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(54) Title: PRESERVATIVE-FREE COMPOSITIONS COMPRISING A COMPLEX OF A CORTICOSTEROID AND HPBCD FOR THE TREATMENT OR PREVENTION OF AN INFLAMMATORY DISEASE THROUGH NASAL ADMINISTRATION

(57) Abstract: Preservative-free compositions comprising a complex of a corticosteroid and HPBCD for the treatment or prevention of an inflammatory disease through nasal administration.

PRESERVATIVE-FREE COMPOSITIONS COMPRISING A COMPLEX OF A CORTICOSTEROID AND HPBCD FOR THE TREATMENT OR PREVENTION OF AN INFLAMMATORY DISEASE THROUGH NASAL ADMINISTRATION

FIELD OF THE INVENTION

The present invention relates to a liquid composition comprising a complex of hydroxypropyl-beta-cyclodextrin (HPBCD) or derivatives thereof and a corticosteroid for use as a nasal spray in the treatment or prevention of inflammatory diseases.

In recent years, the number of respiratory diseases has substantially increased through multiple factors.

BACKGROUND

EP1799231 to the University of Liège proposes the direct administration of cyclodextrins for the treatment of bronchial inflammatory diseases preferably asthma and chronic obstructive pulmonary disease (COPD). However, the use of preservative-free nasal sprays comprising HPBCD, and a corticosteroid is not disclosed.

US2006120967 and US2006045850 to QPHARMA disclose nasal formulations of cyclodextrins comprising preservatives. However, the use of preservative-free nasal sprays comprising HPBCD, and a corticosteroid is not disclosed.

International patent application WO2021048322A1 to Aquilon Pharmaceuticals discloses spherical microparticles for use in the treatment and prevention of respiratory diseases comprising one or more carriers, preferably HPBCD and one or more active pharmaceutical ingredients, preferably budesonide. However, the use of preservative free-nasal sprays comprising HPBCD, and a corticosteroid is not disclosed.

BE1029585 to Aquilon Pharmaceuticals discloses an inhalable composition comprising a complex of HPBCD and budesonide or ciclesonide for use in the topical prevention or topical treatment of viral respiratory diseases. However, the use of preservative free-nasal sprays comprising HPBCD, and a corticosteroid is not disclosed.

EP3151836 to the University of Liège and Paul Maes discloses the use of HPBCD in conjunction with the corticosteroid budesonide for the treatment and prevention of

bronchial inflammatory diseases, preferably for chronic obstructive pulmonary disease, such as chronic bronchitis, obstructive bronchiolitis, emphysema, pulmonary fibrosis, cystic fibrosis and most preferably for tobacco-induced chronic obstructive pulmonary disease and cystic fibrosis disease. However, the use of preservative-free nasal sprays comprising HPBCD, and a corticosteroid is not disclosed.

EP1894559 of Pari discloses several corticosteroids solubilized through cyclodextrins for the treatment of a long list of human diseases, comprising viral sinusitis. EP1894559 teaches that the nasal administration requires a preservative to ensure its sterility after the withdrawal of a dose. Consequently, the use of preservative-free-nasal sprays comprising HPBCD, and a corticosteroid is not disclosed.

WO2021001349 to Aquilon Pharmaceuticals discloses a liquid composition comprising one or more cyclodextrins or pharmaceutically acceptable derivatives thereof for use in the prevention or treatment of nasal inflammations, wherein the treatment or prevention of nasal inflammations is a topical treatment. A preferred cyclodextrin is HPBCD. However, the use of preservative-free nasal sprays comprising HPBCD, and a corticosteroid is not disclosed.

EP0423240B1 to the University of Pennsylvania discloses the use of a beta-cyclodextrin as a blocking agent for the preparation of a medicament for inhibiting infection of cells by a virus. However, the use of preservative-free nasal sprays comprising HPBCD, and a corticosteroid is not disclosed.

WO2019067145 to ASDERA LLC discloses cyclodextrin compositions and methods that may be useful in the treatment and/or prevention of respiratory diseases, including, but not limited to the protection from virus or bacterial infections. However, the use of preservative-free-nasal sprays comprising HPBCD, and a corticosteroid is not disclosed.

There still is a need for an efficient treatment of nasal inflammations that have a sufficient shelf life without the need for preservatives.

SHORT DESCRIPTION OF THE INVENTION

The inventors have surprisingly found that the use of hydroxypropyl-beta-cyclodextrin (HPBCD) improves the shelf life and stability of preservative-free nasal sprays comprising corticosteroids. The inventors in particular found that an HPBCD solution comprising a corticosteroid can be aseptically filtered to obtain a sterile product. Such a sterile product can be stored over a long time without preservatives.

Accordingly, a first aspect of the invention is a liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease,

- Wherein the liquid composition comprises a complex of a corticosteroid and hydroxypropyl-beta-cyclodextrin (HPBCD); and
- Wherein the liquid composition is preservative-free.

In another aspect,

- wherein no further active pharmaceutical ingredient is present in therapeutically effective amounts for which HPBCD is used to deliver an active pharmaceutical ingredient to other parts of the body than the respiratory system or the bronchial epithelium;
- wherein no further active pharmaceutical ingredient is present in therapeutically effective amounts for which HPBCD is used to increase the solubility of the further active pharmaceutical ingredient in water;
- wherein no preservative is present, wherein the preservative is selected from the group consisting of benzalkonium chloride, phenylethyl alcohol, benzyl alcohol, sodium benzoate, chlorbutanol, phenoxyethanol, cetrimide and 2-(ethylmercuriomercapto)benzoic acid sodium salt, sodium bisulfite, sodium bisulfate, sodium thiosulfate, thimerosal, phenylmercuric acetate, phenylmercuric nitrate, methylparaben, polyvinyl alcohol and phenylethyl alcohol hyaluronic acid, benzoic acid, potassium sorbate, and essential oils preferably from fruit extracts;
- wherein no further cyclodextrin is present, wherein the further cyclodextrin is an alpha or gamma-cyclodextrin; and/or
- wherein no further thickening agent, emulsifier, and stabilizer is present, preferably no xanthan gum is present.

In another aspect, the composition comprises citric acid and/or natrium citrate as a pH buffer.

In another aspect, the composition has a pH from 2 to 8 , preferably from 3,5 to 6,5 and even more preferably from 4.0 to 5.5.

In another aspect, the viscosity of the liquid composition is in the range of about 0,01 mPa.s to about 10 mPa.s, preferably in the range of about 0,5 mPa.s to about 5 mPa.s and most preferably in the range from about 0,8 mPa.s to about 3 mPa.s at 20 °C as measured according to USP.

In another aspect, the corticosteroid is selected from the group consisting of ciclesonide, mometasone furoate, beclomethasone dipropionate, budesonide, and fluticasone propionate.

In another aspect, the liquid composition comprises HPBCD in an amount from 1 mg/ml to 100 mg/ml, preferably from about 5 mg/ml to about 80 mg/ml, even more preferably from 10 mg/ml to about 80 mg/ml.

In another embodiment, the liquid composition comprises HPBCD in an amount from 8.00 mg/ml to 60 mg/ml.

In another aspect, the liquid composition comprises the corticosteroid in an amount from 0,20 mg/ml to 1 mg/ml, preferably from 0,020 mg/ml to 0,70 mg/ml, preferably from about 0,05 mg/ml to about 0,5 mg/ml and more preferably from about 0,1 mg/ml to 0,25 mg/ml.

In another aspect, the liquid composition comprises the corticosteroid in an amount f from 0,005 mg/ml to 1 mg/ml, preferably from 0,01 mg/ml to 0,09 mg/ml and more preferably from 0,02 mg/ml to 0,07 mg/ml.

In another aspect, the HPBCD is administered in an amount of 0.1 mg to 105 mg per day, or from 0.1 mg to 30 mg per day, preferably in the amount of 0.5 mg to 20 mg per day, even more preferably in the amount of 1 mg to 10 mg per day.

In another aspect, the HPBCD is administered in an amount of 0.1 mg to 105 mg per day, preferably from of 5 mg to 80 mg per day, preferably from 10 mg to 50 mg/day.

In another aspect, the HPBCD is administered in an amount of 10 mg to 50 mg per day.

In another aspect, the corticosteroid is administered in the amount of 0.020 mg to 1 mg per day, or of 0.020 mg to 0,700 mg per day, preferably in the amount of 0.05 mg to 0,5 mg per day, even more preferably in the amount of 0.05 mg to 0,40 mg per day, even more preferably in the amount of 0,07 mg to 0,30 mg per day.

In another aspect, the corticosteroid is administered in the amount of 0,07 mg/day to 0,4 mg/day.

In another aspect, the corticosteroid is administered in the amount of 50 µg/100µl per dose.

In another aspect, the corticosteroid is administered in the amount of 400 µg/800 µl per day.

In another aspect, the liquid composition is administered to children aged from 2 to 6 years per inhalation, wherein the HPBCD is administered in the amount of 0,05 mg to 50 mg per day, or of 0,05 mg to 0,20 mg per day and wherein the corticosteroid, preferably budesonide or the ciclesonide, is administered per inhalation in an amount of 0,15 mg to 0,50 mg per day, or of 0,15 mg to 0,20 mg per day.

In another aspect, the liquid composition is administered to children aged from 6 to 14 years per inhalation, wherein the HPBCD is administered in the amount of 0,1 mg to 50 mg per day, or of 0,1 mg to 20 mg per day and wherein the corticosteroid is administered per inhalation in an amount of 0,25 mg to 1 mg per day, or of 0,25 mg to 0,5 mg per day.

Another aspect is a nasal spray device, comprising the liquid composition for use as nasal spray in the treatment or prevention of an inflammatory disease,

- Wherein the liquid composition comprises a complex of a corticosteroid and hydroxypropyl-beta-cyclodextrin (HPBCD); and
- Wherein the liquid composition is preservative-free.

Another aspect is a nasal spray device for delivering the liquid composition for use as nasal spray in the treatment or prevention of an inflammatory disease

- Wherein the liquid composition comprises a complex of a corticosteroid and hydroxypropyl-beta-cyclodextrin (HPBCD); and
- Wherein the liquid composition is preservative-free.

Another aspect is a method of topical prevention or topical treatment of a nasal inflammatory disease, wherein a composition comprising a complex of HPBCD or a pharmaceutically acceptable derivative thereof and a corticosteroid is administered in a therapeutically effective amount without treatment-limiting side-effects to a subject in need thereof, wherein the liquid composition is preservative-free.

Another aspect is a method of nasal care which comprises intranasally spraying to a subject in need thereof a liquid composition:

- Wherein the liquid composition comprises a complex of a corticosteroid and hydroxypropyl-beta-cyclodextrin (HPBCD); and
- Wherein the liquid composition is preservative-free.

DETAILED DESCRIPTION OF THE INVENTION

Liquid preservative free composition for use as nasal spray

The present invention concerns a liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease,

- Wherein the liquid composition comprises a complex of a corticosteroid and hydroxypropyl-beta-cyclodextrin (HPBCD); and
- Wherein the liquid composition is preservative-free.

Treatment

The terms "treatment" or "treat" describe any treatment of respiratory viral disease for example by inhalation of an aerosol or a micronized powder in view of reducing the symptoms or causes of respiratory viral disease.

Prevention

The term "prevention" means any delay of the onset or any prevention of a disease.

Liquid composition

The present invention concerns a liquid composition comprising a complex of HPBCD (HPBCD) or a pharmaceutically acceptable derivative thereof and corticosteroid for use as a nasal spray in the treatment or prevention of an inflammatory disease.

In one embodiment, the liquid composition is free of alpha or gamma-cyclodextrin.

In other embodiments, the liquid composition comprises one or more further cyclodextrins, for example alpha-cyclodextrin, beta-cyclodextrins, gamma-cyclodextrin, and particularly 2-hydroxypropyl-gamma-cyclodextrin, sulfobutylether-beta-cyclodextrin, and methyl-beta-cyclodextrin.

The term "liquid" as used herein refers to a composition that may be administered by inhalation. In particular, the term "liquid" means that the composition is capable of being micronized for inhalation purposes to an average particle size of 1 micrometer to 20 micrometers, preferably 1 micrometer to 10 micrometers and even more preferably 1 to 5 micrometers. Suitable devices for micronization for inhalation include metered dose inhaler or nebulizers.

Preferably, the liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease is a liquid composition,

- wherein no further active pharmaceutical ingredient is present in therapeutically effective amounts for which HPBCD is used to deliver an active pharmaceutical ingredient to other parts of the body than the respiratory system or the bronchial epithelium;
- wherein no further active pharmaceutical ingredient is present in therapeutically effective amounts for which HPBCD is used to increase the solubility of the further active pharmaceutical ingredient in water;
- wherein no preservative is present, wherein the preservative is selected from the group consisting of benzalkonium chloride, phenylethyl alcohol, benzyl alcohol, sodium benzoate, chlorbutanol, phenoxyethanol, cetrimide and 2-(ethylmercuriomercapto)benzoic acid sodium salt, sodium bisulfite, sodium bisulfate, sodium thiosulfate, thimerosal, phenylmercuric acetate, phenylmercuric nitrate, methylparaben, polyvinyl alcohol and phenylethyl alcohol hyaluronic acid, benzoic acid, potassium sorbate, and essential oils preferably from fruit extracts;
- wherein no further cyclodextrin is present, wherein the further cyclodextrin is an alpha or gamma-cyclodextrin; and/or
- wherein no further thickening agent, emulsifier, and stabilizer is present, preferably no xanthan gum is present.

Liquid aqueous composition

In one embodiment, the composition of the invention is aqueous, which means that it is preferably a liquid composition comprising water as the predominant liquid constituent. Accordingly, in some embodiments, the liquid composition is a composition comprising HPBCD, water and optionally one or more other components suitable for use in pharmaceutical delivery such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, or excipients, and antimicrobial preservatives. Typically, these components are present in very low amounts, typically in the range of 0,1 to 5 mg/ml.

In another embodiment, the viscosity of the liquid aqueous composition is in the range of about 0,0,1 mPa.s to about 10 mPa.s, preferably in the range of about 0,5 mPa.s to about 5 mPa.s and most preferably in the range from about 0,8 mPa.s to about 3 mPa.s at 20

°C as measured by the EU or U.S. Pharmacopoeia (USP) 911 - Viscosity (Capillary Viscometer Methods).

In another embodiment, the composition comprises an effective amount of HPBCD, salt or derivative thereof and a pharmaceutically acceptable carrier. A preferred composition for nebulization comprises HPBCD, NaCl and water.

When administered in aerosol form, it is further preferred for safety and tolerability reasons that water is the only liquid present in the composition. However, in some cases it may be acceptable even for liquids for inhalation to comprise some amount of other liquids, in particular one or more organic solvents having a relatively low inhalation toxicity such as ethanol, propylene glycol, or glycerol. In one embodiment, these liquids are present in very low amounts, typically in the range of 0,1 to 5 mg/ml.

The aqueous composition is suitable for administration as an aerosol. In particular, it is designed for use as a nasal spray for the prevention or treatment of an inflammatory disease affecting a region of the upper respiratory tract, such as the nasal mucosa or the paranasal sinuses. In another embodiment, the aqueous composition is designed for inhalation for the prevention or treatment of respiratory viral disease affecting the lower airways, in particular the bronchial system.

The aqueous composition may be an isotonic or hypertonic. A solution is isotonic when its effective osmotic concentration is the same as that of the cytosol inside the cells of the respiratory system. A solution is hypertonic if it has a greater concentration of solutes than the cytosol inside the cells of the respiratory system.

In another embodiment, the pH of the composition is from 2 to 8 , preferably from 3,5 to 6,5 and even more preferably from 4.0 to 5.5. The preferred pH may be obtained by adding a pH buffer. Preferable pH buffers are citric acid/citrate/ascorbic acid or citric acid/citrate/EDTA.

In order to adjust the pH, surface tension, viscosity, osmolality, stability, taste and other properties of the composition, one or more further excipients may be used. For example, the composition may comprise one or more excipients selected from pharmaceutically acceptable organic acids, salts of organic acids, inorganic acids, inorganic salts, bases, sugars, sugar alcohols, stabilizers, antioxidants, surfactants, and taste masking agents.

The composition of the present invention enables aqueous and dry powder formulations whose properties allow highly efficient and convenient aerosol or dry powder delivery using currently available aerosol generating devices, or dry powder inhalers.

Accordingly, a further object of the invention is the use of the composition of the invention for the treatment or prevention of an inflammatory disease through the administration of a nasal spray by an aerosol or a micronized powder.

Aerosolization, in the sense of the present invention, means any spraying process that produces droplets. The size of the droplets may vary. Typically, the size of the droplets is between 1 and 100 microns, preferably, between 1,5 and 10 microns and even more preferably between 2 and 7 microns.

Micronization, in the sense of the present invention, means any process to decrease the particle size of dry powders or a suspension to between 1 and 100 microns, preferably, between 1,5 and 10 microns and even more preferably between 2 and 7 microns.

pH of the liquid composition

In one embodiment, the pH of the liquid composition for use as nasal spray in the treatment or prevention of an inflammatory disease has a pH from 2 to 8 , preferably from 3,5 to 6,5 and even more preferably from 4.0 to 5.5.

Preservative-free

The composition of the present invention is preservative-free. Preservatives are generally used to ensure the microbial stability of a liquid composition and increase its shelf life.

In one embodiment, the preservative is selected from the group consisting of cetyl pyridinium chloride, phenol, benzethonium chloride, butylparaben, methyl paraben, ethyl paraben, propyl paraben, benzalkonium chloride, thimerosal, chlorobutanol, phenylethyl alcohol, benzyl alcohol, potassium sorbate, sodium benzoate, sorbic acid or combinations thereof.

In one embodiment, the liquid composition of the present invention is free or organic solvents, such as alcohols.

Further disclaimed substances

In one embodiment, the composition is free of flavonoids agents, such as Citrox. In another embodiment, the composition is free of oils.

Topical treatment

The composition of the present invention is for topical treatment, particularly by inhalation. The term “topical” means that the composition of the invention is applied to the respiratory system, in particular to the nasal mucosa or the bronchial epithelium, for example by intranasal application or through inhalation of an aerosol generated by an aerosol-generating device. In some embodiments the treatment is a respiratory topical treatment in the sense that no other tissue or part of the body than the respiratory system, the nasal mucosa are targeted by the use of the invention.

Active pharmaceutical ingredient

The term "active pharmaceutical ingredient" or “API” refers to any substance or combination of substances used in a finished pharmaceutical product, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings. Preferably, the term “active pharmaceutical ingredient" refers to a molecule that is intended to be biologically active, for example for the purpose of treating inflammatory, autoimmune, or pulmonary disease, disorder, or condition. Even more preferably, the term “active pharmaceutical ingredient" refers to substances whose placing on the market requires a marketing authorization, for example as foreseen under directive 2001/83/EC of 6 November 2001 on the Community Code relating to medicinal products for human use.

Inflammatory disease

The inflammatory disease may be any inflammatory disease independently of the cause. The inflammatory disease may be

- Allergen-induced;
- Autoimmune-induced, and/or
- Pathogen-induced, such bacterial or viral inflammations, in particular respiratory viral disease.

Steroids

Steroids are anti-inflammatory compounds which are commonly also referred to as steroids, corticoids, glucocorticoids, corticosteroids or cortisol analogues. Examples of such corticosteroids include aldosterone, beclomethasone, betamethasone, budesonide, cloprednol, cortisone, cortivazol, deoxycortone, desonide, desoximetasone,

dexamethasone, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluorometholone, flurandrenolone, fluticasone, fluticasone propionate, halcinonide, hydrocortisone, icomethasone, meprednisone, methylprednisolone, mometasone paramethasone, mometasone furoate monohydrate, prednisolone, prednisone, tixocortol, triamcinolone, beclomethasone diproprionate, dexamethasone 21-isonicotinate, fluticasone propionate, icomethasone enbutate, tixocortol 21-pivalate, and triamcinolone acetonide, or combinations thereof

Preferred corticosteroids are beclomethasone, budesonide, flunisolide, fluticasone, ciclesonide, mometasone, or any compounds comprising the active moiety of any of these corticosteroids, such as salts, derivatives, and prodrugs thereof. In particular corticosteroids selected from the group consisting of fluticasone and budesonide. A preferred corticosteroid is budesonide.

Budesonide is also named (R,S)- 1 1 (3,16a, 17,21 -tetrahydroxypregna- 1 ,4-diene-3,20-dione cyclic 16, 17-acetal with butyraidehyde or 16, 17-(butylidenebis(oxy))- 1 1 ,21 -dihydroxy-, (1 1 -β,16-a)-pregna-l ,4-diene-3,20-dione. The chemical formula, molecular weight and CAS number for Budesonide are C25H34O6, MW: 430.5 and 51333-22-3, respectively. Budesonide is a racemate consisting of a mixture of the two diastereomers 22 R and 22 S. Budesonide is commercially available as a mixture of the two isomers (22R and 22 S). Commercial formulations of budesonide in solution are provided by AstraZeneca LP (Wilmington, Del.) under the trademark Pulmicort.

The molar ratio between the corticosteroid and the HPBCD may vary widely. In some embodiments, the molar ratio is from about 1:1 to about 1:400, preferably from about 1:1 to about 1:300 preferably from about 1:1 to about 1:100, preferably from about 1:1 to 1:75 and even more preferably from about 1:1 to about 1: 50.

In one embodiment, no further active pharmaceutical ingredient than a corticosteroid is present in the liquid composition in therapeutically effective amounts for which HPBCD is used to deliver an active pharmaceutical ingredient to other parts of the body than the respiratory system or the bronchial epithelium.

In one embodiment, no further active pharmaceutical ingredient than a corticosteroid is present in the liquid composition in therapeutically effective amounts for which HPBCD is used to increase the solubility of the further active pharmaceutical ingredient in water.

HPBCD

HPBCD is an oligosaccharide composed of glucopyranose units. The major unsubstituted cyclodextrins are usually prepared by the enzymatic degradation of starch. HPBCD is a chemically modified cyclodextrin which may have increased water solubility over unmodified cyclodextrins.

Also comprised are pharmaceutically acceptable derivatives of HPBCD as long as they are structurally and functionally similar to HPBCD.

Bronchodilators

In some embodiments, the composition does not comprise any bronchodilators such as formoterol. In other embodiments, the composition further comprises bronchodilators such as formoterol.

Effective amount

The terms "effective amount" or "therapeutically effective amount," as used herein, refer to an amount of an active agent as described herein that contributes to achieving one or more desirable clinical outcomes, such as those described in the "treatment" description above. An appropriate "effective" amount in any individual case may be determined using standard techniques known in the art, such as a dose escalation study.

In some embodiments, as used herein, the term "therapeutically effective amount" is meant to refer to an amount of an active agent or combination of agents effective to ameliorate, delay, or prevent the symptoms. Determination of a therapeutically effective amount is well within the capabilities of the skilled person.

In one embodiment, an effective amount of the liquid composition for use as nasal spray in the treatment or prevention of an inflammatory disease is administered.

Concentration and daily dosage of cyclodextrin

In one embodiment, the composition of the present invention is a liquid, preferably an aqueous composition.

In the case of an aqueous composition, the amount or content of the cyclodextrin in the composition is selected to ensure a sufficiently low viscosity at ambient temperature in view of inhalation. The dynamic viscosity, which may also be influenced by the choice and quantity of the further excipients, also has a clear influence on the particle size distribution of the aerosol formed by nebulization and on the efficiency of nebulization.

In one embodiment, the viscosity may be adjusted to a range of about 0.8 to about 3 mPas at ambient temperature. In another embodiment, the dynamic viscosity of the composition is in the range of about 0.8 to about 2.5 mPas or even about 0.9 to about 1.3 mPas at ambient temperature.

Typically, the HPBCD concentration in the composition according to the present invention is in the range from about 1 millimolar to about 100 millimolar, preferably from 5 millimolar to about 50 millimolar, and more preferably from about 7 millimolar to about 40 millimolar. Other preferred concentrations range from about 10 millimolar to about 30 millimolar and from about 15 millimolar to about 25 millimolar.

In another embodiment, the liquid composition comprises HPBCD in an amount from 1 mg/ml to 300 mg/ml, preferably from 1 mg/ml to 200 mg/ml, even more preferably from 1 mg/ml to 100 mg/ml.

In one embodiment, the liquid composition comprises HPBCD in an amount from 1 mg/ml to 100 mg/ml, preferably from about 5 mg/ml to about 80 mg/ml and more preferably from about 8.00 mg/ml to 60 mg/ml.

In a preferred embodiment, the liquid composition comprises HPBCD in an amount from 1 mg/ml to 100 mg/ml, preferably from about 10 mg/ml to about 80 mg/ml, and more preferably from about 8.00 mg/ml to 60 mg/ml.

In another embodiment, the HPBCD is administered per inhalation in the amount of 0.1 mg to 30 mg per day, preferably in the amount of 0.5 mg to 20 mg per day, even more preferably in the amount of 1 mg to 10 mg per day.

In another embodiment, the HPBCD is administered in an amount of 0.1 mg to 105 mg per day, preferably from of 5 mg to 80 mg per day, preferably from 10 mg to 50 mg/day.

In one embodiment the HPBCD is administered in the amount of 0.1 mg to 30 mg per day. In another embodiment, the HPBCD is administered per inhalation in the amount of 0.5 mg to 20 mg per day. In another embodiment, the HPBCD is administered per inhalation in the amount of 1 mg to 10 mg per day.

In another embodiment, the HPBCD is administered to children aged up to two years per inhalation in the amount of 0.1 mg to 0.5 mg per day.

In another embodiment, the HPBCD is administered to children aged from two to 6 years per inhalation in the amount of 0.5 mg to 1 mg per day.

In another embodiment, the HPBCD is administered to children aged from 6 years to 14 years per inhalation in the amount of 1 mg to 2 mg per day.

In another embodiment, the HPBCD is administered to children aged up to two years per inhalation in the amount of 0.1 mg to 1,0 mg per day and wherein the corticosteroid, preferably the budesonide or the ciclesonide, is administered in an amount of 0,05 mg to 0,12 mg per day.

In another embodiment, the HPBCD is administered to children aged from 2 to 6 years in the amount of 0,05 mg to 0,20 mg per day and wherein the corticosteroid is administered per inhalation in an amount of 0,15 mg to 0,20 mg per day.

In another embodiment, the HPBCD is administered to children aged from 6 to 14 years in the amount of 0,1 mg to 20 mg per day and wherein the corticosteroid is administered per inhalation in an amount of 0,25 mg to 0,5 mg per day.

the liquid composition is administered to children aged from 6 to 14 years per inhalation, wherein the HPBCD is administered in the amount of 0,1 mg to 50 mg per day, or of 0,1 mg to 20 mg per day and wherein the corticosteroid is administered per inhalation in an amount of 0,25 mg to 1 mg per day, or of 0,25 mg to 0,5 mg per day.

Concentration and daily dosage of corticosteriod

In another embodiment, the liquid composition comprises a corticosteroid in an amount from 0,020 mg/ml to 0,70 mg/ml, preferably from about 0,05 mg/ml to about 0,5 mg/ml and more preferably from about 0,1 mg/ml to 0,25 mg/ml.

In another embodiment, the liquid composition comprises a corticosteroid in an amount from 0,02 mg/ml to 2 mg/ml, preferably from 0,06 to 1,2 mg/ml and more preferably from 0,1 mg/ml to 0,8 mg/ml.

In preferred embodiment, the liquid composition comprises the corticosteroid in an amount from 0,005 mg/ml to 1 mg/ml, preferably from 0,01 mg/ml to 0,09 mg/ml and more preferably from 0,02 mg/ml to 0,07 mg/ml.

In one embodiment, the daily dosage of the steroid compound typically ranges from 1 microgram to 500 micrograms, preferably from about 30 micrograms to about 200 micrograms per day. In some embodiments, the daily dose of the steroid compound is from 50 micrograms to 150 micrograms and even more preferably from 75 micrograms to 125 micrograms.

In another embodiment, the corticosteroid is administered per nasal spray in the amount of 0.020 mg to 0,700 mg per day, preferably in the amount of 0.05 mg to 0,5 mg per day, even more preferably in the amount of 0,07 mg to 0,25 per day.

In another embodiment, the corticosteroid is administered per nasal spray in the amount of 0.020 mg to 1 mg per day, or of 0.020 mg to 0,700 mg per day, preferably in the amount of 0.05 mg to 0,5 mg per day, even more preferably in the amount of 0,07 mg to 0,30 mg per day.

In another embodiment, the corticosteroid is administered in the amount of 0.020 mg to 1 mg per day, or of 0.020 mg to 0,700 mg per day, preferably in the amount of 0.05 mg to 0,5 mg per day, even more preferably in the amount of 0.05 mg to 0,4 mg per day, even more preferably in the amount of 0,07 mg to 0,30 mg per day.

Further ingredients

The liquid composition, preferably the aqueous liquid composition for use as nasal spray in the treatment or prevention of an inflammatory disease may comprise further ingredients, such as buffering agents; antioxidants; chelating agents and pH-adjusting agents.

Examples of further ingredients include PEG400, Citric acid monohydrate, Tri-Sodium citrate dihydrate, EDTA and NaCl.

Aerosol generating device

In one embodiment, the liquid compositions of the present inventions are administered through an aerosol-generating device, in particular a nasal spray device.

In one embodiment, the nasal spray device is a Rayleigh-jet based inhalers commercially available for example from Medspray. Such nozzle units are based on plain orifice nozzles, creating Rayleigh jets. A 2-micron hole creates a jet, breaking up into mono-disperse 4 micron droplet trains. The diameter of the droplets is twice the size of the orifice. The hole size can be engineered to meet specific requirements of devices. Spray nozzle chips are typically made with technologies generally seen in computer chips.

Effect

The present inventors have found that the nasal administration of a liquid composition comprising a complex of HPBCD, and a corticosteroid is particularly suitable for the prevention or treatment of an inflammatory disease without any need for preservatives.

The HPBCD acts as a stabilizer for the corticosteroid liquid composition. Thus, the shelf-life of the liquid composition is surprisingly increased, and the microbiological stability is surprisingly maintained similar to preservative-based formulations. This renders the use of preservatives unnecessary.

Whilst other compounds may be present, there is no need for administering further active pharmaceutical ingredients than the corticosteroid to obtain a positive effect in respect of the inflammatory disease.

In one embodiment, no further active pharmaceutical ingredient than a corticosteroid is present in the composition of the present invention, wherein HPBCD is used as solubilizing excipient or as a drug delivery system.

EXAMPLES

Following examples are given for illustration purposes. However, they are not meant to limit the invention in any way.

Example 1:

The following liquid compositions were tested:

Example w%	**1**	**2**	**3**	**4**	**5**
Ciclesonide	0,068				
Mometasone Furoate		0,028			
Beclometasone Dipropionate			0,028		
Budesonide				0,068	
Fluticasone Propionate					0,027
HP-Betadex	8,00	8,00	8,00	8,00	8,00
PEG400	5	5	5	5	5
Citric Acid Monohydrate	0,0306	0,0306	0,0306	0,0306	0,0306

Example w%	1	2	3	4	5
Tri-Sodium Citrate Dihydrate	0,05	0,05	0,05	0,05	0,05
EDTA	0,2214	0,2214	0,2214	0,2214	0,2214
NaCl	0,6	0,6	0,6	0,6	0,6
Purified Water	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100

The microbial stability test was performed over 2 years.

No Microbial growth was observed.

Example 2:

The following preservative-free (without benzalkonium chloride composition was tested:

Nasal Compoition_1 Based on Mometasone Furoate and HP-Betadex	
Component	**Quantity (mg/100 ml)**
Mometasone Furoate	35,71
HP-Betadex	16071,43
Citric acid monohydrate	104,00
Sodium citrate dihydrate	170,00
PEG 400	3000,00
Sodium chloride	167,97
Pure water	85800,89
TOTAL	105350,00
Density	*1,0535*
Batch size (mg)	*105350,00*
Batch size (g)	105,350
Batch size (ml)	*100,00*

ratio HP-Betadex/Mometasone Furoate:	*450*

The stability test results were as follows:

Storage Conditions	Test parameters	Specifications	Units	T_0	T_{1W}	T_{2W}	T_{3W}	T_{4W}
	HPLC							
	UV	Maximum wavelength	nm	245	245	245	245	245
5°C	Assay of MOF	90.0 – 110.0	%	100,6	100,6	103,9	101,3	99,2
25°C/ 60%RH			%	99,4	100,2	98,7	9,.8	95,9

Example 3:

The composition of example 3 is as follows:

Component	Quantity (mg/100 ml)
Beclometasone Dipropionate	30,00
HP-Betadex	16500,00
Citric acid monohydrate	104,00
Sodium citrate dihydrate	170,00
PEG 400	3000,00
Sodium chloride	91,175
Pure water	85401,825
TOTAL	105300
Density	*1,053*
Batch size (mg)	*105350,00*

Component	**Quantity (mg/100 ml)**
Batch size (g)	105,350
Batch size (ml)	*100,00*
ratio HP-Betadex/Mometasone Furoate:	*550*

The stability test results were as follows:

Storage Conditions	**Test parameters**	**Specifications**	**Units**	**T_0**	**T_{1W}**	**T_{2W}**	**T_{3W}**
	HPLC						
	UV	Maximum wavelength	nm	240	240	239	239
5°C	Assay of BCDP (glass)	90.0 – 110.0	%	98,3	98,0	97,7	98,0
25°C/60%RH				98,3	98,7	97,9	98,9
40°C/75%RH				98,3	97,1	93,9	89,9

d

CLAIMS

1. A liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease,
   - Wherein the liquid composition comprises a complex of a corticosteroid and hydroxypropyl-beta-cyclodextrin (HPBCD); and
   - Wherein the liquid composition is preservative-free.
2. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to claim 1,
   - wherein no further active pharmaceutical ingredient is present in therapeutically effective amounts for which HPBCD is used to deliver an active pharmaceutical ingredient to other parts of the body than the respiratory system or the bronchial epithelium;
   - wherein no further active pharmaceutical ingredient is present in therapeutically effective amounts for which HPBCD is used to increase the solubility of the further active pharmaceutical ingredient in water; and/or
   - wherein no preservative is present and wherein the preservative is selected from the group consisting of benzalkonium chloride, phenylethyl alcohol, benzyl alcohol, sodium benzoate, chlorbutanol, phenoxyethanol, cetrimide and 2-(ethylmercuriomercapto)benzoic acid sodium salt, sodium bisulfite, sodium bisulfate, sodium thiosulfate, thimerosal, phenylmercuric acetate, phenylmercuric nitrate, methylparaben, polyvinyl alcohol and phenylethyl alcohol hyaluronic acid, benzoic acid, potassium sorbate, citric acid and essential oils preferably from fruit extracts;
   - wherein no further cyclodextrin is present, wherein the further cyclodextrin is an alpha or gamma-cyclodextrin; and/or
   - wherein no further thickening agent, emulsifier, and stabilizer is present, preferably no xanthan gum is present.
3. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims, wherein the liquid composition has a pH from 2 to 8, preferably from 3,5 to 6,5 and even more preferably from 4.0 to 5.5.
4. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims, wherein the

viscosity of the liquid composition is in the range of about 0,01 mPa.s to about 10 mPa.s, preferably in the range of about 0,5 mPa.s to about 5 mPa.s and most preferably in the range from about 0,8 mPa.s to about 3 mPa.s at 20 °C as measured according to USP.F

5. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims, wherein the corticosteroid is selected from the group consisting of ciclesonide, mometasone furoate, beclomethasone dipropionate, budesonide, and fluticasone propionate.
6. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims, wherein the liquid composition comprises HPBCD in an amount from 1 mg/ml to 100 mg/ml, preferably from about 10 mg/ml to about 80 mg/ml, and more preferably from about 8.00 mg/ml to 60 mg/ml.
7. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims, wherein the liquid composition comprises the corticosteroid in an amount from 0,005 mg/ml to 1 mg/ml, preferably from 0,01 mg/ml to 0,09 mg/ml and more preferably from 0,02 mg/ml to 0,07 mg/ml.
8. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims, wherein the HPBCD is administered in an amount of 0.1 mg to 105 mg per day, preferably from of 5 mg to 80 mg per day, preferably from 10 mg to 50 mg/day.
9. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims, wherein the corticosteroid is administered in the amount of 0.020 mg to 1 mg per day, or of 0.020 mg to 0,700 mg per day, preferably in the amount of 0.05 mg to 0,5 mg per day, even more preferably in the amount of 0.05 mg to 0,4 mg per day, even more preferably in the amount of 0,07 mg to 0,30 mg per day.
10. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims, wherein the liquid composition is administered to children aged from 2 to 6 years per inhalation, wherein the HPBCD is administered in the amount of 0,05 mg to 50 mg per day, or of 0,05 mg to 0,20 mg per day and wherein the corticosteroid is administered

per inhalation in an amount of 0,15 mg to 0,50 mg per day, or of 0,15 mg to 0,20 mg per day.

11. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims, wherein the liquid composition is administered to children aged from 6 to 14 years per inhalation, wherein the HPBCD is administered in the amount of 0,1 mg to 50 mg per day, or of 0,1 mg to 20 mg per day and wherein the corticosteriod is administered per inhalation in an amount of 0,25 mg to 1 mg per day, or of 0,25 mg to 0,5 mg per day.

12. The liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims, wherein inflammatory disease is

- Allergen-induced;
- Autoimmune-induced, and/or
- Pathogen-induced; such bacterial or viral inflammations, in particular respiratory viral disease.

13. A nasal spray device, comprising the liquid composition for use as a nasal spray in the treatment or prevention of an inflammatory disease according to any one of the preceding claims.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/065683

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K47/40 A61K47/50 A61K31/724
ADD.

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 923 702 A1 (UNIVERSITÉ DE LIÈGE [BE]; MAES PAUL [BE]) 30 September 2015 (2015-09-30) paragraph [0001] paragraph [0039] paragraph [0040] - paragraph [0044] paragraph [0055] paragraph [0092] paragraph [0098] -----	1-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 2024	18/09/2024

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/065683

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