al cumplimiento.

25 RESUMEN DE LA INVENCION

De acuerdo con un primer aspecto, la invención proporciona una composición de metformina de transmucosa oral, que comprende un vehículo farmacéuticamente aceptable y una cantidad eficaz de un agente farmacéutico que consiste en metformina o una sal farmacéuticamente aceptable contenida en el referido vehículo, el referido

vehículo es capaz de entregar una cantidad farmacéuticamente efectiva del referido agente farmacéutico a una membrana mucosa oral para su absorción.

De acuerdo con un segundo aspecto, se provee un proceso para realizar la composición de metformina transmucosa oral, que comprende la mezcla de una cantidad efectiva del agente farmacéutico que consiste en metformina o una sal farmacéuticamente aceptable del mismo con una cantidad efectiva de por lo menos, un acelerador de la absorción seleccionado de álcali metal alquil sulfato, glicerina, ácido biliar o sal biliar, lecitina, ácido hialurónico, octilfenoxipolietoxietanol, ácido glicólico, ácido láctico, extracto de camomila, extracto de pepino, ácido oleico, ácido linolénico, aceite de borraja, aceite de enotera, poliglicerina, lisina, polilisina, trioleina, monooleina, monooleatos, monolauratos, mentol, polidocanol alquil éteres, quenodeoxicolato, deoxicolato y sales farmacéuticamente aceptables y análogos de los mismos, para formar una preparación. La preparación se combina con un vehículo farmacéuticamente aceptable adecuado, para realizar la composición actual.

De acuerdo con un aspecto adicional, la invención suministra un método de utilización, y el uso de una, composición que trata varias condiciones seleccionadas de diabetes, pre-diabetes, obesidad y síndrome de ovario policístico. La presente composición puede ser útil para reducir los niveles de glucosa del plasma, reducir la producción de glucosa hepática, reducir los niveles de lípidos, aumentar la sensibilidad a la insulina, disminuir la absorción intestinal de la glucosa, disminuir la hipoglicemia y reducir el apetito. El método consiste en administrar a un sujeto una composición de acuerdo con el primer aspecto, a fin de tratar las referidas condiciones. La invención también suministra el uso de la composición en la fabricación de un medicamento para el tratamiento de las mismas enfermedades. La composición puede ser mantenida en la boca por, por lo menos, 1, 20 o 30 minutos. También, la composición puede ser mantenida en la boca de 1 a 30 minutos, de 1 a 20 minutos o de 1 a 9 minutos.

De acuerdo con un aspecto adicional, la invención suministra una preparación para ser utilizada en la elaboración de una composición de acuerdo con el primer aspecto. La preparación comprende un agente farmacéuticamente aceptable que consiste en metformina o una sal farmacéuticamente aceptable del mismo, y una cantidad efectiva de

por lo menos, un acelerador de la absorción seleccionado de alcali metal alquil sulfato, glicerina, un ácido biliar o una sal biliar, lecitina, ácido hialurónico, octilfenoxipolietoxietanol, ácido glicólico, ácido láctico, extracto de camomila, extracto de pepino, ácido oleico, ácido linolénico, aceite de borraja, aceite de enotera, poliglicerina, lisina, polilisina, trioleina, monooleina, monooleatos, monolauratos, mentol, polidocanol alquil éteres, quenodeoxicolato, deoxicolato y las sales farmacéuticamente aceptables y análogos del mismo, en el cual el agente farmacéutico está presente en una concentración de 5 a 90, 10 a 80, 20 a 80 o 20 a 50 w/w %, y la concentración total de los aceleradores de la absorción es menor a 30, 20, 10, 7, 5, 2, 1, 0.5, o 0.01 w/w % todos basados en el peso total de la preparación.

La presente invención posee una cantidad de ventajas. Al realizar el by-pass del tracto gastrointestinal (GI), se evitan las complicaciones gastrointestinales y los efectos secundarios de las formulaciones orales de metformina y sus sales pueden evitarse. En las formulaciones conocidas que se ingieren, una alta cantidad del agente farmacéutico se requiere por dosis debido al problema de la degradación del tracto GI. Las composiciones actuales que producen el agente farmacéutico a través de membranas de mucosas orales, pueden ser formuladas con menos ingrediente activo. Esto da como resultado ahorros en costos y ayuda a mejorar el perfil del gusto.

BREVE DESCRIPCIÓN DE LAS ILUSTRACIONES

Los precedentes y otros objetos, funciones y ventajas de la invención, serán aparentes en la siguiente descripción más particular de las realizaciones preferidas de la invención, y los diseños que se adjuntan.

La figura 1 es una gráfica que muestra las concentraciones de plasma de metformina plasma (ng/ml) a través del tiempo. La Serie 1 describe la concentración del plasma de la metformina en un individuo al que se le ha administrado 850 mg de una tableta de hidrocloreto de metformina, para ingerir. La Serie 2 y 3 representan las concentraciones de plasma de metformina en dos individuos que masticaron tres chicles de goma de mascar y cada uno contenía 212.5 mg de metformina.

La Figure 2 es un gráfico que muestra la cantidad de metformina liberada de las

composiciones de goma de mascar, de acuerdo con la presente invención a través del tiempo.

La Figura 3 es un gráfico que compara las concentraciones de plasma de metformina (ppm) a través del tiempo en individuos a los que se les administró 429 mg de
5 tableta de metformina para ingerir con los individuos que masticaron goma que contenía 429 mg de metformina.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Sigue descripción de las realizaciones preferidas de la invención.

Composiciones Farmacéuticas

10 En una realización, la invención es una composición de metformina transmucosa oral que comprende:

Una cantidad efectiva de un agente farmacéutico que consiste en metformina o una sal farmacéuticamente aceptable de la misma,

15 Una cantidad efectiva de por lo menos, un acelerador de la absorción elegido de3 un sulfato de alquil metal álcali, glicerina, ácido biliar o sal biliar, lecitina, ácido hialurónico, octilfenoxipolietoxietanol, ácido glicólico, ácido láctico, extracto de camomila, extracto de pepino, ácido oléico, ácido linolénico, aceite de borraja, aceite de
20 enotera, poliglicerina, lisina, polilisina, trioleina, monooleina, monooleatos, monolauratos, mentol, polidocanol alquil éteres, quenodeoxicolato, deoxicolato y sales farmaceúticamente aceptables y análogos de los mismos, y

Un vehículo farmacéuticamente aceptable, dicho vehículo es capaz de entregar una cantidad farmacéuticamente efectiva del referido agente farmacéutico a una membrana mucosa oral, para su absorción.

25 La sal farmacéuticamente aceptable de metformina puede ser hidrocloreuro de metformina.

En una realización, la composición farmacéutica está en forma de goma de mascar

que comprende hidrocloreto de metformina en una concentración de 10 a 50 w/w %, sulfato de lauril de sodio en una concentración de 0.01 a 2 o 0.01 a 0.5 w/w %, glicolato de sodio en una concentración de 0.01 a 2 o 0.01 a 0.5 w/w %, glicerina en una concentración de 2 a 10 o 2 a 7 w/w %, y una base de goma de mascar en una
 5 concentración de alrededor de 10 a 90 , 30 a 75, o 60 a 75 w/w %, todos basados en el peso total de la composición. En otra realización, la composición es en forma de caramelo duro o gragea.

En otra realización, la invención es un proceso para la elaboración de una composición de metformina transmucosa oral que comprende:

10 La mezcla de (a) una cantidad efectiva de un agente farmacéutico que consiste en metformina o sal farmacéuticamente aceptable de la misma con (b) una cantidad efectiva de por lo menos, un acelerador de la absorción seleccionado de álcali metal alquil sulfato, glicerina, ácido biliar o sal biliar, lecitina, ácido hialurónico, octilfenoxipolietoxietanol, ácido glicólico, ácido láctico, extracto de camomila, extracto de pepino, ácido oleico,
 15 ácido linolénico, aceite de borraja, aceite de enotera, poliglicerina, lisina, polilisina, trioleína, monooleína, monooleatos, monolauratos, mentol, polidocanol alquil éteres, quenodeoxicolato, deoxicolato y sales farmacéuticamente aceptables y análogos de los mismos, para formar una pasta Mezcla de la pasta con base de goma; y Formar la mezcla resultante de las tabletas de goma de mascar, cápsulas, cápsulas o chicles.

20 Sales farmacéuticamente aceptables y análogos de cualesquiera aceleradores de la absorción revelada están también dentro del actual rango así como las mezclas o combinaciones de cualquiera de estos componentes.

Los aceleradores de la absorción son aquellos que facilitan la entrega de un agente farmacéutico a través de las membranas mucosas orales. Tal como se utiliza aquí,
 25 "facilitar" se refiere a aumentar la velocidad y/o cantidad del agente farmacéutico entregado a través de la membrana mucosa oral (ej. Por lo menos, alrededor de 5%, 10%, 20%, 25%, 30%, 35%, 40%, 50%, 60%, o 75%) comparado con una composición farmacéutica en la cual el acelerador de la absorción está ausente.

Cada acelerador de la absorción puede estar presente en una concentración de

hasta 30, 20, 15, 10, 5, 2, 1, 0.5, o 0.01 w/w % basándose en el peso total de la composición. La cantidad total de los aceleradores de absorción es menor que 30, preferentemente menor de 20, y más preferentemente, menor de 10 o 7 w/w % basándose en el peso total de la composición.

- 5 Los aceleradores de la absorción son compuestos que forman Micela, que sirven para encapsular el agente farmacéutico y facilitar la entrega a través de las membranas mucosas orales, cuando se forma la composición en una solución en la cavidad oral.

10 Como puede ser observado por aquellos expertos en la materia, una micela es un agregado coloidal de moléculas anfipáticas en las cuales las porciones de hidrofílico polar de la molécula se extienden hacia fuera, mientras que las porciones hidrofóbicas no-polares se extienden hacia adentro. Se cree que la presencia de micelas ayuda significativamente en la absorción del agente farmacéutico tanto debido a su habilidad de absorción mejorada, y además, debido a su tamaño. Asimismo, encapsular los agentes farmacéuticos en micelas protege a los agentes de la degradación rápida.

- 15 Puede ser entendido que cada micela puede contener un agente farmacéutico y uno o más aceleradores de la absorción (es decir, compuestos que forman micela). Preferentemente, por lo menos, dos compuestos que forman Micela son utilizados para formar micelas mixtas. Tal como se utiliza en el presente, el término "micelas mixtas" se refiere a, por lo menos, dos tipos diferentes de micelas cada uno de los cuales ha sido
20 formado utilizando un compuesto diferente de formación de micela. Por ejemplo, las composiciones actuales pueden comprender una mezcla de, por lo menos, dos tipos diferentes de micelas: micelas formadas entre el agente farmacéutico y uno de los compuestos que forman micelas (ej. Sulfato de alquil metal alcali), y las micelas formadas entre el agente farmacéutico y por lo menos, un compuesto adicional de
25 formación de Micela (ej. Glicolato de sodio). Se entiende que cada Micela individual puede formarse de más de un compuesto de formación de micela, también.

Preferentemente, el tamaño de las micelas es mayor a 6 micrones, si bien pueden ser menores, tales como de 1 a 10 nanómetros, o de 1 a 5 nanómetros. La forma de la micela puede variar y puede ser, por ejemplo, prolato, achatado o esférica; las micelas
30 esféricas son las más típicas. Se estima que el tamaño extremadamente pequeño de las

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micelas ayuda a que el agente farmacéutico encapsulado penetre eficazmente a través de la mucosa oral. Por lo tanto, las composiciones actuales ofrecen una biodisponibilidad aumentada de la droga activa, particularmente a través de la mucosa oral, cuando se compara con las preparaciones farmacéuticas conocidas en la técnica.

- 5 Todo sulfato alcali metal alquil puede utilizarse en las composiciones actuales, con la condición de que no surjan problemas de compatibilidad. Preferentemente, el alquil es C8 a C22 alquil, más preferentemente lauril (C12). Cualquier alcali puede ser utilizado, con sodio preferentemente. Mientras que el sulfato de alcali metal alquil está generalmente presente en la concentración de hasta 30 w/w %, una concentración de hasta
- 10 alrededor de 5 w/w % del total de la composición se prefiere. Se prefiere aun más la concentración de hasta alrededor de 1, 0.5 o 0.01 w/w % del total de la composición.

- Tal como se utiliza en el presente, el término "ácido biliar" incluye, aunque no se limita a, los derivados ácidos cólicos tales como cólico, glicólico, quenodeoxicólico, taurocólico, glicodeoxicólico y ácidos taurodeoxicólicos. Cualesquiera ácidos biliares, o
- 15 sales de los mismos, pueden ser utilizados en composiciones de la presente invención. Se prefiere el sodio glicolato. Debido a que la presente invención utiliza concentraciones relativamente bajas de sales biliares, el problema de la toxicidad relacionado con el uso de las referidas sales se minimiza, o puede incluso evitarse.

- La lecitina puede ser saturada o insaturada, y se elige preferentemente de la
- 20 Fosfatidilcolina, fosfatidilserina, sfingomielin, fosfatidiletanolamina, cefalina, y lisolecitina.

- Las sales preferidas del ácido hialurónico son hialuronatos alcali metal, especialmente, hialuronato de sodio, hialuronatos de tierra alcalina, y hialuronato de aluminio. Cuando se utiliza el ácido hialurónico o las sales farmacéuticamente aceptables
- 25 del mismo en las composiciones actuales, una concentración de cerca de 1 y 5 w/w % del total de la composición se prefiere, más preferentemente entre 1.5 y 3.5 w/w %.

 La composición puede comprender asimismo un agente isotónico en una concentración de hasta 30, 20, 15, 10 o 6 w/w % de la composición total. Los agentes isotónicos apropiados incluyen, aunque no se limitan a, los sacáridos, tales como sorbitol

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y manitol, y los alcoholes polihídricos tales como glicerina, poliglicerina, propileno glicol y similares, y el fosfato de sodio dibásico. Se prefiere la glicerina. El agente isotónico sirve para mantener las micelas en la solución. La glicerina puede funcionar tanto como un compuesto formador de micela y como agente isotónico; cuando se utiliza el fosfato de sodio dibásico, también servirá para inhibir el crecimiento bacterial.

Opcionalmente, la composición farmacéutica puede comprender uno o más agentes terapéuticos adicionales (ej. sulfonureas). Tal como se utiliza en el presente, el término "agente terapéutico" se refiere a un agente que mejora una enfermedad o los síntomas relacionados con la enfermedad, incluyendo la prevención o retraso del inicio de los síntomas de la enfermedad, y/o disminuir la gravedad o frecuencia. En una realización, el agente terapéutico se utiliza para tratar la diabetes, pre-diabetes, obesidad o enfermedad del ovario policístico.

Una cantidad efectiva del agente farmacéutico debería incluirse en la presente composición. Tal como se utiliza en el presente, el término "cantidad eficaz" se refiere a una cantidad del agente farmacéutico necesaria para provocar el resultado deseado, tal como la obtención del tratamiento terapéutico esperado o la prevención de una enfermedad en un paciente, o regular una enfermedad fisiológica en un paciente. Por lo tanto, la referida cantidad puede ser entendida por tener un efecto terapéutico y/o profiláctico en un paciente. Se apreciará que la cantidad efectiva variará dependiendo del agente específico utilizado, de los parámetros determinados para el agente, de la naturaleza y seriedad de la enfermedad que está siendo tratada, del paciente que está siendo tratado y las características del vehículo utilizado.

Una "cantidad efectiva" puede ser también la cantidad requerida de modo que las concentraciones más altas de plasma de metformina son aproximadamente iguales a las concentraciones más altas de plasma de metformina en un sujeto al que se le administró una tableta de hidrocloreto de metformina oral (por ejemplo, una tableta de hidrocloreto de metformina que contiene cerca de 50, 100, 250, 500, 750, 800 o 1000 mg de hidrocloreto de metformina). Tal como se utiliza en el presente, "aproximadamente igual" significa que la concentración más alta de plasma de metformina luego de la administración de la composición farmacéutica de la invención (evaluada utilizando mediciones de

biodisponibilidad estándar) está dentro del 10% de la concentración más alta de plasma de metformina, luego de administrar una formulación oral de metformina en tableta.

Se entenderá que cualquier disminución en los niveles de la glucosa del plasma, producción glucosa hepática, niveles de lípidos, absorción intestinal o pérdida de peso
5 pueden ser terapéuticos y/o profilácticos, como puede ser cualquier incremento en la sensibilidad de la insulina. El nivel de dosis precisa debería ser determinado por el médico tratante u otro proveedor de cuidado de la salud, y dependerá de factores conocidos, incluyendo la edad, peso corporal, sexo y salud general del individuo, y la utilización (o no) de terapias concomitantes. Por supuesto, la persona experta notará que
10 las dosis divididas y parciales están también dentro del rango de la invención. La determinación de lo que constituye una cantidad efectiva está dentro de la habilidad de quien practica la técnica.

Las dosis farmacéuticamente efectivas pueden ser extrapoladas desde curvas de respuesta a las dosis, derivadas de sistemas de ensayo in vitro o con modelos animales in.
15 También pueden ser determinados midiendo la biodisponibilidad de las formulaciones orales conocidas del hidrocloreto de metformina. La composición farmacéutica de la invención pueden entonces ser formulada en una dosis que posee una biodisponibilidad que se aproxima a la biodisponibilidad de las formulaciones orales conocidas.

La cantidad de agente farmacéutico puede oscilar entre 50 a 850 miligramos.

20 Típicamente, las composiciones actuales pueden contener cerca de 50 a 500 miligramos por dosis. Dependiendo del régimen de dosis, cada dosis puede contener 50, 112.5, 250 miligramos o 500 miligramos. Se puede observar que la cantidad variará dependiendo de, entre otras cosas, las características de liberación del vehículo empleado. La cantidad del ingrediente activo se ajustará de modo que la cantidad del agente
25 farmacéutico liberado tenga el efecto esperado terapéutico y/o efecto profiláctico.

Cada dosis puede contener entre 5 a 90, más preferentemente de 10 a 80 w/w %, y más preferentemente, entre 20 a 80 o 20 a 50 w/w % del agente farmacéutico basándose en el peso total de la composición, dependiendo de la cantidad del vehículo presente.

Las composiciones presentes contienen opcionalmente un estabilizador y/o

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preservativo. Los compuestos fenólicos son particularmente adecuados para este propósito ya que no solo estabilizan la composición, sino que también protegen contra el crecimiento bacteriano y ayudan a la absorción de la composición. Un compuesto fenólico puede ser entendido como refiriéndose a un compuesto que posee uno o más grupos hidroxilo, adjuntos directamente a un anillo de benceno. Los compuestos fenólicos preferidos de acuerdo con la presente incluyen, fenol y metil fenil (también conocido como m-cresol), y mezclas de los mismos.

Las composiciones de la presente invención pueden comprender asimismo, uno o más de los siguientes: sales inorgánicas; antioxidantes e inhibidores de proteasa. La cantidad de cualquier de estos ingredientes opcionales para ser utilizados en las composiciones actuales, puede ser determinada por algún experto en la materia.

La sal o sales inorgánicas deberían ser aquellas que pudieran proveer estimulación adicional para liberar insulina. Los ejemplos no limitados de las sales inorgánicas son sodio, potasio, calcio y sales de zinc, especialmente, cloruro de sodio, cloruro de potasio, cloruro de calcio, cloruro de zinc y bicarbonato de sodio.

Se utiliza el antioxidante para prevenir la degradación y oxidación de los ingredientes farmacéuticamente activos. El antioxidante puede ser elegido de tocoferol, mesilato de ascorbato, metil parabeno, etil parabeno, ácido ascórbico y mezclas de los mismos, como también otros antioxidantes conocidos en las técnicas farmacéuticas. Un antioxidante preferido es el tocoferol. Los parabenos también ofrecerán preservación a la composición.

Los inhibidores de proteasa sirven para inhibir la degradación del agente farmacéutico por acción de las enzimas proteolíticas. Cuando se utilizan, los inhibidores de proteasa son preferentemente en la concentración de entre 1 y 3 w/w % de la composición. Puede utilizarse cualquier material que pueda inhibir la actividad proteolítica y evitar los problemas de compatibilidad. Los ejemplos incluyen pero no se limitan a la bacitracina y derivados de bacitracina, tales como bacitracina metileno disalicilatos, tripsina de soja, y aprotinina. La bacitracina y sus derivados se utilizan preferentemente en la concentración de entre 1.5 y 2 w/w % de la composición total, mientras que la tripsina de soja y la aprotinina se utilizan preferentemente en una

concentración entre aproximadamente 1 y 2 w/w % de la composición total.

Los expertos en la técnica entienden que los colorantes, agentes saborizantes y las cantidades no terapéuticas de otros compuestos pueden también incluirse en la composición. Cuando se utiliza el mentol como uno de los compuestos formadores de micela, también aportará sabor a la composición.

Los agentes saborizantes pueden ser aceites esenciales, esencias, extractos, talcos, ácidos y otras sustancias capaces de afectar el perfil del gusto. Los sabores que pueden utilizarse incluyen, aunque no se limitan a, coco, café, cola, chocolate, vainilla, pomelo, mentol, licor, anís, damasco, caramelo, miel, ananá, frutilla, frambuesa, frutas tropicales, cerezas, canela, menta, wintergreen (menta herbal), menta suave, eucalipto y sabores de la menta. En otra realización, los sabores se seleccionan del mentol, caramelo, café y cola.

Los colorantes que son utilizados son de origen sintético o natural y pueden ser aprobados para su utilización en alimentos o medicamentos.

El vehículo puede ser formulado en varias formas tales como formas de animal o estrellas para atraer más a los niños.

Las composiciones de la presente invención pueden almacenarse a temperatura ambiente o a baja temperatura.

El agente farmacéutico se administrará a través de las membranas mucosas orales o "mucosa oral". Estas incluyen las membranas de la boca, garganta, laringe y esófago. Se prefieren las membranas de la boca, en particular, la mucosa bucal y sublingual. La mucosa sublingual incluye la membrana de la superficie ventral de la lengua y el piso de la boca, y la mucosa bucal es la cobertura de las mejillas. Las mucosas sublinguales y bucales son relativamente permeables, permitiendo una rápida absorción y una biodisponibilidad aceptable de muchas drogas. Asimismo, las mucosas bucales y sublinguales son convenientes, no evasivas y de fácil acceso. En comparación con el tracto GI y con otros órganos, el ambiente bucal posee una actividad enzimática menor y un pH neutral que permite una vida eficaz más larga de la droga in vivo.

El vehículo está diseñado para liberar una cantidad suficiente del agente farmacéutico y para reside en la boca durante un período de tiempo suficiente para la absorción del agente, de modo de producir un efecto terapéutico y/o profiláctico en un paciente. Para una absorción mejorada, el vehículo preferentemente debe poder moverse en la boca de modo de alcanzar un área de superficie incrementada de las membranas mucosas orales. En las realizaciones preferidas, el vehículo está formulado como un caramelo masticable (ej. Chicle o caramelo blando) o como caramelo duro o pastilla para chupar, que puede ser masticado o chupado durante un período de tiempo suficiente mientras el caramelo se mueve por las membranas mucosas orales. La cantidad de agente farmacéutico liberado es superior a 50, 60, 70, 80, o 90% durante el período de tiempo en que el vehículo reside en la boca. Este período de tiempo es de 1 a 30, preferentemente entre 1 a 20, y más preferentemente entre aproximadamente 1 a 10 minutos. Cuando se libera en la boca y disuelve en la saliva, el agente farmacéutico estará presente en forma micelar ya que es encapsulado por los aceleradores de absorción de formación micelar. El experto en la técnica entenderá rápidamente cómo realizar vehículos adecuados basados en las enseñanzas del presente y en el conocimiento común de la técnica.

Proceso para la Realización de la Composición

La presente invención también suministra un proceso para la elaboración de la composición farmacéutica de la presente invención. Las composiciones presentes pueden prepararse mezclando una cantidad efectiva de un agente farmacéutico que consiste en metformina o una sal farmacéuticamente aceptable del mismo, con una cantidad eficaz de por lo menos, un acelerador de la absorción elegido de álcali metal alquil sulfato, glicerina, ácido biliar o sal biliar, lecitina, ácido hialurónico, octilfenoxipoliétoxietanol, ácido glicólico, ácido láctico, extracto de camomila, extracto de pepino, ácido oleico, ácido linolénico, aceite de borraja, aceite de enotera, poliglicerina, lisina, polilisina, trioleína, monooleína, monooleatos, monolauratos, mentol, polidocanol alquil éteres, quenodeoxicolato, deoxicolato y sales farmacéuticamente aceptables y análogos de los mismos, para formar una preparación para ser combinada con un vehículo farmacéuticamente aceptable.

El proceso puede comprender la etapa de agregar uno o más ingredientes

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seleccionados de los agentes isotónicos, estabilizadores, preservantes, antioxidantes, inhibidores de la proteasa y sales inorgánicas.

La mezcla puede ser efectuada mediante la utilización de un agitador de alta velocidad tal como un Batidor de la Serie HD profesional de Ayuda en la Cocina, para
5 uso en laboratorio o similar.

Para realizar una composición de goma de mascar, el proceso puede comprender asimismo las siguientes etapas:

Mezclar la preparación con base de goma; y

Elaborar la mezcla resultante en tabletas tipo goma de mascar, cápsulas, cápsulas
10 o chicles.

Las cantidades específicas de los ingredientes pueden determinarse por el experto en la técnica basándose en los lineamientos generales que se disponen en el presente.

Método del Tratamiento

La invención proporciona un método para el tratamiento de enfermedades tales
15 como diabetes, pre-diabetes, obesidad y síndrome del ovario policístico, que comprenden administrar a un sujeto una composición de acuerdo con el primer aspecto de la invención. Las presentes composiciones pueden ser útiles para disminuir el nivel de glucosa del plasma en un sujeto (ej. Nivel de glucosa posprandial), disminuir la producción de glucosa hepática, disminuir los niveles de los lípidos, aumentar la
20 sensibilidad a la insulina, disminuir la absorción intestinal de la glucosa, disminuir la hipoglicemia, disminuir el disminuir el peso corporal y/o reducir el apetito.

Donde la composición es forma de caramelo masticable o caramelo duro o pastilla, el método incluye masticar y/o chupar un caramelo durante un período de tiempo suficiente para la liberación y absorción del agente farmacéutico en forma micelar, a fin
25 de producir un efecto terapéutico y/o profiláctico en un paciente.

La composición farmacéutica puede suministrarse en una sola dosis (ej. Una pieza o goma o caramelo) o puede suministrarse en dosis múltiples que se administran en serie.

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La frecuencia de la administración y la cantidad de metformina o su sal tomada por dosis serán determinadas por la prescripción del doctor, basándose en la naturaleza y la gravedad de la enfermedad a ser tratada y en otros factores, incluyendo aunque no limitándose a, el sexo, peso, salud y edad del sujeto.

- 5 El método puede también incluir las etapas de administración de uno o más agentes terapéuticos para tratar la diabetes, pre-diabetes, obesidad, y/o síndrome del ovario polycístico y/o producir pérdida de peso. Los agentes terapéuticos para las enfermedades anteriores son conocidos en la técnica, y la dosis de una terapia combinada puede ser determinada por el médico o practicante. Por ejemplo, una composición
- 10 farmacéutica de la invención puede ser administrada al mismo tiempo como otro/s agente/s terapéutic/os, o alternativamente en diferentes momentos del día. En particular, la composición farmacéutica de la invención puede administrarse en combinación con la insulina para el tratamiento de la diabetes. Cuando se utilizan las composiciones farmacéuticas de la invención en combinación con insulina, la cantidad de insulina
- 15 requerida para el control de la diabetes puede reducirse.

- Tal como se utiliza en el presente, “diabetes” o “diabetes mellitus” se refiere a la enfermedad caracterizada por la hiperglicemia. La hiperglicemia puede ser el resultado de un perjuicio absoluto o relativo en la secreción de insulina y/o acción de la insulina. Los métodos para detectar la hiperglicemia son conocidos en la técnica y generalmente,
- 20 implican la medición de los niveles de glucosa del plasma. En los pacientes asintomáticos, la diabetes puede ser diagnosticada cuando se cumplen los criterios diagnósticos de la hiperglicemia en ayuno: un plasma (o suero) nivel de glucosa de ≥ 140 mg/dL (≥ 7.77 mmol/L) (recomendado por el Grupo Nacional de Datos de Diabetes (NDDG)) luego del ayuno en dos ocasiones en un adulto o niño; o cuando el sujeto tiene
- 25 altos niveles de glucosa en el plasma, en ayunas, > 126 mg/dL (> 6.99 mmol/L) (recomendado por la Asociación Americana de Diabetes). La Diabetes incluye la diabetes tipo 1 (diabetes mellitus dependiente de la insulina), en la cual el sujeto produce poca insulina o ninguna, y la diabetes tipo 2 (diabetes mellitus no dependiente de la insulina), en la cual la hiperglicemia resulta tanto de una respuesta de segregación afectada de
- 30 insulina a la glucosa y/o eficacia disminuida de la insulina para estimular el insumo de glucosa por los músculos esqueléticos y restringe la producción de la glucosa hepática

(resistencia a la insulina).

5 Tal como se utiliza en el presente, “pre-diabetes” se refiere a la enfermedad que ocurre cuando los niveles de glucosa del plasma del sujeto son mayores que los normales, pero no lo suficientemente altos para un diagnóstico de diabetes tipo 2. Los métodos para la medición de niveles glucosa del plasma, son conocidos en la técnica.

10 Tal como se utiliza en el presente, el “síndrome del ovario policístico” o “anovulación crónica hiperandrogénica” es una enfermedad que puede causar amenorrea, no obstante, se caracteriza usualmente por menstruaciones irregulares, obesidad leve, y hirsutismo, generalmente al comienzo de los años de la pubertad y luego, empeora con el tiempo. Muchos pacientes tienen abundante mucus cervical al ser examinados y altos estrógenos libres. Los niveles de la mayoría de los andrógenos en circulación tienden a elevarse gradualmente. Los ovarios pueden agrandarse con cápsulas suaves, engrosadas, o pueden ser de tamaño normal. Generalmente, los ovarios pueden contener 2- a 6-mm de quistes foliculares y una hiperplasia tecal rodea las células granulosas. Pueden haber
15 grandes quistes que contienen células atréticas.

Tal como se utiliza en el presente, “obesidad” se refiere a tener un peso corporal que excede el 30% del peso corporal ideal, tal como lo determina un profesional médico, y/o poseer un índice de masa corporal mayor a 27, aproximadamente, tal como lo determina el profesional médico.

20 Los términos “terapéutico,” “tratamiento,” y “tratar” tal como se utiliza en el presente, se refieren a mejorar una enfermedad o síntomas relacionados con una enfermedad, que incluye la prevención o demora en el inicio de los síntomas de la enfermedad, y/o disminución de la gravedad o frecuencia de los síntomas de la enfermedad.

25 Los síntomas de la diabetes y pre-diabetes incluyen, aunque no se limitan a la dislipidemia, obesidad, hipertensión arterial, y complicaciones microvasculares y macrovasculares, por ejemplo, aterosclerosis, retinopatías, nefropatías y neuropatías. Los síntomas de la obesidad incluyen, aunque no se limitan a la diabetes (ej. Diabetes tipo 2), enfermedad de las arterias coronarias, enfermedad oclusiva arterial periférica, infarto de

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miocardio, enfermedad oclusiva arterial periférica, dislipidemias (ej. hiperlipidemia), infarto, anormalidades venosas crónicas, problemas ortopédicos, desórdenes del sueño como la apnea, enfermedad de reflujo del esófago, hipertensión, artritis, infertilidad, abortos y cáncer (ej. Cáncer colorectal, cáncer de mama).

5 EJEMPLOS

Elaboración de la Preparación tipo Pasta

Una preparación para ser utilizada en la elaboración de una composición, de acuerdo con la presente invención, del siguiente modo.

Ejemplo 1

10 Hidrocloruro de metformina en polvo (disponible en Spectrum Chemicals), glicolato de sodio en polvo (disponible en NutriScience Innovations, LLC), y sulfato de lauril de sodio en polvo (disponible en Charles Tennant y Bioshop) se colocaron en una pantalla tipo red 100 y las partículas que atravesaron la pantalla se utilizaron para realizar la preparación.

15 A temperatura ambiente y a una humedad relativa de 25 a 65%, 123.51 gramos de glicerina líquida (disponible en Canada Colors and Chemicals Ltd.) se vertió lentamente en una máquina mezcladora de alta velocidad, y se agitó durante aproximadamente dos o tres minutos. A lo anterior, se añadió 4.83 gramos de glicolato de sodio en polvo, y dos ingredientes se mezclaron durante dos o tres minutos. 4.82 gramos de sulfato de lauril de
20 sodio en polvo se agregó y la mezcla se mezcló durante dos o tres minutos más para producir una solución opaca. 1000 gramos del hidrocloruro de metformina en polvo, se agregaron mediante la mezcla durante otros 15 a 20 minutos para formar una pasta homogénea, que posee una textura tipo masa.

25 La pasta formada está de acuerdo con la presente invención y contiene hidrocloruro de metformina en una concentración de 88.25 w/w %, glicerina en una concentración de 10.90 w/w %, glicolato de sodio en una concentración de 0.43 w/w % y sulfato de lauril de sodio en una concentración de 0.43 w/w %, todo basado en el peso total de la preparación de la pasta.

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Ejemplo 2

El protocolo del Ejemplo 1 se repitió nuevamente con cantidades apenas diferentes, de los ingredientes del inicio para producir una pasta de acuerdo con la presente invención que posee hidrocloreto de metformina en una concentración de 76.98 w/w %, glicerina en una concentración de 22.28 w/w %, glicolato de sodio en una concentración de 0.37 w/w % y sulfato de lauril de sodio en una concentración de 0.37 w/w %, todo basado en el peso total de la preparación de la pasta.

En los ejemplos 1 y 2, la cantidad de glicerina utilizada para hacer la pasta puede reducirse a fin de producir una pasta que posee, por lo menos, 10 w/w % de glicerina basada en el peso total de la pasta. La preparación de la pasta puede combinarse con un vehículo farmacéuticamente aceptable para producir una composición de acuerdo con la presente invención.

Preparación de la Composición de Goma de Mascar

Ejemplo 3

La pasta de acuerdo con el ejemplo 2 anterior, se elaboró en una composición de goma de mascar (chicles) de acuerdo con otro aspecto de la invención. Cada chicle contiene hidrocloreto de metformina en una concentración de 212.5 w/w %, glicerina en una concentración de 6.15 w/w %, glicocolato de sodio en una concentración de 0.10 w/w %, y sulfato de lauril de sodio en una concentración de 0.10 w/w %, todo basado en el peso total de la composición del chicle. El equilibrio de cada chicle consiste en la base de goma.

Mientras que la goma de mascar de este ejemplo contiene glicerina en una concentración de 6.15 w/w %, la cantidad inicial de la glicerina utilizada para hacer la pasta puede ser ajustada en forma descendente para producir un chicle que tenga tan poco como 3 w/w % de glicerina basado en el peso total del chicle.

Ejemplo 4

La cantidad de ingredientes utilizados en el Ejemplo 3 para elaborar la pasta se

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ajustó para producir una composición de goma que comprende 850 mg de hidrocloreto de metformina, 246 mg de glicerina, 4 mg de glicolato de sodio y 4 mg de sulfato de lauril de sodio.

En ambos Ejemplos 3 y 4, la goma de mascar fue preparada de acuerdo con un método conocido, del siguiente modo. Un material matriz que consiste en elastómeros, emulsificadores y ceras se molió y colocó en una mezcladora de goma de mascar tradicional. Los ingredientes adicionales (endulzantes, saborizantes, y agentes colorantes) se agregaron luego para formar una base de goma gustosa. La pasta fue luego agregada a la base de goma en un ratio de 276 partes de pasta aproximadamente, hasta 1000 partes de base de goma y todos los ingredientes se mezclaron para formar una masa de goma de mascar homogénea. La masa de goma cálida luego se extrajo de la mezcladora y se formaron piezas de goma de mascar utilizando sistemas convencionales y máquinas. Las piezas de goma se dejaron endurecer y se revistieron con una capa de dragée opcional, que contenía agentes colorantes y saborizantes adicionales.

Se pueden elaborar composiciones de goma de mascar de acuerdo con la presente invención utilizando otros métodos conocidos, tales como aquellos descritos en las Patentes de Estados Unidos, Nos. 5,487,902, 6,344,222, 6,432,383 y 5,470,566, cuyas enseñanzas constan en el presente como referencia.

Preparación de Caramelos y Cápsulas

Por ejemplo, la pasta puede elaborarse en forma de caramelos y pastillas utilizando los métodos conocidos tales como los revelados en la Patente de EEUU. 5,470,566, por ejemplo, cuyas enseñanzas constan en el presente como referencia.

También puede utilizarse para hacer cápsulas masticables tal como se describen, por ejemplo, en la Publicación de la Solicitud de Patente de Estados Unidos No. EEUU. 2003/0095925 A1, cuyas enseñanzas constan en el presente como referencia.

Ensayos Relacionados con la Administración de Goma de Metformina

La goma de mascar del Ejemplo 3 descrita anteriormente, contiene 212.5 mg de hidrocloreto de metformina por chicle, se administró a dos sujetos, individuos A y B.

Los sujetos ayunaron de un día para otro y la mañana siguiente, se les dio un chicle a la hora = 0 el cual masticaron durante 30 minutos y luego lo desecharon. Luego de esperar 10 minutos, se les dio otro chicle a los sujetos para masticar durante 30 minutos. Los sujetos luego esperaron cuatro horas y masticaron un tercer chicle antes de la primer comida durante 30 a 40 minutos, aproximadamente. La concentración de la metformina en el plasma de los individuos A y B (en ng/ml) se midió en la hora 0 y se muestra en la Figura 1. La Serie 2 representa la concentración del plasma de metformina para el individuo A. La Series 3 la concentración del plasma de metformina para el individuo B.

Una semana antes, al individuo B se le suministró una tableta de 850 mg de hidrocloreto de metformina vendida en relación con la marca comercial, GLUCOPHAGE, de Bristol-Meyers Squib Co. La tableta fue ingerida en la mañana a la hora = 0 luego de haber ayunado de un día para el otro. La concentración de la metformina en el plasma del individuo B (en ng/ml) se midió comenzando a la hora 0 y se muestra en la Figura 1 (ver Serie 1).

Las concentraciones más altas en el plasma de metformina ocurren luego de aproximadamente 300 minutos en el sujeto de control a quien se le administró GLUCOPHAGE y en uno de los sujetos al que se le administró la goma de metformina. La concentración de plasma alto de metformina en un segundo sujeto al que se le administró goma de metformina ocurrió aproximadamente a los 360 minutos. A uno de los individuos a los que se le dio la goma, la concentración más alta de plasma fue superior a 2000 ng/ml comparado con un pico inferior a 1500 ng/ml en el sujeto que recibió una tableta de GLUCOPHAGE. Estos resultados indican que la goma es tan o más efectiva que las tabletas para entregar el hidrocloreto de metformina en el torrente sanguíneo de los seres humanos, a pesar de tener concentraciones mucho menores de hidrocloreto de metformina por dosis de tres-chicles.

Liberación del Hidrocloreto de metformina de la Goma de mascar

La preparación de la pasta del Ejemplo 2 se elaboró en tres composiciones diferentes de goma de mascar, utilizando el método conocido descrito anteriormente. Se utilizaron las bases de goma saborizada. Los números de serie utilizados para identificar a cada base de goma y la composición de la goma de mascar composición producida

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utilizando cada base, se identifican a continuación.

Composición de goma de mascar 5475-01-1 elaborada utilizando base de goma sabor cola 25084;

5 Composición de goma de mascar 5475-04-1 elaborada utilizando base de goma sabor caramelo 25046; y

Composición de goma de mascar 5475-05-1 elaborada utilizando base de goma sabor caramelo café 25046.

10 Las composiciones de la goma de mascar pueden ser en forma de chicles de un gramo. Los chicles contienen cerca de 210, 217 y 214 mg de hidrocloreuro de metformina respectivamente. Debe entenderse que la cantidad real del hidrocloreuro de metformina puede variar en cualquier dirección hasta 5 %.

15 Cada chicle fue colocado en una máquina de chicles con una solución tamponadora. El chicle fue masticado a una ritmo de 60 masticados por minuto durante 20 minutos. La cantidad de hidrocloreuro de metformina liberado en la solución tamponadora se midió utilizando cromatografía líquida de alto rendimiento ("HPLC") a la hora = 2, 5, 10 y 20 minutos cuando se liberó el porcentaje de hidrocloreuro de metformina. Los resultados se resumen en la Tabla 1 a continuación y se muestra el porcentaje de la droga liberada (ver Figura 2).

Tabla 1

Muestra	Ensayo mg/g	Liberación %			
		Tiempo de Masticado			
		2 min.	5 min.	10 min.	20 min.
5475-01-1	210	57	91	89	95
5475-04-1	217	78	93	90	98
5475-05-1	224	78	91	93	94

Material de datos analíticos encontrados ad hoc 9/04.43.06.

20 El índice de liberación inicial para la composición de goma 5475-01-1 es más lenta que para otras composiciones debido a la utilización de una base de goma de

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liberación más lenta.

Los resultados generales muestran que la liberación de hidrocloreuro de metformina es bastante rápida en todas las composiciones, con por lo menos 90% del agente farmacéutico liberado luego de cinco minutos de masticar.

5 *Ejemplo 5*

Ensayos que Comparan la Goma Metformina con las Tabletas de Metformina en el mismo Nivel de Dosis

Goma de mascar que posee la misma composición que la composición del Ejemplo 3, excepto que la cantidad de hidrocloreuro de metformina es 214.5 mg por chicle (a diferencia de 212.5 mg) y se administró a un grupo de diez voluntarios saludables (6 hombres, 4 mujeres), con una edad promedio de 30 a 29.8 años respectivamente y un BMI promedio de 23.9 y 21.49 respectivamente. A la hora = 0, a cada sujeto se le administraron dos chicles para masticar con una dosis total de 429 mg hidrocloreuro de metformina.

Como control, otro día, al mismo grupo de sujetos se le administró una tableta de 429 mg de hidrocloreuro de metformina que está a la venta en relación con la marca comercial, GLUCOPHAGE, por Bristol-Meyers Squib Co.

Las muestras de plasma (300 microlitros) obtenidos de los sujetos se sometieron a una extracción de fase sólida (spe) con un intercambio débil antes del análisis con HPLC.

La concentración de la metformina en el plasma de los sujetos (en ppm) se midió comenzando a la hora = 0 minutos, y la muestra adicional ocurrió a las 5, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 540, 720, 1440 minutos (24 horas). Los volúmenes se detallan en la Figura 3.

Un análisis de las Areas Correspondientes bajo la Curva (AUC) por ANOVA (ensayo f) y un ensayo en pares t indicaron que no existe una diferencia significativa en las concentraciones del plasma de los sujetos a los que se les administró la goma comparados con los sujetos que recibieron la tableta GLUCOPHAGE, a pesar de que las

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concentraciones de plasma con la goma tienden a ser mayores. Las concentraciones altas de metformina del plasma ocurrieron a aproximadamente, 200 minutos en ambos grupos de sujetos, con la concentración de plasma alto de casi 0.8 ppm en los sujetos que recibieron la goma en contraposición a casi 0.6 ppm en los sujetos que recibieron la
5 tableta GLUCOPHAGE.

Los resultados indican que la goma es, al menos, tan eficaz como las tabletas en cuanto a entregar hidrocloreuro de metformina al torrente sanguíneo de los seres humanos.

Si bien la invención fue particularmente mostrada y descrita con referencia a las realizaciones preferidas de la misma, los expertos en la técnica entienden que se pueden
10 realizar diversos cambios en la forma y detalles sin alejarse del alcance de la invención, acompañada de las reivindicaciones adjuntas.

REIVINDICACIONES

1. Una preparación para ser utilizada en la elaboración de una composición de metformina de transmucosa oral, que consiste en:

un agente farmacéutico que consiste en metformina o una sal farmaceuticamente aceptable del mismo , y

una cantidad eficaz de por lo menos, un acelerador de la absorción seleccionado de álcali metal alquil sulfato, glicerina, ácido biliar o sal biliar, lecitina, ácido hialurónico, octilfenoxipolietoxietanol, ácido glicólico, ácido láctico, extracto de camomila, extracto de pepino, ácido oleico, ácido linolénico, aceite de borraja, aceite de enotera, poliglicerina, lisina, polilisina, trioleina, monooleina, monooleatos, monolauratos, mentol, polidocanol alquil éteres, quenodeoxicolato, deoxicolato y sales farmaceuticamente aceptables y análogos de los mismos, en el cual el agente farmacéutico está presente en una concentración de aproximadamente 5 a 90 w/w % basado en el peso total de la preparación.

2. Una composición de metformina de transmucosa oral que comprende:

una cantidad eficaz de un agente farmacéutico que consiste en metformina o una sal farmaceuticamente aceptable del mismo, de por lo menos un acelerador de la absorción seleccionado de álcali metal alquil sulfato, glicerina, ácido biliar o sal biliar, lecitina, ácido hialurónico, octilfenoxipolietoxietanol, ácido glicólico, ácido láctico, extracto de camomila, extracto de pepino, ácido oleico, ácido linolénico, aceite de borraja, aceite de enotera, poliglicerina, lisina, polilisina, trioleina, monooleina, monooleatos, monolauratos, mentol, polidocanol alquil éteres, quenodeoxicolato, deoxicolato y sales farmaceuticamente aceptables y análogos de los mismos,

un vehículo farmaceuticamente aceptable, siendo el referido vehículo capaz de entregar una cantidad farmaceuticamente efectiva del referido agente farmacéutico a una membrana mucosa oral para su absorción.

3. La composición de la reivindicación 2, en la cual cada acelerador de la absorción está presente en una concentración de, por lo menos, aproximadamente 30 w/w % de la

composición total y la concentración total de los aceleradores de la absorción es menor a 30 w/w % aproximadamente, de la composición total.

4. La composición de la reivindicación 3, en la cual cada acelerador de la absorción está presente en una concentración menor a 7 w/w % , aproximadamente, de la composición total.

5. La composición de cualquiera de las reivindicaciones 2 a 4, en la cual álcali metal alquil sulfato es un álcali metal C8 a C22 alquil sulfato.

6. La composición de la reivindicación 5, en la cual el álcali metal C8 a C22 alquil sulfato es sulfato de lauril de sodio.

7. La composición de cualquiera de las reivindicaciones 2 a 6, que comprende asimismo un agente isotónico, presente en una concentración de hasta 30 w/w % aproximadamente, de la formulación total.

8. La composición de la reivindicación 7, en la cual el agente isotónico es glicerina.

9. La composición de cualquiera de las reivindicaciones 2 a 8, que comprende asimismo una sal de ácido biliar.

10. La composición de la reivindicación 9, en la cual la referida sal biliar es glicolato de sodio.

11. La composición de cualquiera de las reivindicaciones 2 a 10, en la cual el referido acelerador de la absorción es un compuesto formador de micela, para encapsular el agente farmacéutico cuando la composición se forma en una solución en la cavidad oral.

12. La composición de cualquiera de las reivindicaciones 2 a 11, en la cual la sal farmacéuticamente aceptable de metformina es hidrocloreto de metformina.

13. La composición de cualquiera de las reivindicaciones 2 a 12, en la cual la cantidad del agente farmacéutico es de 100 a 850 miligramos, aproximadamente, por dosis.

14. La composición de la reivindicación 13, en la cual la cantidad del agente farmacéutico es de aproximadamente 100 a 500 miligramos por dosis.

15. La composición de la reivindicación 14, en la cual la cantidad del agente farmacéutico es aproximadamente 250 a 500 miligramos por dosis.

16. La composición farmacéutica de cualquiera de las reivindicaciones 2 a 15, en la forma de goma de mascar que comprende hidrocloreto de metformina en una concentración de 10 a 50 w/w %, aproximadamente, sulfato de lauril de sodio en una concentración de 0.01 a 2 w/w %, aproximadamente, glicolato de sodio en una concentración de 0.01 a 2 w/w %, aproximadamente, glicerina en una concentración de 2 a 10 w/w %, aproximadamente, y una base de goma de mascar en una concentración de aproximadamente, 10 a 90 w/w %, todos basados en el peso total de la composición.

17. La composición de cualquiera de las reivindicaciones 2 a 15, en la cual el referido vehículo es una caramelo duro o pastilla.

18. La composición de cualquiera de las reivindicaciones 1 a 17, en la cual la membrana es una membrana bucal.

19. Un proceso para la elaboración de una composición de metformina de transmucosa oral, que comprende:

una mezcla de (a) una cantidad eficaz del agente farmacéutico que consiste en metformina o una sal farmacéuticamente aceptable del mismo con (b) una cantidad eficaz de por lo menos, un acelerador de la absorción seleccionado de álcali metal alquil sulfato, glicerina, ácido biliar o sal biliar, lecitina, ácido hialurónico, octilfenoxipolietoxietanol, ácido glicólico, ácido láctico, extracto de camomila, extracto de pepino, ácido oleico, ácido linolénico, aceite de borraja, aceite de enotera, poliglicerina, lisina, polilisina, trioleína, monooleína, monooleatos, monolauratos, mentol, polidocanol alquil éteres, quenodeoxicolato, deoxicolato y sales farmacéuticamente aceptables y análogos de los mismos, para formar una pasta

una mezcla de pasta con una base de goma; y

elaboración de la mezcla resultante en tabletas de goma de mascar, cápsulas, o chicles.

20. La composición de cualquiera de las reivindicaciones 2 a 18 para ser utilizada en el tratamiento de la diabetes en un sujeto.
21. El uso de la composición de cualquiera de las reivindicaciones 2 a 18 en el tratamiento de la diabetes en un sujeto.
22. El uso de la composición de cualquiera de las reivindicaciones 2 a 18 en la fabricación de un medicamento para el tratamiento de la diabetes.
23. Un método de tratamiento de la diabetes que comprende administrar a un sujeto la composición de cualquiera de las reivindicaciones 2 a 18.
24. El método de la reivindicación 23, en el cual la composición se mantiene en la boca durante, por lo menos, 1 minuto.
25. El método de la reivindicación 24, en el cual la composición se mantiene en la boca de 1 a 30 minutos.
26. El método de la reivindicación 25, en el cual la composición se mantiene en la boca de 1 a 20 minutos.
27. El método de la reivindicación 26, en el cual la composición se mantiene en la boca de 1 a 9 minutos.
28. El método de la reivindicación 24, en el cual la composición se mantiene en la boca durante, por lo menos, 30 minutos.
29. El método de la reivindicación 24, en el cual la composición se mantiene en la boca durante, por lo menos, 20 minutos.
30. Un método de aumentar la sensibilidad a la insulina en un sujeto, que comprende administrar a un sujeto la composición de cualquiera de las reivindicaciones 2 a 18.
31. Un método de reducir la absorción intestinal de la glucosa en un sujeto, que comprende administrar a un sujeto la composición de cualquiera de las reivindicaciones 2 a 18.

32. Un método de reducir la hipoglicemia en un sujeto, que comprende administrar al sujeto la composición de cualquiera de las reivindicaciones 2 a 18.
33. Un método de reducir el peso corporal de un sujeto, que comprende administrar al sujeto la composición de cualquiera de las reivindicaciones 1 a 31.
34. Un método de reducir el apetito del sujeto, que comprende administrar al sujeto la composición de cualquiera de las reivindicaciones 2 a 18.
35. Un método para tratar la obesidad de un sujeto, que comprende administrar al sujeto la composición de cualquiera de las reivindicaciones 2 a 18.
36. Un método para tratar el síndrome del ovario policístico en un sujeto, que comprende administrarle a un sujeto la composición de cualquiera de las reivindicaciones 2 a 18.

RESUMEN DE LA REVELACIÓN

- La invención se relaciona con las composiciones farmacéuticas transmucosas orales que comprenden metformina o una sal farmacéuticamente aceptable de las mismas, métodos de utilización de las composiciones para tratar diversas enfermedades, incluyendo
- 5 diabetes, métodos para preparar las composiciones, y las preparaciones a ser utilizadas para elaborar las composiciones.

FIGURA 1

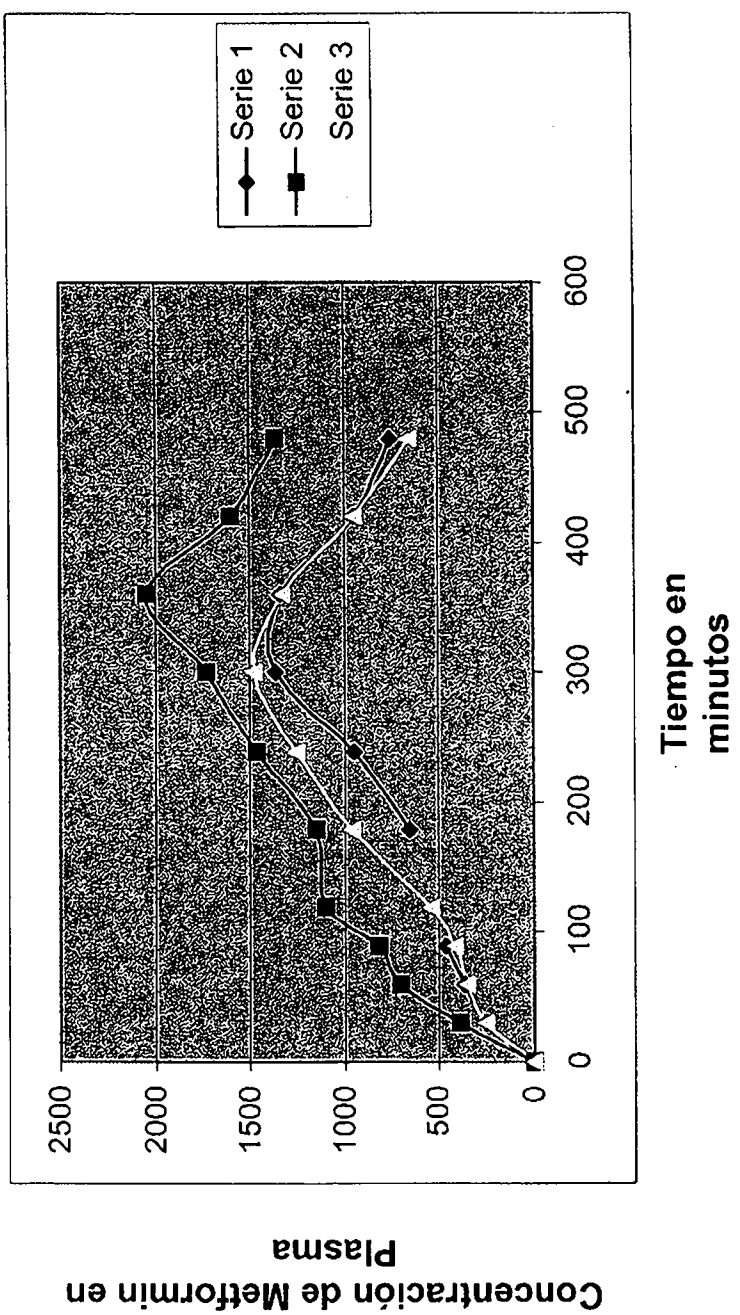


FIGURA 2

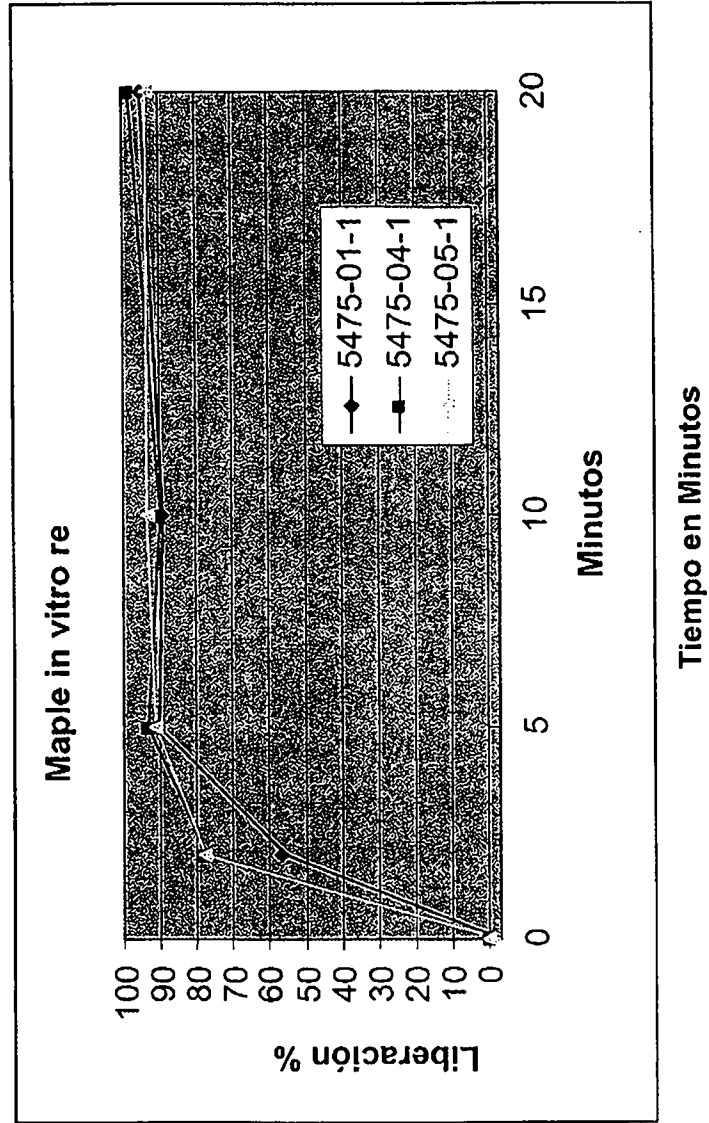
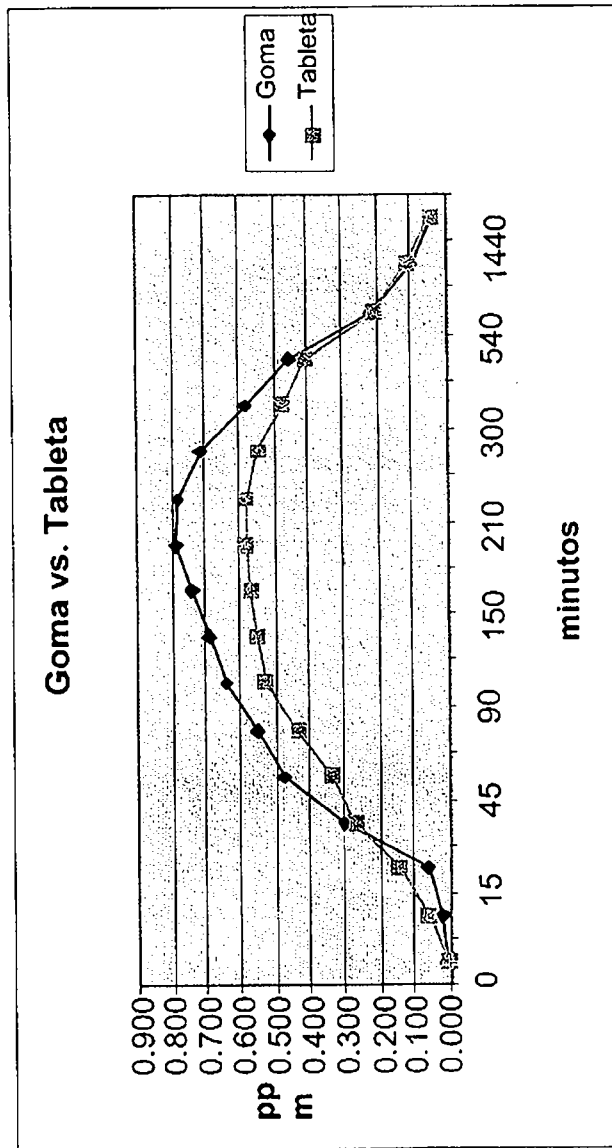


FIGURA 3



Tiempo en
minutos

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	PCT/CA 2006/000472
0-2	International Filing Date	30 MARCH 2006 30.03.06
0-3	Name of receiving Office and "PCT International Application"	RO/CA
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY model] Version 3.51.001.176 MT/FOP 20060101/0.20.4rc.2.7
0-5	Petition The undersigned requests that the present International application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	Canadian Intellectual Property Office (RO/CA)
0-7	Applicant's or agent's file reference	39091-0291DK
I	Title of Invention.	COMPOSITIONS FOR ORAL TRANSMUCOSAL DELIVERY OF METFORMIN
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	GENEREX PHARMACEUTICALS INC.
II-5	Address	33 Harbour Square Suite 202 Toronto, Ontario M5J 2G2 Canada
II-6	State of nationality	CA
II-7	State of residence	CA
II-8	Telephone No.	416.364.2551
II-9	Facsimile No.	416.364.9363
II-10	e-mail	info@generex.com

39091-0291DK

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PCT REQUEST

Original (for SUBMISSION)

III-1	Applicant and/or Inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	GLUSKIN, Anna E.
III-1-5	Address	33 Harbour Square Suite 2409 Toronto, Ontario M5J 2G2 Canada
III-1-6	State of nationality	CA
III-1-7	State of residence	CA
III-2	Applicant and/or Inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	QAZI, Muhammad Waseem Tahir
III-2-5	Address	21 Horner Court Richmond Hill, Ontario L4B 3G6 Canada
III-2-6	State of nationality	CA
III-2-7	State of residence	CA
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	KAO, Dolly
IV-1-2	Address	RIDOUT & MAYBEE LLP 1 Queen Street East Suite 2400 Toronto, Ontario M5C 3B1 Canada
IV-1-3	Telephone No.	416.868.1482
IV-1-4	Facsimile No.	416.362.0823
IV-1-5	e-mail	dkao@ridoutmaybee.com
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	RIDOUT & MAYBEE LLP

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PCT REQUEST

Original (for SUBMISSION)

V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	30 March 2005 (30.03.2005)
VI-1-2	Number	60/666,475
VI-1-3	Country	US
VII-1	International Searching Authority Chosen	Canadian Intellectual Property Office (ISA/CA)
VIII	Declarations	Number of declarations
VIII-1	Declaration as to the identity of the inventor	-
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	1
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-

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PCT REQUEST

Original (for SUBMISSION)

VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)). In a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application GENEREX PHARMACEUTICALS INC. is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i) v)		an assignment from GLUSKIN, Anna E. to GENEREX PHARMACEUTICALS INC., dated 29 March 2006 (29.03.2006)
VIII-2-1(i) v)		an assignment from QAZI, Muhammad Waseem Tahir to GENEREX PHARMACEUTICALS INC., dated 29 March 2006 (29.03.2006)
VIII-2-1(i) x)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

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PCT REQUEST

Original (for SUBMISSION)

VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17 (iii) and 51bis.1(a)(iii)) Name	in relation to this international application GENEREX PHARMACEUTICALS INC. is entitled to claim priority of earlier application No. 60/666,475 by virtue of the following:
VIII-3-1(i v)		an assignment from GLUSKIN, Anna E. to GENEREX PHARMACEUTICALS INC., dated 29 March 2006 (29.03.2006)
VIII-3-1(i v)		an assignment from QAZI, Muhammad Waseem Tahir to GENEREX PHARMACEUTICALS INC., dated 29 March 2006 (29.03.2006)
VIII-3-1(i x)	This declaration is made for the purposes of:	all designations

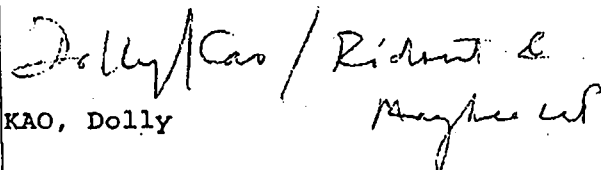
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PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	21	-
IX-3	Claims	5	-
IX-4	Abstract	1	✓
IX-5	Drawings	3	-
IX-7	TOTAL	36	
Accompanying Items		paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract	3	
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	 KAO, Dolly	
X-1-1	Name (LAST, First)		
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	30 MARCH 2006 30.03.06
10-2	Drawings:	✓
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/CA
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	PCT/CA 2006/000472	
0-1	International Application No.		
0-2	Date stamp of the receiving Office	30 MARCH 2006 30.03.06	
0-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet		
0-4-1	Prepared Using	PCT-SAFE [EASY model] Version 3.51.001.176 MT/FOP 20060101/0.20.4rc.2.7	
0-9	Applicant's or agent's file reference	39091-0291DK	
2	Applicant	GENEREX PHARMACEUTICALS INC. ET AL ^u	
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (CAD)
12-1	Transmittal fee T	⇒	300
12-2-1	Search fee S	⇒	1600
12-2-2	International search to be carried out by	CA	
12-3	International filing fee (first 30 sheets) I1	1273	
12-4	Remaining sheets	6	
12-5	Additional amount (X) I4		
12-6	Total additional amount I2	84	
12-7	I1 + I2 = i	1357	
12-12	EASY Filing reduction R	-91	
12-13	Total International filing fee (i-R) I	⇒	1266
12-14	Fee for priority document Number of priority documents requested	0	
12-15	Fee per document (X) 0		
12-16	Total priority document fee: P	⇒	
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒	3166
12-19	Mode of payment	other VISA	
12-20	Deposit account Instructions The receiving Office	Canadian Intellectual Property Office (RO/CA)	
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above	✓	
12-20-3	Authorization to charge the fee for priority document	✓	
12-21	Deposit account No.	600000242	
12-22	Date	30 March 2006 (30.03.2006)	
12-23	Name and signature	KAO, Dolly <i>Dolly/Kao / Ridout & Mayhew</i> CLP	

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PCT

Original (for SUBMISSION)

13-2-6	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
13-2-7	Validation messages Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
	Validation messages Contents	Green? Priority 1. The priority document is not enclosed. (The applicant must furnish it within 16 months from the earliest priority date claimed)

7C

From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 06 July 2006 (06.07.2006)	To: KAO, Dolly RIDOUT & MAYBEE LLP 1 Queen Street East Suite 2400 Toronto, Ontario M5C 3B1 CANADA
Applicant's or agent's file reference 39091-0291DK	IB (22)
International application No. PCT/CA2006/000472	IMPORTANT NOTIFICATION
International filing date (day/month/year) 30 March 2006 (30.03.2006)	International publication date (day/month/year) Not yet published
Priority date (day/month/year) 30 March 2005 (30.03.2005)	
Applicant GENEREX PHARMACEUTICALS INC. et al	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable)* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
30 March 2005 (30.03.2005)	60/666,475	US	20 June 2006 (20.06.2006)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Athina Nickitas-Etienne
Facsimile No. +41 22 338 82 70	Facsimile No. +41 22 338 89 95 Telephone No. +41 22 338 94 43

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TORONTO
RIDDOUT & MAYBEE LLP

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. ☒ Claim Nos. : 23-36

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 23-36, directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search (PCT Rule 39.1 (iv)). Regardless, this Authority has carried out a search based on the alleged effect(s) or purpose(s)/use(s) of the product defined.

2. ☐ Claim 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. ☐ Claim Nos. :

because they are dependant 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 additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

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 claim 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 claim 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.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000472

A. CLASSIFICATION OF SUBJECT MATTER

IPC: *A61K 31/155* (2006.01), *A61P 3/10* (2006.01), *A61P 3/04* (2006.01), *A61K 47/00* (2006.01)

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* (2006.01); *A61P* (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
DWPI/Delphion; Canadian Patent database- full text plus bibliography; STN-structure and keywords, Scopus, PubMeb, Google™;
metformin, biguanide, oral, transmucosal, absorption enhancer or promoter

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2005/041923 A1 (ALZA CORPORATION) 12 May 2005 (12-05-2005) see abstract; page 3, paragraph [007]; page 12, paragraphs [0075]-[0076]; page 29, paragraph [0132]; page 31, paragraph [0139]; examples, and claims 1-8, 12, 16-17.	1-6, 12-13, 20-23 and 31-35
X Y	WO 99/42086 A1 (MERCK PATENT GMBH) 26 August 1999 (26-08-1999) see abstract; page 3, lines 29-35; page 4, lines 16-17; page 6, lines 24-34; page 7, line 5; page 11, line 35-page 12, line 2; page 13, lines 1-2 & 7-10, and claim 12.	1 2-10 and 12-36
X Y	WO 99/47125 A1 (ANDRX PHARMACEUTICALS, INC.) 23 September 1999 (23-09-1999) see page 3, lines 27-30; page 5, lines 1-15; page 9, lines 5-10; Example 2, claims 1-3, 8-10, 12-13 and 29.	1 2-10 and 12-36

☒ 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 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

24 May 2006 (24-05-2006)

Date of mailing of the international search report

13 July 2006 (13-07-2006)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Authorized officer

Connie Kuang (819) 934-3597

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000472

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 02/036100 A1 (ANDRX CORPORATION) 10 May 2002 (10-05-2002) see abstract; page 2, pages 3-4; page 14; page 15; page 18; Example 1 and claim 29.	1 2-10 and 12-36
Y	WO 91/011132 (FERTIN LABORATORIES LTD) 07 February 1991 (07-02-1991) see abstract; page 3, lines 8-11; page 6, lines 13-14; page 11, lines 9 & 14, and page 17, lines 28-29.	2-10 and 12-36
Y	US 6,432,383 B1 (GENEREX PHARMACEUTICALS INC.) 13 August 2002 (13-08-2002) see abstract; column 4, lines 63-66, and Example 13.	2-36
A	MATHIOWITZ, E. Encyclopedia of Controlled Drug Delivery. New York: John Wiley & Sons, 1999, Volumes 1 & 2, ISBN 0-471-14828-8, page 738.	

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2006/000472

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000472

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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
RIDOUT & MAYBEE LLP
One Queen Street East
Suite 2400
TORONTO, Ontario
Canada, M5C 3B1

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing 13 July 2006 (13-07-2006)
(day/month/year)

Applicant's or agent's file reference
39091-0291DK

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/CA2006/000472

International filing date (day/month/year)
30 March 2006 (30-03-2006)

Priority date (day/month/year)
30 March 2005 (30-03-2005)

International Patent Classification (IPC) or both national classification and IPC
IPC: *A61K 31/155* (2006.01), *A61P 3/10* (2006.01), *A61P 3/04* (2006.01), *A61K 47/00* (2006.01)

Applicant
GENEREX PHARMACEUTICALS INC. ET AL

I. This opinion contains indications relating to the following items :

- | | |
|--|--|
| ☒ Box No. I | Basis of the opinion |
| ☒ Box No. II | Priority |
| ☒ Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ Box No. IV | Lack of unity of invention |
| ☒ Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ Box No. VI | Certain documents cited |
| ☐ Box No. VII | Certain defects in the international application |
| ☒ Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA
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50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Date of completion of this opinion
08 June 2006 (08-06-2006)

Authorized officer
Connie Kuang (819) 934-3597

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Box No. I **Basis of this opinion**

1. With regard to the language, this opinion has been established 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)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form
 - ☐ furnished subsequently to this Authority for the purposes of search.
- 3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments :

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Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary :

The validity of the priority claims has been established because the International Searching Authority has in its possession a copy of the earlier application whose priority has been claimed.

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claim Nos. 23-36

because:

☒ the said international application, or the said claim Nos. 23-36 relate to the following subject matter which does not require an international search (*specify*):

Claims 23-36 are directed to a method for treatment of the human or animal body by surgery or therapy. For the assessment of claims 23-36 on the question of whether or not they define subject matter that has industrial applicability, no unified criteria exists in the PCT Contracting States.

☐ the description, claims or drawings (*indicate particular elements below*) or said claim Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>2-36</u>	YES
	Claims <u>1</u>	NO
Inventive step (IS)	Claims	YES
	Claims <u>1-36</u>	NO
Industrial applicability (IA)	Claims <u>1-22</u>	YES
	Claims	NO

2. Citations and explanations :

The following documents are cited in the present opinion:

- D1: WO 99/42086 A1 (MERCK PATENT GMBH) 26 August 1999 (26-08-1999)
D2: WO 99/47125 A1 (ANDRX PHARMACEUTICALS, INC.) 23 September 1999 (23-09-1999)
D3: WO 02/036100 A1 (ANDRX CORPORATION) 10 May 2002 (10-05-2002)
D4: WO 91/01132 (FERTIN LABORATORIES LTD) 07 February 1991 (07-02-1991)
D5: US 6,432,383 B1 (GENEREX PHARMACEUTICALS INC.) 13 August 2002 (13-08-2002)

D1 discloses an orally administrable galenic form allowing improved absorption by the transmembrane or paracellular route comprising metformin or its pharmaceutically acceptable salt and an absorption-promoting agent (e.g., monolaurate, monooleate, unsaturated fatty acid with 18 carbon atoms, bile acids or bile acid salts, sodium glycocholate, or polyglycerols). The quantity of metformin or its pharmaceutically acceptable salt present in the galenic form varies between 0.001 and 95% by weight.

D2 discloses a controlled release antihyperglycemic tablet comprising a core containing 50-98% by weight of metformin or its pharmaceutically acceptable salt, a binding agent, and an absorption enhancer (e.g., a bile salt, oleic acid, or sodium lauryl sulfate).

D3 discloses a controlled release oral solid dosage form treating non-insulin-dependent diabetes mellitus (NIDDM) comprising a core containing 50-98% by weight of metformin or its pharmaceutically acceptable salt, a binding agent, and an absorption enhancer (e.g., a bile salt, oleic acid, or sodium lauryl sulfate).

D4 discloses a chewing gum composition with accelerated, controlled release of active agents comprising one or more active agents (e.g., guanidine and biguanidine), a chewing gum base, and at least one solubilizer (e.g., monolaurate, monooleate, or sodium lauryl sulfate).

D5 discloses a mixed micellar pharmaceutical formulation comprising insulin and at least one absorption enhancing compounds selecting from lecithin, hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening of primrose oil, glycerin, polyglycerin, lysine, polylysine, triolein and mixtures thereof. The amount of each absorption enhancer is present in a concentration of from 1 to 10 wt./wt. % of the total formulation, and the total concentration of absorption enhancers are less than 50 wt./wt. % of the formulation. The formulation suitable for delivery through oral mucosal membranes may be in chewable form.

(Continued in the Supplemental Box)

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Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claim 1 does not comply with Article 6 of the PCT. The inclusion of "bile salt" and "chenodeoxycholate, deoxycholate" in the same selected group causes a lack of clarity since chenodeoxycholate or deoxycholate fall within the scope of a bile salt.

Claim 2 does not comply with Article 6 of the PCT for being directed to the desired result rather than to the combination necessary to achieve that result as described in the description. The wordings such as "*said carrier being capable of delivering a pharmaceutically effective amount of said pharmaceutical agent to an oral mucosal membrane for absorption*" render the scope of present claim unclear. It appears possible to define the subject matter in more concrete terms, viz. in terms of how the effect is to be achieved, namely by specifying the pharmaceutically acceptable carrier. As the claim is currently formulated, the skilled person does not know whether or not a particular compound is a carrier having said function. Thus the scope of the claim cannot be readily defined, an undue burden being placed on others seeking to establish the extent of protection.

Claims 3-4 and 7 do not comply with Article 6 of the PCT because of the inclusion of "up to about" and "less than about". These expressions imply that some undefined values outside of the specified range are intended to be covered, without specifying what those values are. Firstly, it is unclear if the expression refers to a range as a whole or only the last number of the range. Secondly, "about" and "up to" or "less than" contradict each other as when "about" refers to a range of values above the set number, "up to" or "less than" infers values equal to or smaller than the set number.

Claim 9 does not comply with Article 6 of the PCT because a bile acid salt is already included in claim 2. Therefore, it is not clear what is the additional feature of the present claim adds to claim 2.

Claim 11 does not comply with Article 6 of the PCT for being directed to the desired result rather than to the combination necessary to achieve that result as described in the description. The wordings such as "*said absorption enhancer is a micelle forming compound capable of forming micelles ...*" render the scope of present claim unclear. It appears possible to define the subject matter in more concrete terms, viz. in terms of how the effect is to be achieved, namely by specifying the absorption enhancer. As the claim is currently formulated, the skilled person does not know whether or not a particular compound is an absorption enhancer having said function. Thus the scope of the claim cannot be readily defined, an undue burden being placed on others seeking to establish the extent of protection.

Claim 18 does not comply with Article 6 of the PCT . The word "membrane" has no antecedent in claim 1.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

Novelty

Claim 1 of the present application refers to an oral transmucosal metformin composition comprising metformin or a pharmaceutically acceptable salt thereof and at least one absorption enhancer, for instance, sodium lauryl sulfate, bile acid or salt, oleic acid, linolenic acid, monooleates, monolaurates wherein metformin or a pharmaceutically acceptable salt thereof is present in a concentration of from 5 to 90 w/w % based on the total weight of the composition. D1, D2 and D3 disclose, as discussed above, the same subject matter as that of claim 1. Hence, claim 1 is not considered to be novel in the sense of PCT Article 33(2).

None of the prior art discloses an oral transmucosal metformin composition comprising metformin or a pharmaceutically acceptable salt thereof, at least one absorption enhancer, and a pharmaceutically acceptable carrier which delivers metformin to an oral mucosal membrane for absorption, the process for making an oral transmucosal metformin composition in a chewing gum form, and the use of the oral transmucosal metformin composition in treating diabetes. Therefore the subject matter of claims 2-36 is considered novel in the sense of PCT Article 33(2).

Inventive step

Lacking novelty, the subject matter of claim 1 does not fulfill the requirements of PCT Article 33(3).

Claims 2-10 and 12-36 lack inventive step with respect to D1-D3 in view of D4-D5. D1-D3 disclose an oral metformin composition comprising metformin or a pharmaceutically acceptable salt thereof and at least one absorption enhancer. D1-D3 fail to disclose that this oral metformin composition further comprises a pharmaceutically acceptable carrier which delivers metformin to an oral mucosal membrane for absorption (e.g., a hard candy or lozenge), and this oral metformin composition is formulated in a chewing gum form. However, D4 teaches a chewing gum composition comprising guanidine or biguanidine as an active agent, a chewing gum base, and at least one solubilizer (e.g., monolaurate, monooleate, or sodium lauryl sulfate) which functions as an absorption enhancer. D5 teaches a pharmaceutical formulation comprising insulin and at least one absorption enhancing compounds which can be formulated in chewable form. In light of the above teachings, to employ metformin or a pharmaceutically acceptable salt thereof with an absorption enhancer and a pharmaceutically acceptable carrier in a form of chewing gum would have been obvious to a person skilled in the art. In addition, it is well known in the art that the use of chewing gum as a delivery system for medicines has proven especially suitable when an absorption of the medicine via the mucous membrane of the mouth is required in such cases when it is desirable to avoid the so-called "first pass" effect (see D4, page 3, lines 6-11). With respect to the addition of an isotonic agent, the dose of the pharmaceutical agent, the process for making an oral transmucosal metformin composition in a chewing gum form and the time period of the composition maintained in the mouth, would not be considered inventive because these features are not described as being related to particular technical effects and, therefore, represents only trivial modifications. Claims 30-36 are obvious since the use of metformin to increase sensitivity to insulin, and to treat diabetes, hypoglycemia, polycystic ovary disease and obesity is known in the art.

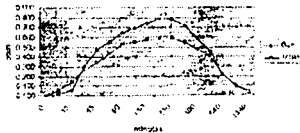
Claim 11 lacks inventive step with respect to D5. D5 discloses a micelle forming absorption enhancer (see column 3, lines 61-67). Therefore, the person skilled in the art could easily perceive to use an absorption enhancer which is a micelle forming compound into metformin composition without any inventive effort exerted.

Industrial applicability

The subject matter of claims 1-22 is considered to be industrially applicable and thus complies with the requirements of PCT Article 33(4).

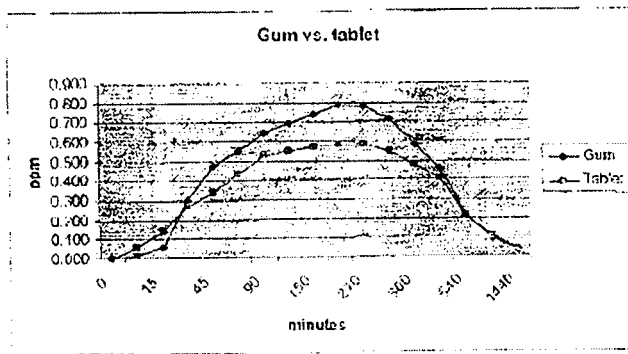
Metformin Plasma Concentration
(ppm)

Gumva tablet



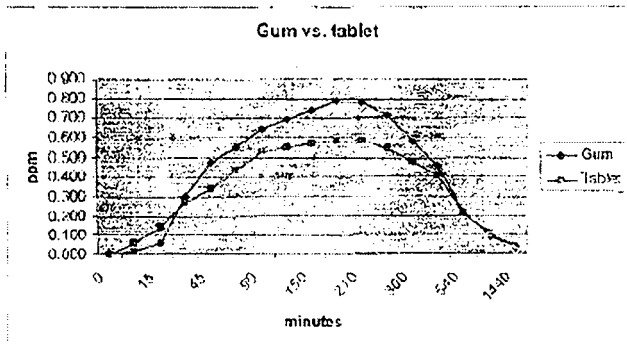
Time in minutes

Metformin Plasma Concentration
(ppm)



Time in minutes

**Metformin Plasma Concentration
(ppm)**



Time in minutes



No. 07-087492- -00000-0000

Fecha: 2007-08-27 16:01:52 Dep. 2020 NUECREACION
Tra 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 92

Industria y Comercio
SUPERINTENDENCIA

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☒

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Firma Responsable

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
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Bogotá, D.C., Colombia