



(86) Date de dépôt PCT/PCT Filing Date: 2001/01/02  
(87) Date publication PCT/PCT Publication Date: 2001/08/02  
(45) Date de délivrance/Issue Date: 2011/06/21  
(85) Entrée phase nationale/National Entry: 2002/07/22  
(86) N° demande PCT/PCT Application No.: US 2001/000028  
(87) N° publication PCT/PCT Publication No.: 2001/054741  
(30) Priorités/Priorities: 2000/01/25 (US60/177,922);  
2000/10/31 (US09/702,939)

(51) Cl.Int./Int.Cl. *A61L 9/04* (2006.01),  
*A61M 11/00* (2006.01), *A61M 15/00* (2006.01)

(72) Inventeurs/Inventors:  
ADJEI, AKWETE L., US;  
CUTIE, ANTHONY J., US;  
SUN, JOHN Z., US;  
SEXTON, FREDERICK A., US

(73) Propriétaire/Owner:  
KOS LIFE SCIENCES, INC., US

(74) Agent: OGILVY RENAULT LLP/S.E.N.C.R.L.,S.R.L.

(54) Titre : FORMULATION MEDICINALE EN AEROSOL  
(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 a  $\beta$ -cell hypoglycemic agent and a fluid carrier.

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
2 August 2001 (02.08.2001)

PCT

(10) International Publication Number  
**WO 01/54741 A1**

- (51) International Patent Classification<sup>7</sup>: **A61L 9/04**, A61M 11/00, 15/00
- (74) Agent: **ROSENSTOCK, Jerome**; Frommer Lawrence & Haug LLP, 745 Fifth Avenue, New York, NY 10151 (US).
- (21) International Application Number: PCT/US01/00028
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (22) International Filing Date: 2 January 2001 (02.01.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/177,922 25 January 2000 (25.01.2000) US  
09/702,939 31 October 2000 (31.10.2000) US
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant: **AEROPHARM TECHNOLOGY, INC.** [—/US]; Raritan Center, Campus Plaza 9, 18 Mayfield Avenue, Edison, NJ 08837 (US).
- (72) Inventors: **ADJEL, Akwete, L.**; 15 Tillman Court, Bridgewater, NJ 08807 (US). **CUTIE, Anthony, J.**; 10 Tillman Court, Bridgewater, NJ 08807 (US). **SUN, John, Z.**; 1519 Forest Haven Boulevard, Edison, NJ 08817 (US). **SEXTON, Frederick, A.**; 161 Kemp Avenue, Fair Haven, NJ 07704 (US).
- Published:**  
— with international search report  
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



**WO 01/54741 A1**

(54) Title: A MEDICINAL AEROSOL FORMULATION

(57) Abstract: This invention relates to a medicinal aerosol formulation and more particularly, to a medicinal aerosol formulation containing a  $\beta$ -cell hypoglycemic agent and a fluid carrier.

## A MEDICINAL AEROSOL FORMULATION

### BACKGROUND OF THE INVENTION

#### 5 Field of the Invention

This invention relates to a medicinal aerosol formulation, and more particularly, to a medicinal aerosol formulation comprising a  $\beta$ -cell or  $\alpha$ -cell hypoglycemic.

#### Description of the Related Art

10 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,  $\beta_2$  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  $\mu\text{m}$  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 metered dose inhaler (MDI) or air, such as in the case of a dry powder inhaler (DPI). Alternatively, formulations can be prepared in solution 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.

25 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.

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

### SUMMARY OF THE INVENTION

It has surprisingly been found that a novel and stable medicinal aerosol formulation of a  $\beta$ -cell or  $\alpha$ -cell hypoglycemic medicament can be obtained without the use of a surfactant, such as sorbitan trioleate. A suitable  $\beta$ -cell hypoglycemic medicament is one selected from the group consisting of an amylin and insulin; however, other medicament agents possessing antidiabetic activity, including the  $\alpha$ -cell hypoglycemic glucagon, acetohexamide, chlorpropamide, tolazamide, tolbutamide, and glipizide, as well as any mixture of any two or three of the foregoing  $\beta$ -cell hypoglycemic medicaments may be generally included.

### DETAILED DESCRIPTION OF THE INVENTION

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

This invention involves a stable aerosol formulation suitable for delivery which comprises (a) a  $\beta$ -cell hypoglycemic medicament, and (b) a suitable fluid carrier.

A suitable  $\beta$ -cell hypoglycemic medicament is one selected from either an amylin or insulin and any of their derivatives. A suitable synthetic, antidiabetic agent is one selected from an acetohexamide, chlorpropamide, tolazamide, tolbutamide, glipizide, glyburide, glucophage, phentolamine, etc., and a mixture of any two or three of the foregoing medicaments.

The term "insulin" shall be interpreted to encompass natural extracted human insulin, recombinantly produced human insulin, insulin extracted from bovine and/or 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 (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 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. Pat. No. 5,547,929,

5 , insulin analogs including LysPro insulin and humalog insulin, and other "super insulin 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  
10 administered to reduce blood glucose levels.

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 No. 5,686,411, and U.S. Patent No. 5,854,215.

15

For purposes of the formulations of this invention, which are intended for inhalation into the lungs, the medicament is preferably micronized whereby a therapeutically effective amount or fraction (e.g. ninety percent or more) of the medicament is particulate. Typically, the particles have a diameter of less than about 10  
20 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 medicament or drug 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 or an aerosol, such as topically, or via oral or nasal inhalation,  
25 and cause its desired therapeutic effect, typically preferred with one dose, or through several doses. The particulate  $\beta$ -cell hypoglycemic medicament is administered as an aerosol from a conventional valve, e.g., a metered dose valve, through an aerosol adapter also known as an actuator.

The term "amount" as used herein refers to quantity or to concentration as  
30 appropriate to the context. The amount of the  $\beta$ -cell hypoglycemic medicament or mixture of medicaments that constitutes a therapeutically effective amount varies according to factors such as the potency of the particular  $\beta$ -cell hypoglycemic medicament

or medicaments used, the route of administration of the formulation, and the mechanical system used to administer the formulation. A therapeutically effective amount of a particular drug or drugs 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  
5 about 0.001 parts by weight to about 5 parts by weight based on 100 parts by weight of the fluid carrier e.g. propellant.

A suitable fluid carrier is selected. A suitable fluid carrier includes air, a 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  
10  $\text{CHF}_2\text{CHF}_2$ ,  $\text{CF}_3\text{CH}_2\text{F}$ ,  $\text{CH}_2\text{F}_2\text{CH}_3$  and  $\text{CF}_3\text{CHFCF}_3$ , a perfluorocarbon, e.g. a 1-4 carbon perfluorocarbon, such as  $\text{CF}_3\text{CF}_3$ ,  $\text{CF}_3\text{CF}_2\text{CF}_3$ ; or any mixture of the foregoing, having a sufficient vapor pressure to render them effective as propellants. Some typical suitable propellants include conventional chlorofluorocarbon (CFC) propellants such as propellants 11, 12 and 114 or a mixture of any of the foregoing propellants. Non-CFC propellants  
15 such as 1,1,1,2-tetrafluoroethane (Propellant 134a), 1,1,1,2,3,3,3-heptafluoropropane (Propellant 227) or mixtures thereof are preferred. The propellant is preferably present in an amount sufficient to propel a plurality of the selected doses of the drug from an aerosol canister.

A suitable stabilizer is selected. A suitable stabilizer is a "water  
20 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. medicament and fluid carrier, or after the other components, e.g. medicament, 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 of the aerosol formulation, i.e. "developed" or "nascent"  
25 formulation water, and (3) is present in an amount which further stabilizes a 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 formulation not containing the water addition, i.e. containing only nascent formulation  
30 water, such that the drug does not settle, cream or flocculate after agitation so quickly as to prevent reproducible dosing of the drug. Reproducible dosing can be achieved if the

formulation retains a substantially uniform drug concentration for about fifteen seconds to about five minutes after agitation.

The particular amount of the water addition that constitutes an effective amount is dependent upon the particular fluid carrier, e.g. propellant, and on the particular drug or drugs used in the formulation. It is therefore not practical to enumerate specific effective amounts for use with specific formulations of the 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 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 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 in excess of this nascent water concentration is from 500 parts by weight to 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 amount of nascent or developed formulation water. It is also to be stressed that preferably this amount of water addition can be added and initially combined with the other components of the formulation, e.g. an amylin, glucogan and fluid carrier, e.g. 1,1,1,2-tetrahydrofluoroethane. However, the water addition can be added to the resultant formulation after these other components have been processed, e.g. prior to or subsequent to storage.

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 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 medicament, the fluid carrier, the ethanol cosolvent and the water addition, for example, an amylin, 1,1,1,2-tetrafluoroethane, ethanol and the water addition.

Generally the formulations of the invention can be prepared by combining

5 (i) the  $\beta$ -cell hypoglycemic drug or drugs in an amount sufficient to provide a plurality of therapeutically effective doses; (ii) the fluid, e.g. propellant, in an amount sufficient to propel a plurality of doses, e.g. from an aerosol canister; (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; and dispersing the components. The

10 components can be dispersed using a conventional mixer or homogenizer, by shaking, or by ultrasonic energy as well as by the use of a bead mill 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

15 carrier, e.g. 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 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,

20 however, that selection of appropriate valve assemblies for use with aerosol formulations is dependent upon the particular component and other adjuvants used (if any), on the fluid, e.g. propellant, and on the particular drug 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

25 with formulations containing HFC-134a or HFC-227. Therefore certain formulations of 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<sup>TM</sup> (Exxon), Royalene<sup>TM</sup> (UniRoyal), bunaEP (Bayer). Also suitable are diaphragms fashioned by extrusion, injection molding or compression

30 molding from a thermoplastic elastomeric material such as FLEXOMER<sup>TM</sup> GERS 1085 NT polyolefin (Union Carbide).

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

5           The formulation of the invention can be delivered to the respiratory tract and/or lung by oral inhalation in order to treat diabetes and a diabetes related condition 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 treat, e.g., diabetes and a  
10 diabetes related condition.

**WE CLAIM:**

1. A liquid medicinal aerosol suspension formulation which comprises,
  - (a) a medicament selected from the group consisting of an insulin analog, an amylin and a mixture of the foregoing;
  - (b) a fluid propellant carrier; and
  - (c) a stabilizer comprising a water addition added in an amount (1) which is in addition to nascent formulation water and (2) to stabilize the formulation to prevent settling, creaming or flocculation for a time sufficient to allow reproducible dosing of the drug after agitation of the formula.
  
2. A liquid medicinal aerosol suspension formulation which consists essentially of:
  - (a) an amount of beta-cell hypoglycemic medicament selected from the group consisting of an amylin, an insulin and a mixture of the foregoing;
  - (b) a fluid propellant carrier; and
  - (c) a stabilizer comprising a water addition added in an amount (1) which is in addition to nascent formulation water and (2) to stabilize the formulation to prevent settling, creaming or flocculation for a time sufficient to allow reproducible dosing of the drug after agitation of the formula.
  
3. The formulation as defined in claim 2 wherein said medicament is an insulin.
  
4. Use of a formulation as defined in any one of claims 1 to 3 for treating in a human or an animal with diabetes or a diabetes related condition by oral or nasal inhalation.
  
5. A formulation according to claim 1 or 2 in an aerosol canister equipped with a metered dose valve.

6. A method of preparing a liquid medicinal aerosol suspension formulation as defined in claims 1 or 2, which comprises:
  - (a) combining (i) said medicament in an amount sufficient to provide a plurality of therapeutically effective doses and said stabilizer in an effective stabilizing amount and (ii) said fluid propellant carrier in an amount sufficient to propel at least said plurality of pharmaceutically effective doses from an aerosol canister; and
  - (b) dispersing components (i) and (ii).
7. The method as defined in claim 6 which further comprises combining in step (a) a cosolvent and in step (b) dispersing components (i) and (ii) with said cosolvent.
8. The method as defined in claim 7 wherein said cosolvent is ethanol.
9. A metered dose inhaler containing a liquid medicinal suspension aerosol formulation, the formulation comprising:
  - (a) a beta-cell hypoglycemic medicament selected from the group consisting of an insulin analog, an amylin and a mixture of the foregoing;
  - (b) a fluid propellant carrier; and
  - (c) a stabilizer comprising a water addition which is added in an amount (1) which is in excess of nascent formulation water and (2) to stabilize the formulation to prevent settling, creaming or flocculation for a time sufficient to allow reproducible dosing of the drug after agitation of the formulation.
10. The metered dose inhaler as defined in claim 9 which further comprises an anti-diabetic medicament.
11. The metered dose inhaler as defined in claim 10 wherein said anti-diabetic medicament is selected from the group consisting of glucagon,

acetoexamide, tolbutamide, glipizide, glyburide, glucophage, phentolamine, and a mixture of any of the foregoing medicaments.

12. The metered dose inhaler as defined in claim 9 which further comprises glucagon.
13. The metered dose inhaler as defined in claim 12 wherein said beta-cell hypoglycemic is a mixture of an amylin and an insulin analog.
14. The metered dose inhaler as defined in claim 9 wherein said formulation further includes a cosolvent.
15. The metered dose inhaler as defined in claim 14 wherein said cosolvent is ethanol.
16. The formulation as defined in claims 1, 2 or claim 9 wherein said medicament is an amylin.
17. The formulation as defined in claims 1 or 2 which further includes a cosolvent.
18. The formulation as defined in claim 17 where said cosolvent comprises ethanol.
19. The formulation as defined in claims 1 or 9 which further comprises a synthetic anti-diabetic agent.
20. The formulation as defined in claim 19 wherein said agent is selected from the group consisting of glucagon, acetoexamide, chlorpropamide, tolazemide, tolbutamide, glipizide, glyburide, glucophage, phentolamine, and a mixture of any of the foregoing agents.
21. The formulation as defined in claim 19 wherein the medicament is combined with glucagon.

22. The formulation as defined in claims 1, 2 or 9 wherein said fluid carrier is selected from the group of propellants consisting of 1,1,1,2-tetrafluorethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof.
23. The formulation as defined in claims 1, 2 or 9 wherein said fluid carrier is a hydrocarbon selected from the group consisting of n-butane, propane, isopentane and a mixture of any of the foregoing hydrocarbons.
24. A metered dose inhaler containing a liquid medicinal aerosol suspension formulation, the formulation consisting essentially of:
  - (a) a beta-cell hypoglycemic drug in particulate form selected from the group consisting of an amylin, an insulin and a mixture of the foregoing;
  - (b) a fluid propellant carrier; and
  - (c) a water addition stabilizer which is added in an amount (1) which is in excess of nascent formulation water and (2) to stabilize the formulation to prevent settling, creaming or flocculation for a time sufficient to allow reproducible dosing of the drug after agitation of the formulation.
25. The metered dose inhaler as defined in claim 24 wherein said stabilizer is present in said excess in an amount 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.
26. The metered dose inhaler as defined in claim 24 wherein said beta-cell hypoglycemic is an amylin.
27. The metered dose inhaler as defined in claim 24 wherein said beta-cell hypoglycemic is insulin.

28. The metered dose inhaler as defined in claim 24 wherein said fluid carrier is a propellant selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof.
29. The metered dose inhaler as defined in claim 24 wherein said fluid carrier is a hydrocarbon selected from the group consisting of n-butane, propane, isopentane and a mixture of any of the foregoing hydrocarbons.
30. Use of a formulation as defined in any one of claim 1 to 3 for the preparation of a medicament for the treatment of diabetes or a diabetes related condition by oral or nasal inhalation.