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Title: PERFLUOROCARBON AND HYDROFLUOROCARBON FORMULATIONS AND METHODS OF MAKING AND USING SAME

Abstract: A liquid aerosol generating formulation comprising medicament and at least one liquid perfluorocarbon and/or hydrofluorocarbon. The formulation can include at least one surfactant which stabilizes the medicament. An aerosol of medicament particles can be formed by heating the formulation in a flow passage such that the liquid perfluorocarbon and/or hydrofluorocarbon is vaporized and expands out of an outlet of the flow passage. The flow passage can be a heated capillary sized flow passage in a hand held inhaler. The liquid perfluorocarbon and/or hydrofluorocarbon can deliver drugs having low solubility and/or low potency to a patient as a soft mist aerosol requiring minimal patient coordination.
PERFLUOROCARBON AND HYDROFLUOROCARBON FORMULATIONS
AND METHODS OF MAKING AND USING SAME

Field of the Invention

The invention relates generally to aerosol generation. More specifically, the invention relates to aerosol formulations including at least one liquid perfluorocarbon and/or hydrofluorocarbon, aerosol generating devices and methods for making the aerosol formulations and generating aerosols.

Background of the Invention

Aerosols are gaseous suspensions of fine solid or liquid particles. Aerosols are useful in a wide variety of applications. For example, medicated liquids may be administered in aerosol form. Medicated aerosols include materials that are useful in the treatment of respiratory ailments. In such applications, the aerosols may be produced by an aerosol generator and inhaled into a patient's lungs. Aerosols are also used in non-medicinal applications including, for example, industrial purposes.

Aerosol generators are known that include a heated tube for vaporizing liquid. For example, commonly assigned U.S. Patent No. 5,743,251, which is incorporated herein by reference in its entirety, discloses an aerosol generator including a tube and a heater operable to heat the tube to a sufficient temperature to volatilize liquid in the tube. It is disclosed that the volatilized material expands out of an end of the tube and admixes with ambient air, thereby forming an aerosol.

Other aerosol generators including a heated tube for vaporizing liquids to produce an aerosol are described in commonly-assigned U.S. Patent No. 6,234,167 and U.S. Patent Application Nos. 09/956,966 filed September 21, 2001 and 10/003,437 filed December 6, 2001, each being incorporated herein by reference in its entirety.

Summary of the Invention

According to one embodiment, the invention provides a propellant-free liquid
aerosol generating formulation comprising at least one liquid perfluorocarbon and/or hydrofluorocarbon, at least one medicament, and at least one surfactant, the liquid perfluorocarbon and/or hydrofluorocarbon being in a liquid state under ambient conditions. The formulation can optionally include additional components such as additives and/or other liquids. The liquid aerosol generating formulation preferably comprises a solution, a suspension or an emulsion.

According to a preferred embodiment, the liquid perfluorocarbon comprises a straight chain perfluoroalkane, cyclic perfluoroalkane, oxygen containing perfluoroalkane, nitrogen containing perfluoroalkane, or derivative thereof and the liquid hydrofluorocarbon comprises a liquid hydrofluoroalkane, hydrofluoroalkene, hydrofluoroether or derivative thereof. The surfactant preferably stabilizes the medicament in the formulation and can comprise at least one partially or fully fluorinated surfactant including one or more of a fluoroalcohol, fluoroolefin, fluoroalkylacrylate, fluoroalkylstearate, fluoroalkanoic acid and fluoroalkylcitrate and/or the surfactant can comprise at least one nonfluorinated surfactant such as a phospholipid, polyalcohol, polyolefin, sorbitan ester, or mixture thereof. According to a preferred embodiment, the liquid perfluorocarbon and/or hydrofluorocarbon has a boiling point of at least about 40°C, density less than about 2 g/cm³ and/or vapor pressure of about 20 Torr to about 200 Torr.

The medicament preferably comprises solid or liquid particles having a particle size of about 0.05 to about 10 μm. For instance, the medicament can be incorporated in a polymer matrix which is ground to a desired particle size. The concentration of the medicament in the formulation can be selected so as to provide a therapeutically effective amount of a pharmaceutically active drug when formulation is aerosolized. For example, the formulation can be aerosolized by passing a metered amount of the formulation through a capillary sized flow passage which is heated sufficiently to vaporize the liquid perfluorocarbon and/or hydrofluorocarbon and form an aerosol which contains medicament particles. A preferred formulation can include up to about 20% by weight of the medicament and at least 5%, more preferably at least 50% and
most preferably at least 80% by volume of liquid perfluorocarbon and/or hydrofluorocarbon.

According to one embodiment, the invention provides a method of generating an aerosol comprising supplying a liquid aerosol generating formulation containing medicament and at least one liquid perfluorocarbon and/or hydrofluorocarbon to a flow passage, heating the formulation in the flow passage so as to volatilize the liquid perfluorocarbon and/or hydrofluorocarbon and form an aerosol containing the medicament. For drug delivery, the aerosol preferably comprises medicament particles having MMAD of about 0.05 to about 10 μm.

In a preferred embodiment, the flow passage is a capillary sized flow passage and the aerosol is formed in a mouthpiece of a handheld inhaler. The flow passage is preferably heated by a resistance heater located in the handheld inhaler, the inhaler including a power supply and control electronics which controls supply of electrical power to the heater as a function of a control parameter selected to achieve boiling of the liquid perfluorocarbon and/or hydrofluorocarbon while in the flow passage.

**Detailed Description of the Invention**

Liquid aerosol generating formulations, aerosol generating devices and methods for generating aerosols from the liquid formulations are provided.

The liquid aerosol generating formulations can produce aerosols having selected compositions and controlled particle sizes. The liquid formulations are suitable for different applications. For example, for drug delivery applications via inhalation, the liquid formulations can be used to produce aerosols having a desirable mass median aerodynamic diameter (MMAD) for targeted delivery. For pulmonary delivery, particles of smaller size are desired than for tracheobronchial delivery or delivery to the oropharynx or mouth. In preferred embodiments, the liquid formulations can be used to produce aerosols having a controlled particle size that is effective to achieve pulmonary delivery of drug formulations.

The liquid aerosol generating formulation includes at least one liquid perfluorocarbon and/or hydrofluorocarbon and at least one medicament. The liquid
perfluorocarbons and hydrofluorocarbons are in a liquid state under ambient pressure and temperature conditions. According to a preferred embodiment, the liquid formulation is propellant-free and the liquid perfluorocarbon comprises a straight chain perfluoroalkane, cyclic perfluoroalkane, oxygen containing perfluoroalkane, nitrogen containing perfluoroalkane, or derivative thereof and the liquid hydrofluorocarbon comprises a liquid hydrofluoroalkane, hydrofluoroalkene, hydrofluoroether or derivative thereof. The liquid aerosol generating formulation preferably includes at least 5% by volume, more preferably at least 50% and most preferably at least 80% of the liquid perfluorocarbon and/or hydrofluorocarbon. According to a preferred embodiment, the liquid perfluorocarbon and/or hydrofluorocarbon has a boiling point of at least about 40°C or at least about 50°C, density less than about 2 g/cm3 and/or vapor pressure of about 20 Torr to about 200 Torr.

The surfactant preferably stabilizes the medicament in the formulation and can comprise at least one partially or fully fluorinated surfactant such as a fluoroalcohol, fluoroolefin, fluoroalkylacrylate, fluoroalkylstearate, fluoroalkanoic acid and/or fluoroalkylcitrate. For example, in a partially fluorinated surfactant some of the H atoms are replaced by F atoms and in a fully fluorinated surfactant most or all of the H atoms are replaced with F atoms. The surfactant can instead comprise or further include at least one nonfluorinated surfactant such as a phospholipid, polyalcohol, polylefin, sorbitan ester, or mixture thereof.

Various substances can be used as the medicament in the liquid formulations, depending on the desired application. The medicament can be present as a solid or liquid in the formulation. For instance, the formulation can be a suspension which includes solid medicament particles suspended in a liquid. Alternatively, the formulation can be an emulsion wherein the medicament is present as a liquid phase dispersed in a different liquid phase. The formulation can also comprise a solution wherein the medicament is dissolved in a liquid.

In the case of a suspension or emulsion, the medicament preferably comprises solid and/or liquid particles having a particle size of about 0.05 to about 10 μm. The
medicament can be incorporated in a polymer matrix which is ground to a desired particle size. The concentration of the medicament in the formulation can be selected so as to provide a therapeutically effective amount of a pharmaceutically active drug when the formulation is aerosolized. For example, the formulation can be aerosolized by passing a metered amount of the formulation through a capillary sized flow passage which is heated sufficiently to vaporize the liquid perfluorocarbon and/or hydrofluorocarbon and form an aerosol which contains the medicament. A preferred formulation can include up to about 20% by weight of the medicament.

The medicament can comprise various substances which can be incorporated in a liquid aerosol generating formulation. For example, the medicament includes analgesics, anginal preparations, anti-allergics, antibiotics, antihistamines, antitussives, antiemetics, insulin, bronchodilators, diuretics, anticholinergics, hormones, anti-inflammatory agents and mixtures thereof.

The formulation can optionally include up to 20 volume % of at least one solvent or cosolvent, e.g., water, organic liquid such as short chain (C1 -C6) alcohols such as ethyl alcohol (ethanol), n-propyl alcohol, isopropyl alcohol, butanol, glycerin, ethylene glycol, diethylene glycol, propylene glycol, sorbitol, dipropylene glycol, tripropylene glycol, and hexylene glycol. Preferred short chain diols and polyols are propylene glycol and dipropylene glycol. Propylene glycol is especially preferred. The formulation may optionally include one or more other pharmaceutically acceptable excipients (such as ethanol and/or water), flavoring agents, preservatives, additives, antioxidants, stabilizers, and/or other ingredients suitable for inclusion in drug formulations administered via inhalation therapy.

In a preferred embodiment, the liquid formulation is flowed through a capillary sized flow passage in which the liquid perfluorocarbon and/or hydrofluorocarbon is heated to a sufficiently high temperature to vaporize the liquid perfluorocarbon and/or hydrofluorocarbon. The vapor exits the flow passage and admixes with gas, preferably ambient air, to produce an aerosol which is inhaled by a user. The size of the aerosol particles thus produced can be controlled for delivery to the lung.

The capillary passage can have different transverse cross-sectional shapes, such
as round, oval, triangular, square, rectangular, other polygonal shapes, or the like, as well as other non-geometric shapes. Different portions of the capillary passage can have different cross-sectional shapes. As described below, the size of the capillary passage can be defined by its transverse cross-sectional area. For a capillary passage having a round cross-section, the size of the flow passage may be defined by its diameter. Alternatively, the capillary passage may be non-circular in cross section and the size of the capillary passage may be defined by its width. For example, the capillary passage can have a maximum width of 0.01 to 10 mm, preferably 0.05 to 1 mm, and more preferably 0.1 to 0.5 mm. Alternatively, the capillary passage can be defined by its transverse cross-sectional area, which can be 8 x 10-3 to 80 mm², preferably 2 x 10-3 to 8 x 10-1 mm², and more preferably 8 x 10-3 to 2 x 10-1 mm².

Details of an aerosol generator which can be used to aerosolize the liquid formulation are described in commonly assigned U.S. Patent Nos. 5,743,251; 6,234,167 and 6,516,796, the entire disclosures of which are hereby incorporated by reference. Other suitable aerosol generators are described in commonly assigned U.S. Patent Application No. 10/341,521 filed January 14, 2003, the entire disclosure of which is hereby incorporated by reference. Control schemes for heating the flow passage are described in commonly assigned U.S. Patent No. 6,501,052, the entire disclosure of which is hereby incorporated by reference, and in commonly assigned U.S. Patent Application No. 10/206,320 filed July 29, 2002, the entire disclosure of which is hereby incorporated by reference.

As described in commonly-assigned U.S. Provisional Patent Application No. 60/408,295 filed September 6, 2002, which is incorporated herein by reference in its entirety, embodiments of the capillary passage can comprise an outlet section, which controls the velocity of vapor exiting the outlet end of the capillary passage, i.e., the exit velocity of the vapor, so as to control the particle size of aerosol generated by the aerosol generating device.

The material forming the capillary passage can be any suitable material, including metals, plastics, polymers, ceramics, glasses, or combinations of these materials. Preferably, the material is a heat-resistant material capable of withstanding
the temperatures and pressures generated in the capillary passage, and also resisting the repeated heating cycles utilized to generate multiple doses of aerosols. In addition, the material forming the capillary passage preferably is non-reactive with the liquid that is aerosolized.

In another alternative embodiment, the capillary passage can be formed in a polymer, glass, metal and/or ceramic monolithic or multilayer (laminated) structure (not shown). Suitable ceramic materials for forming the capillary passage include, but are not limited to, alumina, zirconia, silica, aluminum silicate, titania, yttria-stabilized zirconia, or mixtures thereof. A capillary passage can be formed in the monolithic or multilayer body by any suitable technique, including, for example, machining, molding, extrusion, or the like.

In embodiments, the capillary passage can have a length from 0.5 to 10 cm, and preferably from 1 to 4 cm.

The fluid supplied from a liquid source is heated in the capillary passage to form a vapor during operation of the aerosol generating device. In a preferred embodiment, the capillary comprises metal tubing heated by passing an electrical current along a length of the capillary via a first electrode and a second electrode. However, as described above, the capillary passage can have other alternative constructions, such as a monolithic or multi-layer construction, which include a heater such as a resistance heating material positioned to heat the fluid in the capillary passage. For example, the resistance heating material can be disposed inside of, or exterior to, the capillary passage.

The capillary passage may comprise an electrically conductive tube provided with a downstream electrode and an upstream electrode. In this embodiment, the capillary is a controlled temperature profile (CTP) construction, such as disclosed in copending and commonly assigned U.S. Application Serial No. 09/957,026, filed September 21, 2001, which is incorporated herein by reference in its entirety. In the controlled temperature profile capillary, the downstream electrode has an electrical resistance sufficient to cause it to be heated during operation of the aerosol generating device, thereby minimizing heat loss at the outlet end of the capillary tube.
The tube forming the capillary passage can be made entirely of stainless steel or any other suitable electrically conductive materials. Alternatively, the tube can be made of a non-conductive or semi-conductive material incorporating a heater made from an electrically conductive material, such as platinum. Electrodes connected at spaced positions along the length of the tube or heater define a heated region between the electrodes. A voltage applied between the two electrodes generates heat in the heated region of the capillary passage based on the resistivity of the material(s) making up the tube or heater, and other parameters such as the cross-sectional area and length of the heated region section. As the fluid flows through the capillary passage into the heated region between the first and second electrodes, the fluid is heated and converted to a vapor. The vapor passes from the heated region of the capillary passage and exits from the outlet end. The volatilized fluid is preferably entrained in ambient air as the volatilized fluid exits from the outlet, causing the medicament particles to form an aerosol. In a preferred embodiment, the MMAD of the aerosol is about 0.05 to about 10 μm.

The temperature of the liquid in the capillary passage can be calculated based on a parameter such as the measured or calculated resistance of the heating element. For example, the heating element can be a portion of a metal tube, or alternatively a strip or coil of resistance heating material. Control electronics can be used to regulate the temperature of the capillary passage by monitoring the resistance of the heater. To illustrate operation of the aerosol generating device, a target temperature for the capillary passage can be about 50°C for purposes of vaporizing the liquid perfluorocarbon and/or hydrofluorocarbon (PFC and HFC).

The control electronics can perform various selected functions in the aerosol generating device. For example, the control electronics can control the temperature profile of the capillary passage during operation of the aerosol generating device. The control electronics can also control the output of the display. The display is preferably a liquid crystal display (LCD). The display can depict selected information pertaining to the condition or operation of the aerosol generating device. The control electronics can also control the operation of fluid supply to the capillary passage during operation of the
aerosol generating device; monitor an initial pressure drop in the mouthpiece caused by
inhalation and sensed by a pressure sensor; and monitor the condition of the battery unit
that provides electrical power to components of the aerosol generating device.

Preferably, the aerosol particles have a MMAD between about 0.05 μm and
about 10 μm. As described above, the aerosol generating device can provide aerosols
having a controlled particle size, including aerosols sized for the targeted delivery of
drugs to the lung. These aerosols offer a number of advantages for delivering drugs to
the deep lung. For example, mouth and throat deposition are minimized, while
deposition in the deep lung is maximized, especially when combined with a breath hold.

Moreover, by using the liquid perfluorocarbon and/or hydrofluorocarbon, medicaments
having low solubility and/or low potency can be aerosolized via vaporization of the
liquid perfluorocarbon and/or hydrofluorocarbon.

Operation of the preferred aerosol generating device for delivering aerosolized
medicaments is as follows. First, a liquid formulation comprising the liquid
perfluorocarbon and/or hydrofluorocarbon and medicament is delivered to the heated
capillary passage. The liquid vaporizes in the capillary passage and exits as a vapor jet
from an outlet of the capillary passage. The vapor jet carries with it the medicament
and forms a highly concentrated, soft mist aerosol. As described above, application of
heat to vaporize the liquid is typically achieved by resistive heating from passing an
electric current through the heater. The applied power is adjusted to maximize the
conversion of the fluid into a vapor.

As will be appreciated, the aerosol generating device is capable of controlled
vaporization and aerosol formation of drug formulations. The aerosol generating device
can provide immediate delivery of aerosol to a patient, thereby not wasting lung
capacity, which may be limited due to the health of the patient. Also, the aerosol
generating device can provide consistent delivery of controlled amounts of drug
formulation to a patient. In addition, the aerosol generated by the aerosol generating
device can be relatively unaffected by relative humidity and ambient temperature.

The above-described exemplary modes of carrying out the invention are not
intended to be limiting. It will be apparent to those of ordinary skill in the art that
modifications thereto can be made without departure from the spirit and scope of the invention as set forth in the accompanying claims. For instance, while a heated capillary tube has been described as the preferred construction of the capillary passage, the capillary passage can comprise one or more channels in a laminate having a heater arranged along the channel(s), multiple capillary tube arrangements, a passage having a heater located inside the passage, coaxial arrangements including an annular channel for fluid flow, or the like.
WHAT IS CLAIMED IS:

1. A propellant-free liquid aerosol generating formulation comprising at least one liquid perfluorocarbon and/or hydrofluorocarbon, at least one medicament, and optionally at least one surfactant, the liquid perfluorocarbon and/or hydrofluorocarbon being in a liquid state under ambient conditions.

2. The aerosol generating formulation of Claim 1, wherein the liquid perfluorocarbon comprises a straight chain perfluoroalkane, cyclic perfluoroalkane, oxygen containing perfluoroalkane, nitrogen containing perfluoroalkane, or derivative thereof and the liquid hydrofluorocarbon comprises a liquid hydrofluoroalkane, hydrofluoroalkene, hydrofluoroether or derivative thereof.

3. The aerosol generating formulation of Claim 1, wherein the surfactant stabilizes the medicament in the formulation and comprises at least one partially or fully fluorinated surfactant including a fluoroalcohol, fluoroolefin, fluoroalkylacrylate, fluoroalkylstearate, fluoroalkanoic acid, and/or fluoroalkylcitrate and/or the surfactant comprises at least one nonfluorinated surfactant such as a phospholipid, polyalcohol, polyolefin, sorbitan ester, or mixture thereof.

4. The aerosol generating formulation of Claim 1, wherein the liquid aerosol generating formulation comprises a solution, suspension or emulsion.

5. The aerosol generating suspension formulation of Claim 1, wherein the suspension contains up to about 20% by weight of the medicament and at least 80% by volume of the liquid perfluorocarbon and/or hydrofluorocarbon.

6. The aerosol generating suspension formulation of Claim 1, wherein the medicament comprises solid or liquid particles having a particle size of about 0.05 to about 10 μm, the medicament being optionally incorporated in a polymer matrix which is ground into medicament particles.
7. The aerosol generating suspension formulation of Claim 6, wherein the liquid perfluorocarbon and/or hydrofluorocarbon has a boiling point of at least about 40°C, density less than about 2 g/cm³ and/or vapor pressure of about 20 Torr to about 200 Torr.

8. The aerosol generating suspension formulation of Claim 1, wherein the solution further contains an organic solvent in an amount up to 20% by weight, the organic solvent being selected from short chain (C1-C6) alcohols including ethanol, n-propyl alcohol, isopropyl alcohol, butanol, glycerin, ethylene glycol, diethylene glycol, propylene glycol, sorbitol, dipropylene glycol, tripropylene glycol, and/or hexylene glycol.

9. The aerosol generating solution of Claim 1, wherein the solution further contains water in an amount of up to 20% by weight.

10. A method of generating an aerosol comprising supplying a liquid aerosol generating formulation comprising at least one medicament and at least one liquid perfluorocarbon and/or hydrofluorocarbon to a flow passage wherein the liquid perfluorocarbon and/or hydrofluorocarbon being in a liquid state under ambient conditions, heating the formulation in the flow passage sufficiently to vaporize the liquid perfluorocarbon and/or hydrofluorocarbon and form an aerosol which contains the medicament.

11. The method of Claim 10, wherein the vaporized liquid perfluorocarbon and/or hydrofluorocarbon expands out of an outlet of the flow passage and the aerosol comprises medicament particles having an MMAD of less than about 10 μm.

12. The method of Claim 10, wherein the formulation is propellant-free and further includes at least one surfactant.
13. The method of Claim 10, wherein the liquid perfluorocarbon comprises a straight chain perfluoroalkane, cyclic perfluoroalkane, oxygen containing perfluoroalkane, nitrogen containing perfluoroalkane, or derivative thereof and the liquid hydrofluorocarbon comprises a liquid hydrofluoroalkane, hydrofluoroalkene, hydrofluor ether or derivative thereof.

14. The method of Claim 12, wherein the surfactant stabilizes the medicament in the formulation and comprises at least one partially or fully fluorinated surfactant including a fluoroalcohol, fluoroolefin, fluoroalkylacrylate, fluoroalkylstearate, fluoroalkanoic acid, and fluoroalkylcitrate and/or the surfactant comprises at least one nonfluorinated surfactant such as a phospholipid, polyalcohol, polyolefin, sorbitan ester, or mixture thereof.

15. The method of Claim 10, wherein the liquid aerosol generating formulation comprises a solution, suspension or emulsion.

16. The method of Claim 10, wherein the formulation contains up to about 20% by weight of the medicament and at least 80% by volume of liquid perfluorocarbon and/or hydrofluorocarbon.

17. The method of Claim 10, wherein the medicament comprises solid or liquid medicament particles having a particle size of about 0.05 to about 10 \( \mu \text{m} \) wherein the medicament is optionally incorporated in a polymer matrix which is ground into the medicament particles.

18. The method of Claim 17, wherein the liquid perfluorocarbon and/or hydrofluorocarbon has a boiling point of at least about 40°C, density less than about 2 g/cm3 and/or vapor pressure of about 20 Torr to about 200 Torr.
19. The method of Claim 10, wherein the flow passage is a capillary sized flow passage and the aerosol is formed in a mouthpiece of a handheld inhaler.

20. A method of preparing the aerosol generating formulation of Claim 1, comprising incorporating medicament in a polymer matrix, forming medicament-containing particles by grinding the polymer matrix with the medicament incorporated therein, and forming the formulation as a liquid suspension by mixing the medicament-containing particles with the at least one liquid perfluorocarbon and/or hydrofluorocarbon.

21. An aerosol generator comprising:
a flow passage adapted to receive a liquid aerosol generating formulation from a liquid supply, the liquid formulation comprising at least one liquid perfluorocarbon and/or hydrofluorocarbon and at least one medicament;
a heater operable to heat the liquid formulation in at least a portion of the flow passage sufficiently to vaporize the at least one liquid perfluorocarbon and/or hydrofluorocarbon and generate an aerosol containing the medicament.

22. The aerosol generator of Claim 21, wherein the aerosol generator comprises a hand held inhaler having a mouthpiece and the flow passage comprises a capillary sized flow passage having an outlet in fluid communication with an interior of the mouthpiece.

23. The aerosol generator of Claim 21, wherein the heater is a resistance heater comprising a section of a metal capillary tube and the flow passage comprises the interior of the metal capillary tube.

24. The aerosol generator of Claim 21, wherein the aerosol generator comprises a hand held inhaler having a power supply and control electronics which controls supply of electrical power to the heater as a function of a control parameter
selected to achieve boiling of the liquid perfluorocarbon and/or hydrofluorocarbon in the flow passage.

25. The aerosol generator of Claim 21, wherein the liquid supply comprises a reservoir containing the liquid formulation under a pressure of no greater than about atmospheric pressure.

26. The aerosol generator of Claim 21, wherein the liquid formulation is a propellant-free solution, suspension or emulsion and includes less than 20 weight % of the medicament, more than 20 volume % of the liquid perfluorocarbon and/or hydrofluorocarbon, and up to 20 weight % surfactant.

27. The aerosol generator of Claim 21, wherein the aerosol generator is a hand held inhaler having a valving mechanism which delivers metered amounts of the liquid formulation to the flow passage.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 9/00, 9/72, 9/14, 9/16, 39/00
US CL : 424/45, 489, 426, 434, 450, 490
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)
U.S. : 424/45, 489, 426, 434, 450, 490

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

Electronic database consulted during the international search (name of data base and, where practicable, search terms used)
WEST, STN (CAPLUS, MEDLINE), NPL (SCIRUS)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>WO 00/00215 (ALLIANCE PHARMACEUTICAL CORP) 6 January 2000 (06.01.2000), entire document especially pages 9, 23, 26, 33, 34, 36, 39, 49, 51 and 53.</td>
<td>1-27</td>
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Further documents are listed in the continuation of Box C.

*I* later document published after the international filing date which may throw doubt on priority claim(s) or which is cited to establish the publication date of another document or other special reason (as specified)

*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

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