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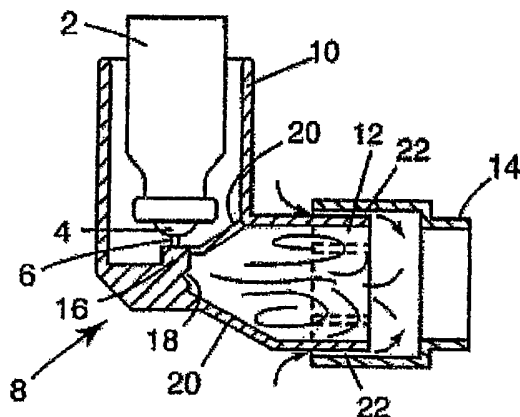
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(54) Title: MEDICAMENT DELIVERY FORMULATIONS, DEVICES AND METHODS



(57) Abstract: Disclosed are medicinal compositions, and devices, methods and systems which use same, comprising a propellant and at least one medicinally active compound, said propellant comprising at least one fluoroolefin having at least two but less than seven carbon atoms.

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MEDICAMENT DELIVERY FORMULATIONS, DEVICES AND METHODS

FIELD OF THE INVENTION

This invention relates to medicament delivery compositions, systems, devices and methods. In particular aspects, this invention relates to medicinal aerosol formulations, methods and devices, such as those used in connection with pulmonary, nasal, buccal or topical administration of medicaments.

BACKGROUND OF THE INVENTION

Metered dose inhalers (MDIs) have long been used to deliver medicaments, such as bronchodilator drugs and steroids, to the areas of patients needing treatment. Compared with oral administration of bronchodilators, inhalation therapy using MDIs frequently has the advantage of relatively rapid onset of action and relatively low instance of systemic side effects.

In general, MDIs are dependent upon the propulsive force of a propellant to help transport the medicament to the area or areas needing treatment, which sometimes are referred to herein as the "target area." The propellant has heretofore generally comprised a mixture of liquefied chlorofluorocarbons (CFC's) selected to have the vapor pressure necessary to produce the desired propulsive force while at the same time providing stability of the medicament formulation. Methane and ethane series CFCs, such tetrachloromethane (CFC-11), trichlorofluoromethane (CFC-12) and 1,2 dichlorotetrafluoroethane (CFC -114), have commonly been used as propellants in aerosol formulations for inhalation administration.

The use of CFCs has environmental drawbacks. It is now known that CFC's tend to react with the ozone layer around the earth and thereby result

in some level of ozone depletion. As a result various governmental and international organizations have been engaged in efforts to reduce or eliminate the use of CFCs. The volume of CFCs which have been used in connection with MDIs may be considered low compared to other uses, such as refrigerants and blowing agents. Nevertheless, a potential ozone depletion advantage may be achieved by reducing or eliminating CFCs from MDIs and other medicament delivery systems.

Because of the potential damage to the earth's ozone layer caused by chlorine-containing compounds (such as chlorofluorocarbons (CFCs), hydrochlorofluorocarbons (HCFCs) and the like), there has thus been an increasing need for new fluorocarbon and hydrofluorocarbon compounds and compositions that offer alternatives with reduced ozone depletion potential. For example, efforts are under way to replace chlorine-containing propellants with non-chlorine-containing compounds that will not deplete the ozone layer, such as hydrofluorocarbons (HFCs).

U.S. Pat. No. 5,776,434 – Purewal, et al. has recognized the ozone depletion problem of CFCs and has proposed the use of a non-chlorine containing compound, namely, 1,1,1,2-tetrafluoroethane (sometimes referred to herein as HFA-134a or HFC-134a) as a propellant for medicinal aerosol formulations when used in combination with a surface active agent and an adjuvant having a higher polarity than 1,1,1,2-tetrafluoroethane. However, in 1998 the International Programme on Chemical Safety (IPCS), published a Concise International Chemical Assessment Document (No. 11) indicating that 1,1,1,2-tetrafluoroethane has a significant global warming potential.

HFC-227ea (1,1,1,2,3,3,3-heptafluoropropane) has also been proposed as low ozone depletion potential substitute for CFCs in MDIs. However, this compound also has a significant global warming potential.

U.S. Patent 6,111,150 describes chlorofluor- and fluoro-substituted

propenes as being "useful as an intermediate of medicines..." (col.2, l. 4).
However, there is no disclosure or suggestion of MDIs or any other propellant
materials used in MDIs. U.S. Patent Nos. 3,723,318 and 3,884,826 each
describes the use of trifluoropropene in connection with aerosol propellants
and refrigerants, but there is no disclosure or suggestion in these patents
relating to MDIs, nor is there any disclosure or suggestion regarding the use
of tetrafluoropropene as an aerosol or in connection with MDIs.

Bromine-containing halocarbon additives have been suggested for use
in connection with efforts to reduce the flammability of numerous materials,
including aerosol propellants, in U.S. Patent 5,900,185 – Tapscott. The
additives described in this patent are said to be characterized by high
efficiency and short atmospheric lifetimes, that is, low ozone depletion
potential (ODP) and a low global warming potential (GWP). The patent
discloses the use of such compounds in amounts of from about 0.1 to about
20 percent by weight.

While the brominated olefins described in Tapscott may have some
level of effectiveness in connection with use as anti-flammability agents in
connection with certain materials, there is no disclosure of the use of such
materials as an aerosol or propellant. Furthermore, it is believed that such
compounds may also have certain disadvantages. For example, applicants
have come to recognize that many of the compounds identified in Tapscott
will have a relatively low efficiency as a blowing agent due to the relatively
high molecular weight of such compounds. In addition, it is believed that
many of the compounds disclosed in Tapscott will encounter problems when
used as a blowing agent due to the relatively high boiling point of such
compounds. Moreover, it is understood by applicants that many compounds
which have a high level of no means substitution may possess undesirable
toxicity properties and/or other undesirable properties, such as potentially

environmentally undesirable bioaccumulation.

Thus, applicants have recognized a need for compounds, compositions, systems, devices and methods for medicament delivery that at once provide relatively low ozone depletion potential and relatively low global warming potential. Moreover, applicants have recognized that any composition, including any propellant contained therein, must also possess properties which ensure the efficacy of the medicament, such as medicament stability, low- or no- toxicity, and compatibility with the other components of the medicament delivery system.

SUMMARY

Applicants have found that many of the shortcomings of the prior compositions can be overcome and/or that many of the above-noted needs can be satisfied by medicinal compositions, and by devices, methods and systems which use same, comprising a propellant and at least one medicinally active compound, said propellant comprising at least one fluoroolefin, preferably hydrofluoroolefin, which is a medicinally acceptable carrier for said medicinally active compound and having at least two but less than seven, preferably less than six, and even more preferably less than five carbon atoms. As used herein, the term medicinally acceptable carrier refers to materials which are at least not substantially harmful to the intended recipient of the medicinally active compound. As used herein, the term fluoroolefin means an organic compound comprising at least carbon and fluorine and at least one carbon-carbon double bond, with other substituents being optionally present. As used herein, the term hydrofluoroolefin means an organic compound comprising carbon, hydrogen and fluorine and at least one carbon-carbon double bond, with other substituents being optionally present, although in certain preferred embodiments chlorine is not present.

As used herein, the terms "medicinal," "medicament," and the like are used in their ordinary broad sense to refer to any and all materials or substances which have, or at least are believed to have, the property of healing, treating or relieving disease, injury or other ailment, and/or the pain or other symptoms of same, and/or of diagnosing same, such would include for example drugs and biologically active substances. Thus, the term "medicinally active compound," is used herein to refer to a compound or combinations of compounds which are effective, or at least are believed to be effective, in a medicinal sense.

In certain preferred embodiments, the fluoroolefin of the present invention comprises, preferably comprises in major proportion, and even more preferably consists essentially of, one or more compounds of Formula I as follows:



where X is a C₂ or a C₃ unsaturated, substituted or unsubstituted, alkyl radical, each R is independently F, Br, I, Cl or H, and z is 1 to 3, but where it is generally not preferred for R to be Cl. In preferred embodiments, the Formula I compound is tetrafluoropropene, more preferably 1,1,1,3-tetrafluoropropene (HFO-1234ze) and/or 1,1,1,2-tetrafluoropropene (HFO-1234yf). The term HFO-1234ze is used herein generically to refer to 1,1,1,3-tetrafluoropropene, independent of whether it is the cis- or trans- form. The terms "cisHFO-1234ze" and "transHFO-1234ze" are used herein to describe the cis- and trans- forms of 1,1,1,3-tetrafluoropropene respectively. The term "HFO-1234ze" therefore includes within its scope cisHFO-1234ze, transHFO-1234ze, and all combinations and mixtures of these. In certain preferred embodiments, the composition comprises, the trans- isomer of 1,1,1,3-tetrafluoropropene.

In certain of the preferred composition of the present invention the

propellant does not have a substantial negative effect on atmospheric chemistry. More specifically, in the preferred compositions the propellant of the present invention has a very low or negligible contribution to ozone depletion in comparison to some of the heretofore commonly used halogenated species. The preferred compositions thus have the advantage of not contributing substantially to ozone depletion. The preferred compositions also do not contribute substantially to global warming compared to many of the hydrofluoroalkanes which have been commonly used.

BRIEF DESCRIPTION OF THE DRAWING

The invention will now be described with reference to the accompanying drawings in which:

FIG. 1 represents a cross-section through an inhaler in accordance with one embodiment of the invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

I. THE COMPOSITIONS

It is contemplated that the compositions of the present invention can be used in a wide variety of forms, and all such forms are within the broad scope of the present invention. In general, it is preferred that present compositions are in a form suitable for delivery to the particular site on or in the human or other mammal needing treatment, or to a site which is the preferred location for introduction into the body, even if the treatment or diagnosis is required at other areas. For example, the preferred compositions of the present invention are generally well adapted for delivery through the mouth, nose, ears and/or other mucosal membranes, or by transdermal application. It is possible, therefore, that the compositions of the present invention may be delivered to the lungs for treatment of a malady occurring in

the lungs or as a mechanism for introducing the medicament into the system (e.g., bloodstream) of the user in order to treat a malady elsewhere.

5 The amount of medicinal compound(s) present relative to the amount of propellant can vary widely in accordance with the present invention, and all such proportions are believed to be adaptable for use within the scope
hereof, provided of course that the total amount of medicinally active agent is therapeutically effective, or at least believed to be therapeutically effective by the doctor or other professional prescribing the medicament. In certain
10 preferred embodiments, however, the present compositions comprise at least about 50% by weight, and even more preferably from about 60% to about 99%, or more, by weight, of propellant based upon the total weight of the composition. Furthermore, it is preferred in certain embodiments that the composition comprise from about 0.01% to about 0.5% by weight of medicinally active compounds, although it is appreciated that lesser or
15 greater amounts may be used depending upon the particular medicament, the prescribed dosage and other numerous factors.

A. THE MEDICINALLY ACTIVE COMPOUND

20 Although it is contemplated that the medicinally active compounds of the invention may be present in a wide variety of forms, it is preferred in many embodiments that the medicinally active agent or compound is part of a solution, dispersion, suspension, emulsion, or the like. As explained in more detail hereinafter, the medicinal compounds of the present invention are frequently present as particles having various sizes and other physical
25 properties, although fine particulate form is generally preferred for the formation of stable, substantially uniform dispersions, suspensions, etc. of the medicinal compounds. It will be appreciated, in addition, that in certain embodiments two or more medicinally active substances are included in the

present compositions, and in yet further embodiments, at least one of said medicinally active substances is present in a dissolved form in a liquid phase and/or at least one other of said medicinally active substances is present in suspended form in a fluid, preferably a liquid phase.

5 In certain embodiments, the medicinal compounds of the present invention are preferably used in micronized or micro-particulate form. Such forms preferably exhibit a relatively hollow and porous morphology, and also preferably have a mass average aerodynamic diameter (MAAD) of not greater than about 10 microns, but preferably less than about 5 microns.
10 Medicinal compounds of this type are preferred for use in many MDI applications. The use of such micro-particulate medicinal compounds in combination with the propellant components of the present invention is believed to produce especially stable and effective compositions.

 One problem associated with many medicinal compositions,
15 particularly those adapted for use in connection with MDIs, is the tendency of the individual particles of the medicinally active compound to agglomerate. As described in detail hereinafter, certain embodiments of the present invention include one or more adjuvants to stabilize the composition against this and other types of undesirable change. In addition, certain embodiments
20 hereof enhance the stability of the composition by using and/or altering particle morphology to reduce attractive forces between the dispersed components and to reduce density differences, thereby retarding degradation of the suspensions, dispersions, etc. by flocculation, sedimentation or creaming. Such enhancements in certain embodiments may facilitate uniform
25 dose delivery by MDIs, and allow for more concentrated dispersions. In such preferred embodiments, at least a substantial proportion of the medicinally active particles, and preferably a major proportion, have hollow and/or porous perforated microstructures that substantially reduce attractive forces, such as

van der Waals forces. Without being bound by or to any particular theory of operation, the use of perforated (or porous) microstructures or microparticulates that are permeated or filled by the surrounding fluid or suspension medium (which generally includes the propellant of the present invention), is believed to significantly reduce disruptive attractive forces between the particles. Moreover, the components of the dispersions may be selected to minimize differences in polarizabilities (i.e. reduced Hamaker constant differentials) and further stabilize the preparation. In certain preferred embodiments, the dispersions of the present invention are substantially homogeneous with only minor differences in density between particles, preferably as defined by the perforated microparticulates and the suspension medium. Such perforated microparticles are disclosed in U.S. Patent No. 6,638,495, which is incorporated herein by reference.

With respect to the particular type of medicinal compound or agent, those skilled in the art will appreciate that any therapeutic or diagnostic agent may be incorporated into the present composition, preferably the dispersions of the present invention. For example, the medicinal compound may be selected from the group consisting of antiallergics, bronchodilators, bronchoconstrictors, pulmonary lung surfactants, analgesics, antibiotics, leukotriene inhibitors or antagonists, anticholinergics, mast cell inhibitors, antihistamines, antiinflammatories, antineoplastics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, corticosteroids, short acting beta-agonists, long-acting beta-agonists, genetic material, viral vectors, antisense agents, proteins, peptides, anti-asthma medication and combinations of any two or more thereof. Particularly preferred medicinal agents for use in accordance with the invention include anti-allergics, peptides and proteins, bronchodilators and anti-inflammatory steroids for use in the treatment of respiratory disorders, such as asthma and

chronic obstructive pulmonary disorder (COPD), by inhalation therapy.

Exemplary medicaments or bioactive agents may be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl, or morphine; anginal preparations, e.g. diltiazem; mast cell inhibitors, e.g. cromolyn sodium; antiinfectives, e.g. cephalosporins, macrolides, quinolones, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. fluticasone propionate, beclomethasone dipropionate, flunisolide, budesonide, mometasone furoate, tripedane, cortisone, prednisone, prednisilone, dexamethasone, betamethasone, or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, epinephrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, salbutamol (albuterol), salmeterol xinafoate, terbutaline; diuretics, e.g. amiloride; anticholinergics, e.g. ipratropium bromide, tiotropium, atropine, or oxitropium; lung surfactants e.g. Surfaxin, Exosurf, Survanta; xanthines, e.g. aminophylline, theophylline, caffeine; therapeutic proteins and peptides, e.g. DNase, insulin, glucagon, LHRH, nafarelin, goserelin, leuprolide, interferon, rhu IL-1 receptor, macrophage activation factors such as lymphokines and muramyl dipeptides, opioid peptides and neuropeptides such as enkaphalins, endorphins, renin inhibitors, cholecystokinins, DNase, growth hormones, leukotriene inhibitors and the like. In addition, bioactive agents that comprise an RNA or DNA sequence, particularly those useful for gene therapy, genetic vaccination, genetic tolerization, or antisense applications, may be incorporated in the disclosed dispersions as described herein. Representative DNA plasmids include pCMV.beta. (available from Genzyme Corp, Framington, Mass.) and pCMV-.beta.-gal (a CMV promotor linked to the E. coli Lac-Z gene, which codes for the enzyme .beta.-galactosidase), and any combination of two or more of these. In many prefer embodiments, at least two different medicinally

active compounds in combination, are included in the composition.

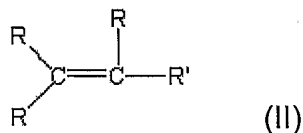
B. THE PROPELLANT

5 In preferred embodiments, one of the primary functions of the propellant of the present invention is to provide a source of kinetic energy to aid in delivery of the medicinal compounds to the desired site. MDIs, for example, generally depend upon the propulsive force of the propellant system used in its manufacture. The propellant system preferably not only provides the desired vapor pressure to, but it also at least does not degrade, and
10 preferably enhances the stability of the suspension. It is contemplated that the present propellant systems may be used to deliver solubilized or suspended agents and/or, in preferred embodiments, to deliver selected medicinal compound in fine particulate form to provide a dispersion. Thus, in certain preferred embodiments of the present invention the propellant also
15 serves to carry and/or solubilize and/or suspend one or more of the medicinal compounds of the present invention.

With respect to the preferred compound(s) for use in the present invention, the propellant comprises, preferably consists essentially of, and in some preferred embodiments consists of, at least one fluoroolefin, preferably
20 a hydrofluoroolefin containing from 3 to 4 carbon atoms, preferably three carbon atoms. The hydrofluoroolefin compounds of the present invention are sometimes referred to herein for the purpose of convenience as "HFOs" if they contain at least one hydrogen, at least one fluorine and no chlorine. Although it is contemplated that certain HFOs of the present invention may
25 contain two carbon -- carbon double bonds, such compounds at the present time are not considered to be preferred.

As mentioned above, the present compositions preferably comprise one or more compounds in accordance with Formula I. In preferred

embodiments, the compositions include compounds of Formula II below:



5 where each R is independently F, Br, I, Cl or H, but preferably not Cl

R' is $(\text{CR}_2)_n\text{Y}$,

Y is CRF_2

and n is 0 or 1.

10 In highly preferred embodiments, Y is CF_3 , n is 0 and at least one of the remaining Rs is F.

Applicants believe that, in general, the compounds of the above identified Formulas I and II are generally effective as propellants in medicinal compounds as described herein, particularly in connection with aerosol compositions. However, applicants have surprisingly and unexpectedly found that certain forms of the compounds having a structure in accordance with the formulas described above exhibit a highly desirable low level of toxicity compared to other of such compounds. As can be readily appreciated, this discovery is of potentially enormous and critical importance to the formulation of medicinal compositions, since pharmacologically and medicinally acceptable excipients should generally not have a substantially level of toxicity. More particularly, applicants believe that relatively low toxicity levels are associated with compounds of Formula II, preferably wherein Y is CF_3 , wherein at least one R on the unsaturated terminal carbon is H, and at least one of the remaining Rs is F. Applicants believe also that all structural, geometric and stereoisomers of such compounds are effective and of beneficially low toxicity.

In highly preferred embodiments, especially embodiments comprising

the low toxicity compounds described above, n is zero. In certain highly preferred embodiments the compositions of the present invention comprise, and in certain embodiments consists essentially of, one or more tetrafluoropropenes. As mentioned above, the term "HFO-1234" is used
5 herein to refer to all tetrafluoropropenes. Among the tetrafluoropropenes, HFO-1234yf is particularly preferred in many embodiments. HFO-1234ze, in the cis- and/or trans- forms are may be preferred also in certain embodiemtns. As also mentioned above, the term HFO-1234ze is used herein generically to refer to 1,1,1,3-tetrafluoropropene, independent of
10 whether it is the cis- or trans- form, and the terms "cisHFO-1234ze" and "transHFO-1234ze" are used herein to describe the cis- and trans- forms of 1,1,1,3-tetrafluoropropene respectively.

In certain preferred embodiments, the HFO-1234ze comprises a combination of transHFO-1234ze and cisHFO-1234ze, and more preferably from about
15 90% to about 99% trans on the basis of total HFO-1234ze, with the cis isomer comprising from about 1% to about 10% of the same basis. The propellant compositions of the present invention therefore comprise in certain embodiments a combination of cisHFO-1234ze and transHFO1234ze, preferably in a cis:trans weight ratio of from about 1:99 to about 10:99, more
20 preferably from about 1:99 to about 5:95, and even more preferably from about 1:99 to about 3:97.

Although the properties of cisHFO-1234ze and transHFO-1234ze differ in at least some respects, it is contemplated that each of these compounds is
25 adaptable for use, either alone or together with other compounds including its stereoisomer, in connection with each of the applications, methods, systems and devices described herein. For example, while transHFO-1234ze may be preferred for use in certain systems because of its relatively low boiling point

(-19° C), it is nevertheless contemplated that cisHFO-1234ze, with a boiling point of +9° C, also has utility in connection with the present invention.

Accordingly, it is to be understood that the terms "HFO-1234ze" and 1,1,1,3-tetrafluoropropene refer to both stereo isomers, and the use of this term is intended to indicate that each of the cis-and trans- forms applies and/or is useful for the stated purpose unless otherwise indicated.

HFO-1234 compounds are known materials and are listed in Chemical Abstracts databases. The production of fluoropropenes such as $\text{CF}_3\text{CH}=\text{CH}_2$ by catalytic vapor phase fluorination of various saturated and unsaturated halogen-containing C_3 compounds is described in U.S. Patent Nos. 2,889,379; 4,798,818 and 4,465,786, each of which is incorporated herein by reference. EP 974,571, also incorporated herein by reference, discloses the preparation of 1,1,1,3-tetrafluoropropene by contacting 1,1,1,3,3-pentafluoropropane (HFC-245fa) in the vapor phase with a chromium-based catalyst at elevated temperature, or in the liquid phase with an alcoholic solution of KOH, NaOH, $\text{Ca}(\text{OH})_2$ or $\text{Mg}(\text{OH})_2$. In addition, methods for producing compounds in accordance with the present invention are described generally in connection with pending United States Patent Application entitled "Process for Producing Fluoropropenes" bearing attorney docket number (H0003789 (26267)), which is also incorporated herein by reference.

The present compositions, particularly those comprising HFO-1234 (including HFO-1234yf and HFO-1234ze), are believed to possess properties that are advantageous for a number of important reasons. For example, applicants believe, based at least in part on mathematical modeling, that the fluoroolefins of the present invention will not have a substantial negative affect on atmospheric chemistry, being negligible contributors to ozone depletion in comparison to some other halogenated species. The preferred compositions of the present invention thus have the advantage of not

contributing substantially to ozone depletion. The preferred compositions also do not contribute substantially to global warming compared to many of the halogenated molecules presently in use.

5 In certain preferred forms, compositions of the present invention have a Global Warming Potential (GWP) of not greater than about 1000, more preferably not greater than about 500, and even more preferably not greater than about 150. In certain embodiments, the GWP of the present compositions is not greater than about 100 and even more preferably not greater than about 75. As used herein, "GWP" is measured relative to that of
10 carbon dioxide and over a 100-year time horizon, as defined in "The Scientific Assessment of Ozone Depletion, 2002, a report of the World Meteorological Association's Global Ozone Research and Monitoring Project," which is incorporated herein by reference.

15 In certain preferred forms, the present compositions also preferably have an Ozone Depletion Potential (ODP) of not greater than 0.05, more preferably not greater than 0.02 and even more preferably about zero. As used herein, "ODP" is as defined in "The Scientific Assessment of Ozone Depletion, 2002, A report of the World Meteorological Association's Global Ozone Research and Monitoring Project," which is incorporated herein by
20 reference.

The amount of the fluorolefins, particularly the Formula I compounds, and even more particularly HFO-1234, contained in the propellant component of present compositions can vary widely, depending upon numerous factors relevant to each particular use of the composition, and propellants comprising
25 more than trace amounts and up to and including 100% of the compound are within the broad scope of the present invention. Moreover, the compositions of the present invention can be azeotropic, azeotrope-like or non-azeotropic. In preferred embodiments, the present compositions comprise HFO-1234,

preferably HFO-1234ze, in amounts from about 5% by weight to about 99% by weight, and even more preferably from about 5% to about 95%.

Many compounds that are not fluorolefins, and particularly not in accordance with Formula (I), may be combined with the such compound(s) of the present invention to form the propellant, and the presence of all such compounds is within the broad scope of the invention. In certain preferred embodiments, the present compositions include, in addition to the fluoroolefin compound(s), preferably of Formula (I) and even more preferably HFO-1234ze, one or more other hydrofluoroalkenes, as well as hydrofluoroalkanes, fluorocarbons, perfluorocarbons, fluorocarbon/hydrocarbon diblocks, hydrocarbons, alcohols and ethers.

In certain preferred embodiments, the propellant of the present invention comprises one or more compound(s) of Formula (I), preferably in an amount of about 1 percent by weight to about 99 percent by weight based on the weight of the total propellant, and one or more hydrofluorocarbons (HFCs), such as, for example hydrofluoroethanes (eg., pentafluoroethane (HFC-125), 1,1,2,2-tetrafluoroethane (HFC-134) and 1,1,1,2-tetrafluoroethane (HFC-134a)); and hydrofluoropropanes (eg., 1,1,1,2,3,3,3-heptafluoropropane (HFC-227ea)). The relative amount of the compound(s) of the present invention, particularly the compounds of formula (I), and the above noted additional propellant components, as well as any additional components (described hereinafter) which may be included in present compositions, can vary widely within the broad scope of the present invention according to the particular application for the composition.

C. OTHER COMPONENTS

As is known to those skilled in the art, many modifiers, additives and adjuvants, as well as other propellants, may be included in medicinal

compositions, and all such components are believed to be readily adaptable for use with the compositions of the present invention. For example, medicinal preparations are frequently prepared in the form of powdered preparations, sometimes referred to as micronized powders. However, such
5 powders frequently tend to aggregate due to hydrophobic or electrostatic interactions between the fine particles. Such cohesion may be at least partially overcome by incorporating into the present compositions one or more anti-aggregating agents. One type of anti-aggregating agent believed to be adaptable for use with the present compositions are larger carrier
10 particles, for example, lactose which is thought to inhibit aggregation.

In addition, the present compositions may include one or more other special purpose adjuvants, such as a cosolvent(s) and/or surfactant(s) that enhance the composition. Many embodiments of the present compositions may not need co-solvent(s) and/or surfactant(s), depending upon the
15 interaction between the medically active compound and the propellant. In certain embodiments a cosolvent may be necessary or desirable to help dissolve or suspend the medicinally active compound in the propellant. One important characteristic of the cosolvent which is preferred or required for many embodiments is that the cosolvent be pharmacologically tolerable. In
20 certain of such embodiments, therefore, the co-solvent(s) are selected from the group consisting of pharmacologically tolerable hydrocarbons, pharmacologically tolerable alcohols, pharmacologically tolerable esters, pharmacologically tolerable ethers, water and combinations of any two or more thereof. From among such hydrocarbons, it is preferred in certain
25 embodiments that the compositions comprise one or more of propane, butane, isobutene, n-pentane, isopentane, neopentane. From among such alcohols, it is preferred in certain embodiments that the compositions comprise one or more of ethyl alcohol, isopropyl alcohol, propylene glycol,

and glycerol. From among such esters, isopropyl myristate may be mentioned, and from among such ethers, dimethyl ether may be mentioned. Any two or more of any of these may be used in combination. Of course, it is generally preferred in most embodiments that the cosolvent or combinations of cosolvents be miscible, and even more preferably fully miscible, with the propellant.

Although the amount of cosolvent used in the present compositions may vary widely, depending upon numerous factors including the particular type of medicament and propellant being used, in many embodiments it is preferred that the composition have a propellant:cosolvent weight ratio of from about 50:50 to about 99:1.

For certain embodiments in which the present medicinal composition is in the form of a suspension, and particularly an aerosol suspension, the composition includes also surfactant(s), in addition to, but preferably rather than, a cosolvent. While not intending to be bound by or to any particular theory of operation, it is believed in such embodiments that the surfactant would help to prevent agglomeration of the particles, the adhesion to of the particles to the walls of the container, and provide for lubrication of the dispensing valve. In such embodiments, it is generally preferred that the surfactant, when present, is in the composition in the amount of not greater than about 5% by weight of the composition, although those skilled in the art will appreciate that greater amounts may be included depending upon the particulars of each composition and its intended application. While it is contemplated that certain surfactants or combinations of surfactants may not be fully soluble in the present medicinal compositions, or in the propellant in particular, it is generally preferred to use surfactants which are soluble in the propellant, and preferably substantially fully soluble in the propellant under conditions of storage and/or use. Although the amount of surfactant used in

the present compositions may vary widely, depending upon numerous factors including the particular type of medicament and propellant being used, in many embodiments is preferred that the compositions have a surfactant: medicament weight ratio of from about 1:100 to about 10:1.

5 Exemplary surfactants which may be used, alone or combination with one another in accordance with the present invention include C5-C20 fatty alcohols, C5- C20 fatty acids, C5- C20 fatty acid esters, lecithin, glycerides, propyleneglycol esters, polyoxyethanes, polysorbates, sorbitan esters and
10 include oleic acid, sorbitan mono-, di- or trioleate, and combinations of two or more thereof.

Many embodiments of the present invention, particularly those in which the composition is in the form of a suspension, emulsion or dispersion, and particularly an aerosol thereof, preferably include a stabilizing agent.

15 Stabilizing agents for such suspensions, emulsions and dispersions are well known, and it is contemplated that all such stabilizing agents are adaptable for use in accordance with the present invention. Exemplary stabilizing agents include, either alone or in combination, hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, ascorbic acid, citric acid, benzalkonium
20 chloride, ethylene diamine tetraacetic, and pharmacologically tolerable salts thereof. Although it is contemplated that the stabilizing agents of the present mentioned it may be included in the compositions in widely varying amounts, it is generally preferred in many embodiments that the stabilizing agent is present in an amount of from about 40 to about 100 ppm by weight of the
25 composition.

As mentioned above, many medicinal compositions provide medicinal compounds in micro-particulate form, which preferably exhibits a relatively hollow and porous morphology. Such forms are within the scope of the

present invention and are commonly used in MDIs. The use of such micro-particulate medicinal compounds in combination with the propellant components in accordance with the present invention is believed to produce especially stable compositions.

5 The compositions of the present invention, particularly compositions comprising or consisting essentially of HFO-1234, are capable of providing nonflammable, liquefied gas propellant and aerosols that do not contribute substantially to global warming or ozone depletion. The present compositions therefore provide in certain preferred embodiments substantially
10 nonflammable, liquefied gas propellants having very low Global Warming and Ozone Depletion Potentials.

 Although the present compositions may be prepared in many forms, in certain embodiments the composition is in the form of an aerosol product for medical use. The aerosol in preferred embodiments contains at least one
15 propellant of the present invention along with one or more active medicinal ingredients, and optionally inert ingredients, stabilizers, surfactant, other propellants and/or solvents. The propellant of the present invention preferably at least contributes to, and even more preferably provides substantially all of the force that expels the product in aerosolized form. In
20 accordance with preferred embodiments of the present invention, the propellant is a liquefied gas under conditions of storage and use.

II. DEVICES AND METHODS

 One aspect of the present invention provides a device for the delivery,
25 preferably by inhalation, of a medicament composition of the present invention. In certain preferred embodiments, the device comprises a container, preferably an aerosol canister, containing a pressurized medicament or formulation of the present invention and preferably having a

metered dose dispensing valve operable between non-dispensing and dispensing positions. The present devices preferably also comprise an actuator, which in preferred embodiments comprises a housing adapted to receive the aerosol container and to define a chamber in fluid communication with a patient port for introducing the medicament into the oral and/or nasal cavity of the patient, preferably in the form of a mouthpiece and/or nasal adapter. The actuator also preferably includes a nozzle block adapted to receive the valve stem of the dispensing valve, the nozzle block preferably comprising a passage in fluid communication with the valve stem and terminating in an orifice for directing medicament from the valve stem into the chamber.

By way of example but not by way of limitation, in certain embodiments the invention device is constructed such that airflow due to patient inhalation is prevented or reduced in the vicinity of the orifice at all times or only during dispensing of the medicament from the valve. Either of such arrangements has the effect of substantially reducing the velocity of the emitted spray compared to an inhaler which allows free flow of air in the vicinity of the nozzle block during dispensing of the medicament.

In certain embodiments, the actuator is constructed such that the distance from the nozzle to the mouthpiece is from approximately 1 to 15 cm, preferably 4 to 6 cm, with a chamber/mouthpiece diameter from 1 to 4 cm, 0.5 to 1 cm in the case of a nasal adapter.

In certain preferred but non-limiting embodiments, the actuator possess air inlets which enable the patient to inhale through the patient port, preferably without encountering significant resistance since the patient may have breathing difficulties when taking the medication, for example, during an asthma attack. However, the air inlets, for example in the mouthpiece, preferably do not concentrate the airflow into an area that is too narrow, as

5 this will give a high velocity of incoming air which will deflect the spray onto
the wall of the mouthpiece opposite the air inlets. In certain preferred
embodiments the air inlets are positioned downstream of the nozzle, in the
region of the turbulent zone and/or downstream of the turbulent zone. The
positioning and direction of the air inlets may also affect the deposition of
medicament within the chamber and mouthpiece. In one arrangement air
inlets comprise a series of holes and optionally may be interdispersed with
fluid deflection structures on the wall of the chamber, to direct air into the
turbulent zone to mix air with the aerosol stream. Further, the mouthpiece
10 may be constructed of porous material to allow a multiplicity of finely divided
air vents to provide air flow over a larger surface area.

In certain embodiments the actuator possesses air inlets upstream of
or in the vicinity of the nozzle but the air inlets are blocked when the valve is
fired to release the aerosol spray. The air inlets are opened after the spray
15 has been released by which time the velocity of the stream will have been
reduced and the turbulent zone formed. Upon inhalation, an airflow is
established from the air inlets to the mouthpiece which entrains the residual
aerosol spray. The actuator may include additional air inlets downstream of
the nozzle, as described above with respect to the first embodiment. These
20 downstream air inlets do not need to close during release of the aerosol
spray.

In certain embodiments, a porous membrane is present to introduce air
into or downstream of the turbulent zone. One advantage of the use of such a
membrane is that the air is introduced more uniformly and diffusely around
25 the circumference of the spray, thereby acting as a buffer between the
turbulent flow and the wall. The effect is to reduce drug deposition in the
device. The membrane may optionally be protected from dirt or contact by the
user's lips by an additional part of the mouthpiece. When present, it is

preferred that the porous membrane material (50) must not significantly impede the patient's ability to inhale through the device. A suitable material is Whatmann No. 4 filter paper; but other materials may be used, such as those used in cylindrical air filters or membrane filters, or such as those formed by sintering polymers. A preferred porous membrane material is in the form of a cylinder made by fusing together small pellets of polypropylene.

For certain medicaments, it is preferred to configure the device so as to reduce contact between the medicament and parts of the patient's body that it is not intended to contact. For example, residues of the medicament deposited on internal surfaces of actuators may be fingered and transferred to other body parts. In such cases, the device may be configured to include one or more fluid flow deflectors to allow the spray to pass through, whilst limiting access by the patient to internal surfaces of the actuator. Of course, the device may be configured for intranasal delivery. This is normally quite undesirable, since the medicaments were designed for delivery to the respiratory system and may not have an appropriate effect when deposited in the oropharynx and allowed to enter the digestive tract. In an effort to overcome this problem, certain embodiments of the present device include the provision of a holding volume, commonly called a spacer, in which the medicament is fired. The spacer preferably allows the velocity of the medicament to be reduced and may also allow some propellant evaporation to occur. Spacers can improve the performance of a metered dose inhaler by reducing oropharyngeal deposition.

One preferred embodiment is disclosed in connection with FIG. 1. This device comprises an aerosol canister (2) equipped with a metered dose dispensing valve (4) having a valve stem (6). The actuator, generally shown at (8), comprises a housing (10) which receives the aerosol container (2), a chamber (12) and a mouthpiece (14). A nozzle block (16) receives the valve

stem (6) and has a passage (not shown) terminating in an orifice (18) which directs spray from the aerosol valve into the chamber. The housing comprises solid walls (20) in the vicinity of the nozzle block so that there can be no air flow through the device in the vicinity of the orifice. Air inlet passages (22) are positioned towards the end of the chamber (12) and are directed towards the mouthpiece (14).

In operation, the aerosol valve is fired and a metered dose of aerosol formulation exits the orifice (18) into the chamber (12). Preferably there is no air flow in the vicinity of the orifice (18), in which case the spray is rapidly decelerated and a turbulent zone is formed within the chamber (12). As the patient breathes through the mouthpiece (14) air passes through the inlets (22) towards the mouthpiece (14) forming a sheath of air around the spray of aerosol formulation. In such preferred embodiments as disclosed in Fig. 1, the inhaler provides substantially reduced deposition in the oropharynx of the patient compared with a standard press-and-breathe inhaler, which is also within the scope of the present devices.

In other embodiments the mouthpiece may have a bulbed configuration to provide an increase in cross-sectional area of the mouthpiece downstream of the turbulent zone followed by a decrease in cross-sectional area at the extreme downstream end of the mouthpiece. In such embodiments, the bulbed configuration acts in a similar manner to a conventional spacer.

Certain aspects of the present invention thus provide inhalers, and preferably metered dose inhalers (MDIs) for the treatment of asthma and other chronic obstructive pulmonary diseases and for delivery of medicaments to accessible mucous membranes or intranasally. The present invention thus includes methods for treating ailments, diseases and similar health related problems of an organism (such as a human or animal)

comprising applying a composition of the present invention containing a medicament or other therapeutic component to the organism in need of treatment. In certain preferred embodiments, the step of applying the present composition comprises providing an MDI containing the composition of the present invention (for example, introducing the composition into the MDI) and then discharging the present composition from the MDI.

Although the present invention has been described and exemplified above in connection with certain preferred embodiments, it is not necessarily limited to these examples and embodiments. The scope of the invention is defined in accordance with the claims presented hereinbelow and/or presented hereinafter.

WHAT IS CLAIMED IS:

1. A medicinal composition comprising a propellant and at least one medicinally active compound, said propellant comprising a fluoroolefin which is a medicinally acceptable carrier for said medicinally active compound and having at least two but less than seven carbon atoms.

2. The medicinal composition of claim 1 wherein said fluoroolefin comprises at least one compound of formula Formula I as follows:



where X is a C₂ or a C₃ unsaturated, substituted or unsubstituted, alkyl radical, each R is independently F, Br, I, Cl or H, and z is 1 to 3.

3. The medicinal composition of claim 1 in the form of a medicinal preparation for propellant driven application wherein said at least one medicinally active compound is in the form of a suspension or a solution with said propellant.

4. The medicinal preparation according to claim 3 wherein said medicinally active compound comprises a combination of two or more medicinally active substances solubilized in said propellant.

5. The medicinal preparation according to claim 1 wherein said medically active compound is selected from the group consisting of corticosteroids, anti-inflammatories, anti-allergics, long-acting beta agonists, short-acting beta agonists, anticholinergics, proteins and peptides, anti-infectives, pain management, vaccines, hormones, gene therapy vectors, oligonucleotides, immunoglobulins and anti-IgE monoclonal antibodies.

6. The composition according to claim 1 wherein said medically active compound comprises one or more medically active ingredients selected from the group consisting of Salbutamol (albuterol), chiral albuterol, budesonide, epinephrine, formoterol, salmeterol xinafoate, beclomethasone dipropionate, budesonide, cromoglycinic acid, fenoterol, flunisolide, fluticasone propionate, mometasone furoate, insulin, nedocromil,

orciprenaline, oxitropium bromide, repreterol, disodium cromoglycate, pirbuterol, isoprenaline, adrenaline, rimiterol, terbutalin, tiotropium, ipratropium bromide, epinephrine, omalizumab, the esters, salts, solvates or combinations thereof.

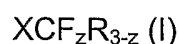
7. The composition of claim 1 further comprising at least one surfactant selected from the group consisting of C5-C20 fatty alcohols, C5- C20 fatty acids, C5- C20 fatty acid esters, lecithin, glycerides, propyleneglycol esters, polyoxyethanes, polysorbates, sorbitan esters and carbohydrates, or combinations thereof.

8. The medicinal composition according to claim 1 wherein the propellant comprises HFO-1234.

9. The medicinal composition of claim 1 wherein said propellant has a Global Warming Potential (GWP) of not greater than about 1000 and/or or an Ozone Depleting Potential (ODP) of not greater than about 0.05.

10. An inhaler for medicinal composition comprising a canister containing a medicament formulation, a chamber capable of fluid communication with said canister, and a patient port for introducing said medicinal composition from said chamber to the oral or nasal cavity of the intended user, said medicinal composition comprising propellant and at least one medicinally active compound, said propellant comprising a fluoroolefin having at least two but less than seven carbon atoms.

11. The inhaler of claim 10 wherein said fluoroolefin comprises at least one compound of formula Formula I:



where X is a C2 or a C3 unsaturated, substituted or unsubstituted, alkyl radical, each R is independently F, Br, I, Cl or H, and z is 1 to 3.

12. A method of treating a mammal comprising administering to the mammal a medicinal formulation comprising at least one propellant and at least one medicinally active compound, said propellant comprising a fluoroolefin having at least two but less than seven carbon atoms.

13. A canister of the type capable of containing the vapor pressure of a propellant contained therein and further containing a medicinal composition suitable for administration to a mammal, said medicinal composition comprising said propellant and at least one medicinally active compound, said propellant being a medicinally

acceptable carrier for said medicinally active compound and comprising a fluoroolefin having at least two but less than seven carbon atoms.

14. A method of making an aerosol formulation suitable for delivery to the lung of a mammal by inhalation comprising the steps of:

(a) providing at least one propellant, said propellant comprising a medicinally acceptable carrier and comprising at least one fluoroolefin having at least two but less than seven carbon atoms;

(b) providing at least one medicinally active compound; and

(c) introducing said medicinally active compound to said propellant such that it is carried in said propellant.

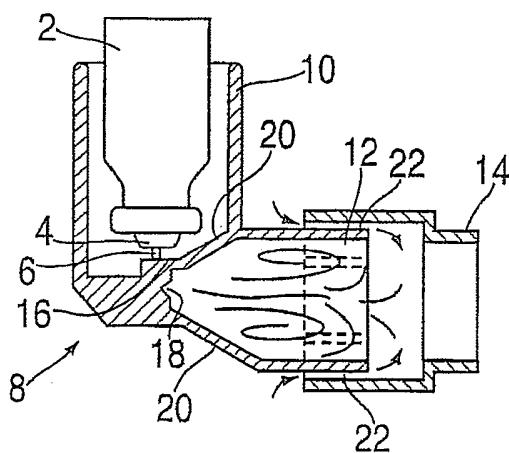


FIG. 1