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(54) Title: A MEDICINAL AEROSOL FORMULATION

(57) Abrégé/Abstract:

This invention relates to a medicinal aerosol formulation and, more particularly, to a medicinal aerosol formulation containing an insulin combination and a fluid carrier.



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A MEDICINAL AEROSOL FORMULATION

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BACKGROUND OF THE INVENTION**Field of the Invention**

This invention relates to a medicinal aerosol formulation for treating diabetes, and more particularly, to a medicinal aerosol formulation comprising a mixture of an insulin or an insulin analog and another β -cell hypoglycemic medicament.

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Description of the Related Art

Delivery of drugs to the lung by way of inhalation is an important means of treating a variety of conditions, including such common local conditions as cystic fibrosis, pneumonia, bronchial asthma and chronic obstructive pulmonary disease and some systemic conditions, including hormone replacement, pain management, immune deficiency, erythropoiesis, diabetes, etc. Steroids, β 2 agonists, anti-cholinergic agents, proteins and polypeptides are among the drugs that are administered to the lung for such purposes. Such drugs are commonly administered to the lung in the form of an aerosol of particles of respirable size (less than about 10 μ m in diameter). The aerosol formulation can be presented as a liquid or a dry powder. In order to assure proper particle size in a liquid aerosol, particles can be prepared in respirable size and then incorporated into a colloidal dispersion either containing a propellant as a pressurized metered dose inhaler (PMDI) or air, such as in the case of a dry powder inhaler (DPI). Alternatively, formulations can be prepared in solution or emulsion form in order to avoid the concern for proper particle size in the formulation. Solution formulations must nevertheless be dispensed in a manner that produces particles or droplets of respirable size.

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For MDI application, once prepared, an aerosol formulation is filled into an aerosol canister equipped with a metered dose valve. In the hands of the patient the formulation is dispensed via an actuator adapted to direct the dose from the valve to the patient.

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What is needed and desired is a stable aerosol formulation for the treatment of diabetes and the conditions related thereto.

SUMMARY OF THE INVENTION

It has surprisingly been found that a novel and stable medicinal aerosol formulation of an insulin or an insulin analog combined with a β -cell hypoglycemic medicament can be obtained without the use of a surfactant, such as sorbitan trioleate. The selected insulin or insulin analog is combined with another β -cell hypoglycemic medicament, and optionally other diabetic medicaments such as, for example, the α cell hormone, glucagon.

Thus, in one aspect of the invention, there is provided a liquid medicinal aerosol suspension formulation which comprises:

- (a) an insulin combination which is an insulin analog combined with at least one other β -cell hypoglycemic medicament; and
- (b) a fluid propellant carrier,

said formulation being without a surfactant.

In particular, the formulation may consist essentially of the aforementioned (a) and (b).

In another aspect of the invention, there is provided use of the formulation of the invention for treating a human or animal with diabetes or a diabetes related condition.

In still another aspect of the invention, there is provided a method of preparing a formulation of the invention which comprises:

- (a) combining (i) said insulin combination in an amount sufficient to provide a plurality of therapeutically effective doses, and (ii) said fluid propellant carrier in an amount sufficient to propel said plurality of therapeutically effective doses from an aerosol canister; and
- (b) dispersing components (i) and (ii).

In yet another aspect of the invention, there is provided a metered dose inhaler containing a formulation of the invention.

In another aspect of the invention, there is provided use of the formulation of the invention, for the preparation of a medicament for treating diabetes or a diabetes related condition by oral or nasal inhalation.

In yet another aspect of the invention, there is provided a formulation of the invention, for use in the treatment of diabetes or a diabetes related condition by oral or nasal inhalation.

DETAILED DESCRIPTION OF THE INVENTION

5 This application makes reference to U. S. Patent 6,261,539, issued July 17, 2001, Adjei et al.

This invention involves a stable aerosol suspension formulation suitable for pressurized delivery which comprises (a) a particulate insulin combination, and (b) a suitable fluid carrier.

10 By an "insulin combination" is meant a selected insulin or insulin analog combined with at least one other β -cell hypoglycemic medicament or drug, such as an amylin.

The term "insulin" shall be interpreted to encompass natural extracted human insulin, recombinantly produced human insulin, insulin extracted from bovine and/or
15 porcine sources, recombinantly produced porcine and bovine insulin and mixtures of any of these insulin products. The term is intended to encompass the polypeptide normally used in the treatment of diabetics in a substantially purified form but encompasses the use of the term in its commercially available pharmaceutical form, which includes additional excipients. The insulin is preferably recombinantly produced and may be dehydrated
20 (completely dried) or in solution.

The terms "insulin analog", "monomeric insulin" and the like are used interchangeably herein and are intended to encompass any form of "insulin" as defined above wherein one or more of the amino acids within the polypeptide chain has been replaced with an alternative amino acid and/or wherein one or more of the amino acids
25 has been deleted or wherein one or more additional amino acids has been added to the polypeptide chain or amino acid sequences which act as insulin in decreasing blood glucose levels. In general, the "insulin analogs" of the present invention include "insulin lispro analogs", as disclosed in U. S. Patent 5,547,929, insulin analogs including LysPro (trade-mark) insulin and HUMALOG (trade-mark) insulin, and other "super insulin

3a

analogs", wherein the ability of the insulin analog to affect serum glucose levels is substantially enhanced as compared with conventional insulin as well as hepatoselective insulin analogs which are more active in the liver than in adipose tissue. Preferred analogs are monomeric insulin analogs, which are insulin-like compounds used for the same general purpose as insulin such as insulin lispro, i.e., compounds which are administered to reduce blood glucose levels.

A suitable β -cell hypoglycemic medicament is one selected from an amylin. An "amylin" includes natural human amylin, bovine, porcine, rat, rabbit amylin, as well as synthetic, semi-synthetic or recombinant amylin or amylin analogs including pramlintide and other amylin agonists as disclosed in U. S. Patent 5,686,411 and U. S. Patent 5,854,215.

Combined with the insulin combination, e.g., an insulin plus an amylin, is another diabetic medicament. Typically this other medicament is the α cell hormone glucagon. Other diabetic medicaments which can be employed are acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage, phentolamine, etc.

For purposes of the formulations of this invention, which are intended for inhalation into the lungs, the insulin combination is preferably micronized whereby a therapeutically effective amount or fraction (e.g., ninety percent or more) of the insulin combination is particulate. Typically, the particles have a diameter of less than about 10 microns, and preferably less than about 5 microns, in order that the particles can be inhaled into the respiratory tract and/or lungs.

The particulate insulin combination is present in the inventive formulations in a therapeutically effective amount, that is, an amount such that the drug can be administered as a dispersion, an aerosol, such as topically, or via oral or

nasal inhalation, and cause its desired therapeutic effect, typically preferred with one dose, or through several doses. The particulate insulin combination is administered as an aerosol from a conventional valve, e.g., a metered dose valve, through an aerosol adapter also known as an actuator.

5 The term "amount" as used herein refers to quantity or to concentration as appropriate to the context. The amount of the insulin combination or formulation that constitutes a therapeutically effective amount varies according to factors such as the potency of the particular insulin or insulin analog and the particular β -cell hypoglycemic medicament or medicaments used, as well as the
10 other diabetic medicaments, if used, the route of administration of the formulation, and the mechanical system used to administer the formulation. A therapeutically effective amount of the insulin combination can be selected by those of ordinary skill in the art with due consideration of such factors. Generally a therapeutically effective amount will be from about 0.001 parts by weight to about 5 parts by weight
15 based on 100 parts by weight of the propellant.

Typically, the insulin combination comprises a selected insulin present in an amount of 0.0001 to about 5 parts by weight of the insulin or insulin analog to about 0.0001 to about 5 parts by weight of the selected β -cell hypoglycemic amylin or mixture thereof e.g. an amylin/insulin mixture. Typically,
20 the mixtures of β -cell hypoglycemic medicaments in their respective ranges could be combined with a glucagon or glucagon analog or other diabetic medicament in a concentration range of about 0.001 to about 10 parts by weight based on 100 parts by weight of the propellant.

A suitable fluid carrier is selected. A suitable fluid includes air, a
25 hydrocarbon, such as n-butane, propane, isopentane, etc., or a propellant. A suitable propellant is any fluorocarbon, e.g. a 1-6 hydrogen containing fluoro carbon, such as CHF_2CHF_2 , $\text{CF}_3\text{CH}_2\text{F}$, $\text{CH}_2\text{F}_2\text{CH}_3$ and $\text{CF}_3\text{CHFCH}_3$; a perfluorocarbon, e.g. a 1-4 carbon perfluorocarbon, such as CF_3CF_3 , $\text{CF}_3\text{CF}_2\text{CF}_3$; or any mixture of the foregoing, having a sufficient vapor pressure to render them effective as propellants.
30 Some typical suitable propellants include conventional chlorofluorocarbon (CFC) propellants such as mixtures of propellants 11, 12 and 114 or a mixture of any of the foregoing propellants. Non-CFC propellants such as 1,1,1,2-tetrafluoroethane

(Propellant 134a), 1,1,1,2,3,3,3-heptafluoropropane (Propellant 227) or mixture thereof are preferred. The propellant is preferably present in an amount sufficient to propel a plurality of the selected doses of drug from an aerosol canister.

Optionally, a suitable stabilizer is selected. A suitable stabilizer is a
5 “water addition”. As used herein a “water addition” is an amount of water which (1) is added, either initially with other components of the aerosol formulation, e.g. insulin combination and propellant, or after the other components, e.g. insulin combination, fluid carrier, are combined and processed, (2) is in addition to the water which is always present and which develops during processing and/or storage
10 of the aerosol formulation, i.e. “developed” or “nascent” formulation water, and (3) is present in an amount which further stabilizes medicinal aerosol formulation having nascent formulation water.

An aerosol formulation preferably comprises the water addition in an amount effective to more effectively stabilize the formulation relative to an identical
15 formulation not containing the water addition, i.e. containing only nascent formulation water, such that the insulin combination does not settle, cream or flocculate after agitation so quickly as to prevent reproducible dosing of the insulin combination. Reproducible dosing can be achieved if the formulation retains a substantially uniform drug concentration for about fifteen seconds to five minutes
20 agitation.

The particular amount of the water addition that constitutes an effective amount is dependent upon the particular propellant and on the particular insulin combination used in the formulation. It is therefore not practical to enumerate specific effective amounts for use with specific formulations of the
25 invention, but such amounts can readily be determined by those skilled in the art with due consideration of the factors set forth above. Generally, however, the water addition must be present in a formulation in an amount in excess of the concentration of the nascent formulation water. Such concentration of nascent formulation water typically ranges up to 300 parts by weight per one million parts
30 by weight of the total weight of the aerosol formulation. Accordingly, the water addition in excess of this nascent water concentration typically ranges from about 10 parts by weight to about 5000 parts by weight per one million parts by weight of the

total aerosol formulation weight. Most preferred is that the concentration of the water addition is from about 500 parts by weight to about 5000 parts by weight per one million parts by weight of the total weight of the medicinal aerosol formulation.

It is to be emphasized that this is an amount which exceeds the
5 amount of nascent or developed formulation water. It is also to be stressed that this amount of water addition can be added and initially combined with the other components of the formulation, e.g. an insulin and an amylin and fluid carrier, e.g. 1,1,1,2-tetrahydrofluoroethane, or added to the resultant formulation after these other components have been processed, e.g. prior to or subsequent to storage.

10 It has surprisingly been found that the formulation of the invention is stable without the necessity of employing a cosolvent, such as ethanol, or surfactants. However, further components, such as conventional lubricants or surfactants, cosolvents, ethanol, etc., can also be present in an aerosol formulation of the invention in suitable amounts readily determined by those skilled in the art. In
15 this regard, reference is made to U.S. Patent No. 5,225,183.

Typically, a co-solvent such as ethanol is added in an amount ranging from 0.5 to 10% by weight of the total weight of the formulation.

A most preferred formulation comprises the insulin combination, the fluid carrier, the ethanol cosolvent and the water addition, for example, an insulin
20 and an amylin medicament, 1,1,1,2-tetrafluoroethane, ethanol and the water addition.

Generally the formulations of the invention can be prepared by combining (i) the selected insulin combination in an amount sufficient to provide a plurality of therapeutically effective doses; (ii) the fluid or propellant in an amount
25 sufficient to propel a plurality of doses e.g. from an aerosol canister; and (iii) optionally, the water addition in an amount effective to further stabilize each of the formulations; and (iv) any further optional components, e.g. ethanol as a cosolvent other diabetic medicaments, e.g. glucagon; and dispersing the components. The components can be dispersed using a conventional mixer or homogenizer, by
30 shaking, or by ultrasonic energy as well as by the use of a beadmill or a microfluidizer. Bulk formulations can be transferred to smaller individual aerosol vials by using valve to valve transfer methods, pressure filling or by using

conventional cold-fill methods. It is not required that a component used in a suspension aerosol formulation be soluble in the fluid carrier, e.g. the propellant. Those that are not sufficiently soluble can be coated onto the drug particles in an appropriate amount and the coated particles can then be incorporated in a
5 formulation as described above.

Aerosol canisters equipped with conventional valves, preferably metered dose valves, can be used to deliver the formulations of the invention. It has been found, however, that selection of appropriate valve assemblies for use with aerosol formulations is dependent upon the particular component and other
10 adjuvants used (if any), on the fluid or propellant, and on the particular insulin combination being used. Conventional neoprene and buna valve rubbers used in metered dose valves for delivering conventional CFC formulations often have less than optimal valve delivery characteristics and ease of operation when used with formulations containing HFC-134a or HFC-227. Therefore certain formulations of
15 the invention are preferably dispensed via a valve assembly wherein the diaphragm is made of a nitrile rubber such as DB-218 (American Gasket and Rubber, Schiller Park, Ill.) or an EPDM rubber such as Vistalon™ (Exxon), Royalene™ (UniRoyal), bunaEP (Bayer). Also suitable are diaphragms fashioned by extrusion, injection molding or compression molding from a thermoplastic elastomeric material such as
20 FLEXOMER™ GERS 1085 NT polyolefin (Union Carbide).

Conventional aerosol canisters, coated or uncoated, anodized or unanodized, e.g., those of aluminum, glass, stainless steel, polyethylene terephthalate, and coated canisters or cans with epon, epoxy, etc., can be used to contain a formulation of the invention.

25 The formulation of the invention can be delivered to the respiratory tract and/or lung by oral inhalation in order to treat diabetes or a condition related to diabetes, which are susceptible of treatment by inhalation. The formulations of the invention can also be delivered by nasal inhalation in order to treat, e.g., diabetes (systemic), or they can be delivered via oral (e.g., buccal) administration in order to
30 treat, e.g., diabetes.

CLAIMS:

1. A liquid medicinal aerosol suspension formulation which comprises a particulate material in a fluid propellant carrier; said particulate material being of particles having a diameter of less than 10 microns; and said particulate material comprising an insulin combination which is an insulin or an insulin analog combined with at least one other β -cell hypoglycemic medicament; said formulation being without a surfactant.
2. The formulation as defined in claim 1, which further includes a co-solvent.
3. The formulation as defined in claim 2, where said co-solvent comprises ethanol.
4. The formulation as defined in claim 1, wherein said insulin combination comprises an insulin which is selected from the group consisting of natural, synthetic, recombinant insulins and a mixture of the foregoing.
5. The formulation as defined in claim 1, wherein said insulin combination comprises an insulin analog selected from the group consisting of pro-insulin, an insulin lispro analog, a super insulin analog and a mixture of the foregoing.
6. The formulation as defined in claim 4, wherein said insulin combination comprises an amylin and an insulin selected from the group consisting of lisproinsulin, insulin, hepatoselective insulin, a recombinant insulin, natural insulin and a mixture of any of the foregoing.
7. The formulation as defined in any one of claims 1 to 3, wherein said insulin combination comprises an amylin medicament.
8. The formulation as defined in any one of claims 1 to 7, wherein said fluid propellant carrier is selected from the group of propellants consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof.
9. The formulation as defined in any one of claims 1 to 7, wherein said fluid propellant carrier is selected from the group of hydrocarbons consisting of n-butane, propane, isopentane and a mixture of the foregoing.

10. Use of a formulation as defined in any one of claims 1 to 9, for treating a human or animal with diabetes or a diabetes related condition.

11. A formulation according to any one of claims 1 to 9, in an aerosol canister equipped with a metered dose valve.

12. A method of preparing a liquid medicinal aerosol suspension formulation according to claim 1, which comprises:

- (a) combining (i) said insulin combination in an amount sufficient to provide a plurality of therapeutically effective doses, and (ii) said fluid propellant carrier in an amount sufficient to propel said plurality of therapeutically effective doses from an aerosol canister; and
- (b) dispersing components (i) and (ii).

13. The method as defined in claim 12, which further comprises combining in step (a), (iii) a stabilizer in an effective stabilizing amount, and in step (b) dispersing components (i) and (ii) with said (iii) stabilizer.

14. The method as defined in claim 13, which further comprises combining in step (a) a co-solvent, and in step (b) dispersing components (i), (ii) and (iii) with said co-solvent.

15. A method as defined in claim 14, wherein said co-solvent is ethanol.

16. A liquid medicinal aerosol suspension formulation which consists essentially of a particulate material in a fluid propellant carrier; said particulate material being of particles having a diameter of less than 10 microns; and said particulate material comprising an insulin combination which is an insulin or insulin analog combined with a β -cell hypoglycemic medicament which is selected from the group consisting of an amylin and an amylin analog in combination with another diabetic medicament selected from the group consisting of glucagon, acetoexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, activin, somatostatin and a mixture of any of the foregoing diabetic medicaments; said formulation being without a surfactant.

17. The formulation as defined in claim 1 or 16, wherein said insulin combination is combined with glucagon.

18. A liquid medicinal aerosol suspension formulation which consists essentially of

- (a) a particulate material in a fluid propellant carrier; said particulate material being of particles having a diameter of less than 10 microns; and said particulate material comprising an insulin combination which is an insulin or insulin analog combined with at least one other β -cell hypoglycemic medicament; and
- (b) a water addition stabilizer added in an amount which is in addition to nascent formulation water;

said formulation being without a surfactant.

19. A metered dose inhaler containing a liquid medicinal aerosol suspension formulation, the formulation comprising:

- (a) a particulate material in a fluid propellant carrier; said particulate material being of particles having a diameter of less than 10 microns; and said particulate material comprising an insulin combination which is an insulin analog combined with at least one other β -cell hypoglycemic medicament combined with a diabetic medicament selected from the group consisting of glucagon, acetohexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage, phentolamine and a mixture of the foregoing diabetic medicaments; and
- (b) a water addition stabilizer which is added in an amount which (1) is in excess of nascent formulation water and (2) stabilizes the formulation to prevent settling, creaming or flocculation for a time sufficient to allow reproducible dosing of the insulin combination after agitation of the formulation;

said formulation being without a surfactant.

20. The metered dose inhaler according to claim 19, wherein said diabetic medicament is glucagon.

21. The metered dose inhaler according to claim 19, wherein said hypoglycemic medicament is combined with a mixture of diabetic medicaments.

22. The metered dose inhaler according to claim 19, wherein said insulin combination comprises insulin analog and a mixture of amylin and glucagon.

23. The metered dose inhaler according to claim 19, wherein said formulation further includes a co-solvent.
24. The metered dose inhaler according to claim 23, wherein said co-solvent is ethanol.
25. A metered dose inhaler containing a liquid medicinal aerosol suspension formulation, the formulation consisting essentially of:
- (a) a particulate material in a fluid propellant carrier; said particulate material being of particles having a diameter of less than 10 microns; and said particulate material comprising an insulin combination which is an insulin analog combined with at least one other β -cell hypoglycemic medicament; and
 - (b) a water addition stabilizer which is added in an amount which (1) is in excess of nascent formulation water and (2) stabilizes the formulation to prevent settling, creaming or flocculation for a time sufficient to allow reproducible dosing of the insulin combination after agitation of the formulation;
- said formulation being without a surfactant.
26. The metered dose inhaler according to claim 25, wherein said stabilizer is added in an amount in said excess, of about 10 parts by weight to about 5000 parts by weight based on one million parts by total weight of the medicinal aerosol formulation.
27. The metered dose inhaler according to claim 25, wherein said insulin combination is
- (a) an insulin or an insulin analog; and
 - (b) an amylin or amylin analog.
28. The metered dose inhaler according to claim 27, wherein said insulin is selected from the group consisting of natural, synthetic, recombinant insulin and a mixture of the foregoing insulins.
29. The metered dose inhaler according to claim 27, wherein said selected insulin is an insulin selected from lispro insulin, hepatoselective insulin, and monomeric insulin and a mixture of the foregoing.

30. The metered dose inhaler according to any one of claims 19 to 29, wherein said fluid propellant carrier is selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof.
31. The metered dose inhaler according to any one of claims 19 to 29, wherein said fluid propellant carrier is a hydrocarbon selected from the group consisting of n-butane, propane, isopentane and a mixture of any of the foregoing hydrocarbons.
32. Use of a formulation as defined in any one of claims 1 to 9, for the preparation of a medicament for treating diabetes or a diabetes related condition by oral or nasal inhalation.
33. A formulation according to any one of claims 1 to 9, for use in the treatment of diabetes or a diabetes related condition by oral or nasal inhalation.