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(54) Title: NOVEL AEROSOL FORMULATION CONTAINING A POLAR FLUORINATED MOLECULE

(57) Abstract: The present invention relates to a stable pharmaceutical aerosol formulation intended for inhalation. The formulation contains an active substance, an aerosol propellant, a polar flurorinated molecule and an excipient. The preferred propellant is HFA 134a or HFA 227 or a mixture thereof.

NOVEL AEROSOL FORMULATION CONTAINING A POLAR FLUORINATED MOLECULE

The present invention relates to a pharmaceutical aerosol formulation for the administration of a pharmaceutically active substance by inhalation.

Pressurised metered dose inhalers (pMDI's) are known in the art. Long standing problems with pMDI's containing suspension formulations include creaming of the suspension, coarse drug suspension, drug flocculation and adhesion to dispensing device.

It has now surprisingly been found that these problems can be overcome with a novel pharmaceutical formulation containing a polar fluorinated molecule in conjunction with a suitable excipient. The formulations of the invention give rise to improved aerosol drug suspension characteristics, i.e. increase of phase separation times (creaming or sedimentation), production of a finer suspension, reduction of particles adhesion to the can walls and inhibition of particle flocculation.

In a first aspect the invention therefore provides a pharmaceutical formulation comprising a drug, an aerosol propellant, a polar fluorinated molecule and an excipient soluble in the polar fluorinated molecule.

Suitable drugs which can be used in the formulation of the invention include all drugs that can be administered via the inhalation route, for example steroids, peptides, oligonucleotides, small organic moecules etc., in particular those administered via a pMDI. Such drugs, which are not limited to those for treating respiratory diseases, include those suitable for administration by nasal delivery and nebulised delivery.

In preferred embodiements, the invention provides stable dispersion for the pulmonary or nasal delivery of one or more bioactive molecules, for local or systemic administration, comprising a fluorinated molecule and an excipient in a propellant or propellant mixture.

The biocative agent may be selected from any therapeutic or diagnostic agent. For example it may be from the group of antiallergics, bronchodilators, bronchoconsitrictors, pulmonary lung surfactants, analgesics, antibiotics, leukotrine inhibitors or antagonists, anticholinergics, mast cell inhibitors, antihistamines, antiinflammatories, antineoplastics, anaesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

Examples of specific drugs which can be formulated according to the invention include mometasone, ipratropium bromide, tiotropium and salts thereof, salemeterol, fluticasone propionate, beclomethasone dipropionate, reproterol, clenbuterol, rofleponide and salts, nedocromil, sodium cromoglycate, flunisolide, budesonide, formoterol fumarate dihydrate, Symbicort™ (budesonide and formoterol), Viozan™, 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide, terbutaline, terbutaline sulphate, salbutamol base and sulphate, fenoterol, 3-[2-(4-Hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propanesulphonamide, hydrochloride. All of the above compounds can be in free base form or as pharmaceutically acceptable salts as known in the art.

Suitable aerosol propellants include those known in the art such as hydrofluoroalkane propellants including 1,1,1,2-tetrafluorethane (P134a) or 1,1,1,2,3,3,3-heptafluoropropane (P227). Preferred propellants include P134a or P227 or a mixture of P134a and P227, in particular a density-matched mixture of the two.

Suitable polar fluorinated molecules include those commercially available from companies such as Apollo chemicals and Fluorochem. Preferably the polar fluorinated molecules are pharmaceutically acceptable and are non-toxic and non-irritant. Suitable polar fluorinated molecules must be miscible in sufficient quantity in the propellant and to be able to solubilise the excipient. The fluorinated molecules are preferably liquid at room temperature, although solids are also possible. Preferably the polar fluorinated molecules are linear, more preferably with a short carbon chain. Most preferably the polar fluorinated molecules have oxygen functionality, i.e. contain an oxygen containing group including fluorinated alcohols, ethers, carboxylic acid, esters, aldehydes and ketones, amines and their mixtures, and any other fluorinated compounds with oxygen based functional groups.

Suitable examples of polar fluorinated molecules include:
n Butyl Pentafluoropropionate, Ethyl Perfluoro n-Dodecanoate, Fluorinert (FC-75), 2,2,3,3,3 Pentafluoropropyl Methyl Ether, Methyl Perfluorodecanoate, 2H Perfluoro-5,8,11-Trimethyl-3,6,9,12-Tetrafluoropropylether, Fluorad (FC-430), 1,1,2,2, Tetrafluoroethyl 2,2,3,3 Tetrafluoropropylether, 1H,1H,2H,2H Perfluorooctan-1-ol, 4,4,4 Trifluorobutan-1-ol, Fomblin (MF 402), Fomblin (ZDOL), Perfluoroheptanoic Anhydride, Methyl Perfluoro 2,5,8,11-Tetramethyl 3,6,9,12, Tetraoxapentadecanoate, N,N-Diethyl-2,3,3,3 Tetrafluoropropionamide, Ethyl 11H-Perfluoroundecanoate, 1H,1H,2H,3H,3H Perfluoro-1,2-Nonandiol, 1H,1H, Perfluorononan-1-ol,

Aflunox (606, 1406, 2507, 6008, 14013), Allyl Heptafluorobutyrate, Allyl Heptafluoroisopropyl Ether, Allyl 1,1,2,3,3,3-Hexafluoropropyl Ether, Allyl Perfluoroheptanoate, Allyl Perfluorooctanoate, Allyl 1H,1H Perfluorooctyl Ether, Allyl Perfluoropentanoate, 4-Amino-2,2-Difluorobutyric Acid, 2-Amino-3-Fluorobutyric Acid, 4-Amino-2-Fluorobutyric Acid, 2-Amino-4-Iminoheptafluoropent-2-ene, 2-Amino-4,4,4-Trifluorobutyric Acid, 3-Amino-4,4,4-Trifluorobutyric Acid, 1,1-Bis(diethylamino)tetrafluoro-1-Propene, Bis(heptafluoroisopropyl)ketone, Bis(hexafluoroisopropyl)maleate, Bis(hexafluoroisopropyl)itaconate, Bis[2-iodo-3-(perfluorooctyl)propyladipate, Bis(pefluorooctyl)itaconate, Bis(perfluorooctyl)maleate, Bis(2,2,2-trifluoroethyl)itaconate, Bis(2,2,2-trifluoroethyl)maleate, 1H,1H-2,5-Bis(trifluoromethyl)-3,6-Dioxaundecafluorononanol, 3,3-Bis(trifluoromethyl)-3-Hydroxypropionic Acid, 2,2 Bis (trifluoromethyl) Propionic Acid, n-Butyl-1,1,2,2-Tetrafluoroethyl Ether, n-Butyl Trifluoroacetate, tert-Butyl Trifluoroacetate, 1,1,1,5,5,6,6,7,7,7-Decafluoro-2,4-Heptanedione, 1H,1H,6H-Decfluorohexan-1-ol, 2H,3H-Decafluoropentane, Diethyl Difluoromalonate, 2,2-Difluoroethanol, 2,2-Difluoroethyl acetate, 2,2-Difluoroethyalamine, DL-4,4-Difluoroglutamic acid, 2,2-Difluoromalonamide, Difluoromethyl, 2,2,3,3,3-Pentafluoropropyl Ether, Difluoromethyl 2,2,2-Trifluoroethyl Ether, Difluoromethy 2,2,2-Trifluoroethyl Ether, 1,3-Difluoro-2-propanol, Dimethyl, Hexafluoroglutarate, Dimethyl Octafluoroadipate, Dimethyl Perfluoroazelate, Dimethyl Perfluoro-1,10-decanedicarboxylate, Dimethyl Perfluorosebacate, Dimethyl Perfluorosuberate, Dimethyl Tetrafluorosuccinate, Dimethyl 2,2,2-Trifluoropropionyl Carbinol, 4-Ethoxy-1,1,2-Trifluorobut-1-ene, Ethyl 3-Amino-4,4,4-trifluorocrotonate, Ethyl Ethoxymethylene-3-oxo-4,4,4-trifluorobutyrate, Ethyl 4-Fluoro-3-methyl-2-pentenoate, Ethyl 2-Fluoropropionate, Ethyl Heptafluorobutyrate, Ethyl Heptafluorobutyrylacetate, Ethyl 3-Hydroxy-4,4,4-trifluorobutyrate, Ethyl 2-Methyl-3-hydroxy-4,4,4-trifluorobutyrate, Ethyl Pentafluoropropionate, Ethyl Perfluoroheptanoate, Ethyl Perfluoro-n-dodecanoate including all compounds like CnF2n+1CO2CH2CH3, n= 4 to 16 (some H substitution possible in the CF chain, and double bonds), Ethyl Perfluoro-n-dodecanoate, Ethyl 7H-Perfluoroheptanoate, Ethyl Perfluorononanoate, Ethyl 9H-Perfluorononanoate, Ethyl Perfluorooctanoate, Ethyl Perfluoropentanoate, Ethyl 5H-Perfluoropentanoate, Ethyl 11H-Perfluoroundecanoate, Ethyl 1,1,2,2-Terafluoroethyl Ether, Ethyl 4,4,4-Trifluorobutyrate, Ethyl 3-(Trifluoromethyl)crotonate, Ethyl 4,4,4-Trifluoro-3-(trifluoromethyl)crotonate, Fluorinert (FC40, FC430, FC70, FC71, FC72, FC77, FC84, FC87, FC104, FC6001, FC6003), DL-2-Fluoro-3-alanine, 2-Fluoroethanol, D-Erythro-4-Fluoroglutamic Acid, 2-Fluoroethyl Methacrylate, DL-4-Fluoroglutamic Acid, L-Erythro-4-Fluoroglutamic Acid, D-Threo-4-Fluoroglutamic Acid, DL-Threo-4, Fluoroglutamic Acid, L-Threo-4-Fluoroglutamic Acid, DL-Erythro-4-Fluoroflutamine, L-Erythro-4-Fluoroglutamine, DL-Threo-4-Fluoroglutamine, DL-Erythro-4-

Fluoroisoglutamine, L-Erythro-4-Fluoroisoglutamine, DL-Threo-4-Fluoroisoglutamine, 3-Fluoro-DL-Norleucine, Flutec (PP1, PP2, PP3, PP9, PP10, PP11, PP25, PP50), Fomblin (M, Y (L-Vac), Y (H-Vac), Z15, MF402, ZDOL), Galden (HT70, HT85, HT90, HT100, HT110, HT135, HT200, HT230, HT250, HT270), 1H,1H Heptafluorobutan-1-ol, 1H,1H-Heptafluorobutyl Acetate, Heptafluorobutyramide, Heptafluorobutyric Acid, Heptafluorobutyric Anhydride, 4,4,5,5,6,6,6-Heptafluorohexanoic Acid, 4,4,5,5,6,6,6-Heptafluorohexan-1-ol, 4,4,5,5,6,6,6-Heptafluorohex-2-en-1-ol, Heptafluorosiopropyl Methyl Ether, 1,1,1,3,5,5,5-Heptafluoropentane-2,4-dione, Heptafluoropenta-2-ol, 2-Heptafluoropropoxy-2,3,3,3-tetrafluoropropan-1-ol, Heptafluoropropyl Methyl Ether, Heptafluoropropyl 1,2,2,2-tetrafluoroethyl Ether, Heptafluoropropyl Trifluorovinyl Ether, 2,2,3,4,4,4-Hexafluorobutan-1-ol, 2,2,3,3,4,4-Hexafluorobutan-1-ol, 2,2,3,4,4,4, Hexafluorobutyl Difluoromethyl Ether, 2,2,3,4,4,4-Hexafluorobutyl Methacrylate, Hexafluoroglutaramide, Hexafluoroglutaric Acid, Hexafluoroisopropanol, 1,1,1,3,3,3-Hexafluoroisopropyl Acrylate, mono-Hexafluoroisopropyl Itaconate, mono-Hexafluoroisopropyl Maleate, 1,1,1,3,3,3-Hexafluoroisopropyl methacrylate, Hexafluoroisopropyl Methyl Ether, Hexafluoroisopropylurethane-N-ethyl Methacrylate, Hexafluoroleucine, Hexafluoro-2-methylisopropanol, Hexafluoro-1,5-pentanediol, 3,3,4,5,5,5-Hexafluoropentan-2-ol, 1,1,2,3,3,3-Hexafluoropropyl Ethyl Ether, 1,1,2,3,3,3-Hexafluoropropyl Methyl Ether, 4,4,4,6,6,6-Hexafluoro-4-(trifluoromethyl)hexan-1-ol, 4,5,5,6,6,6-Hexafluoro4-(trifluoromethyl) hex-2-enoic Acid, 4,5,5,6,6,6-Hexafluoro-4-(trifluoromethyl) hex-2-en-1-ol, Hexafluoro-DL-valine, Isopropyl Trifluoroacetate, N, Methylbis(heptafluorobutyramide), Methyl Heptafluorobutyrate, Methyl Heptafluoropropyl Ketone, Methyl 2,2,3,3,4,4-hexafluorobutyrate, Methyl 2-hydroxy-2-(trifluoromethyl)pen-4-enoate, N-Methyl-N, methoxytrifluoroacetamide, Methyl Nonafluorobutyl Ether, Methyl Nonafluorobutyl Ketone, Methyl 2,2,3,3,4,4,5,5-octafluoropentanoate, Methyl Pentafluorobut-3-enoate, Methyl Pentafluoropropionate, Methyl Pentafluoropropionylacetate, Methyl Perfluorodecanoate, Methyl Perfluorododecanoate, Methyl Perfluoroheptanoate, Methyl 7H-Perfluoroheptanoate, Methy Perfluorohexadecanoate, Methyl Perfluoro(2-methyl-3-oxahexanoate), Methyl Perfluorononanoate, Methyl Perfluorooctadecanoate, Methyl Perfluoropentadecanoate, Methyl Perfluorotetradecanoate, Methyl Perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoate, Methyl Perfluorotridecanoate, Methyl Perfluoroundecanoate, Methyl 2,3,3,3-Tetrafluoropropionate, Methyl Trifluoroacetate, Methyl 4,4,4-trifluoroacetoacetate, 2-Methyl-4,4,4-trifluorobutanol, Methyl 4,4,4,-trifluorocrotonate, Methyl 2-(trifluoromethyl), 3,3,3-trifluoropropionate, Methyl Trifluoropropenoate, Methyl Trifluoropyruvate, (Nonafluoro-n-butyl)epoxide, 2-(Nonafluorobutyl)ethyl acrylate, 2-(Nonafluorobutyl)ethyl methacrylate, 6-(nonafluorobutyl)hexanol, 3-(Nonafluorobutyl)-2-hydroxypropyl Acrylate, 3-(Nonafluoro-n-butyl)prop-2-enol, 3-(Nonafluoro-n-butyl)1,2,-

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