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Prosecution application

Pharmaceutical Formulations for Aerosols with two or more Active Substances

The present invention relates to new pharmaceutical formulations for aerosols with at least two or more active substances for use by inhalation or by the nasal route.

State of the art

In propellant-driven metered dose inhalers (MDI) the active substances can be formulated as solutions or suspensions. The vast majority of aerosol formulations for MDI's are prepared as suspensions, especially if the preparation contains more than one active substance. Formulations in the form of solutions are used only to a limited extent. In these cases, the formulations normally contain only one active substance.

As a rule, in a suspension, the chemical stability of the active substances is noticeably higher than in a solution. Additionally, in a suspension the active substance can be more highly concentrated than in a solution, with the result that suspension type formulation enable higher doses to be administered.

A major disadvantage of suspension-formulations is the fact that over time (e.g. during storage) the suspended particles clump together to form bigger, more or less stable agglomerates or form loose flakes, sediments or floating layers, or in the worst case, particle growth, which significantly impairs the pharmaceutical quality of the product. The size of the particles formed or the

speed of particle growth are influenced by the solubility features of the liquid phase. Thus, ingress of humidity during storage or a desired increase in polarity, e.g. achieved by adding co-solvents, can have a devastating effect on the quality of the medical end product, particularly if the suspended particles have polar structure elements. The suspension can be physically stabilised by the addition of surfactants, by reducing the harmful effects of moisture and/or particle growth so that suspended particles can be held in suspension for longer.

Natural solution-type formulations are not affected by the problems of increasing particle size or de-mixing processes such as sedimentation or flocculation. However, in this case there is a serious risk of chemical degradation. A further disadvantage is the fact that the limited solubility of the ingredients can prevent administration in high doses. In the past, the chlorofluorohydrocarbons TG 11 (trichlorofluoromethane), TG 12 (dichlorodifluoromethane) and TG 114 (dichlorotetrafluoroethane) have proved particularly suitable as solvents. The solubility of the ingredients can be increased by the addition of co-solvents. In addition, it is usually necessary to take additional measures to chemically stabilise the dissolved components.

Up till now, CFCs such as the above-mentioned TG 11, for example, have often been used as propellants. However, since CFCs have been linked with the destruction of the ozone layer, their manufacture and use are being phased out. The intention is to replace them with special fluorohydrocarbons (HFC) which are less destructive to the ozone layer but have completely different solubility features. The toxicological profile and physico-chemical properties such as the steam pressure, for example, determine which HFCs are suitable for MDIs. The most

promising representatives at present are TG 134a (1,1,2,2-tetrafluoroethane) and TG 227 (1,1,1,2,3,3,3-heptafluoropropane).

For inhalative treatment it may be desirable to have aerosol formulations with two or more active substances. In such cases the active substances are formulated in the necessary concentrations as solutions or suspensions, frequently giving rise to problems regarding the chemical stability of the individual substances or the degree of concentration which can be attained. Major problems are encountered if one of the active substances cannot be suspended or is unstable in a suspension-type formulation of this kind or if one of the active substances is chemically unstable or will not dissolve in a solution-type formulation of this kind, particularly when HFC is used as the propellant.

It is therefore one object of the present invention to develop a formulation for metering aerosols having two or more active substances which overcomes the above-mentioned disadvantages.

Description of the invention

Surprisingly, it has been found that a plurality of active substances can be formulated as a solution and a suspension combined in one formulation.

The invention relates to stable aerosol formulations with fluorohydrocarbons as propellants, particularly TG 134a and/or TG 227, consisting of two or more active substances, wherein at least one active substance is formulated as a solution and at least one active substance is formulated as a suspension. The pharmaceutical preparation according to the invention is used for

inhalative treatment, particularly for treating diseases of the pharynx and respiratory tract, e.g. asthmatic diseases and COPD.

In one aspect, the present invention provides a pharmaceutical preparation for propellant driven metered dose inhalers having a fluorohydrocarbon (HFC) as propellant, which contains a combination of two or more active substances characterised in that at least one active substance selected from ipratropium, Fenoterol and salts thereof is present in dissolved form by the use of a co-solvent together with at least one other active substance in the form of suspended particles selected from salbutamol, cromoglycinic acid and salts thereof.

In another aspect, the present invention provides a use of a pharmaceutical composition as described above for the manufacture of a medicament for treating asthmatic diseases or COPD.

Detailed description of the invention

In one embodiment a medicinally useful combination of two or more active substances is used, containing beclometasone, budesonide, cromoglycinic acid, fenoterol, flunisolide, fluticasone, ipratropium bromide, nedocromil, orciprenaline, oxitropium bromide, reproterol, salbutamol (albuterol), salmeterol, terbutalin, N-[[2,2-dimethyl-4-(2-oxo-2H-pyridin-1-yl)-6-trifluoromethyl-2H-1-benzopyran-3-yl]methyl]-N-hydroxy-acetamide, the esters, salts and/or solvates thereof. Which of the above-mentioned active substances is formulated as a solution and which as a suspension in the preparation according to the invention depends on the particular combinations of active substance and can be determined relatively quickly by solution and suspension trials.

In a preferred embodiment, one or more of the following active substances are suspended: budesonide, cromoglycinic acid, nedocromil, reproterol and/or salbutamol (albuterol) or the esters, salts and/or solvates derived from these compounds and one or more of the following substances are dissolved: beclomethasone, fenoterol, ipratropium bromide, orciprenaline and/or oxitropium bromide, N-[[2,2-dimethyl-4-(2-oxo-2H-pyridin-1-yl)-6-trifluoromethyl-2H-1-benzopyran-3-yl]methyl]-N-hydroxy-acetamide or the esters, salts and/or solvates derived from these compounds. Embodiments having two different active substances are preferred.

A particularly preferred embodiment contains dissolved ipratropium bromide, particularly combined with salbutamol

sulphate (albuterol sulphate) as the suspended active substance.

In all the embodiments, the active substances are used in a therapeutically effective quantity, i.e. in a quantity that can induce a successful treatment. The concentration of the active substances and the volume per stroke of spray are adjusted in such a way that the quantity of active substance which is medically necessary or recommended is released by a single spray or by a few sprays.

One embodiment relates to formulations in which the suspended particles are stabilised by the addition of surfactant substances (surfactants) or other suspension-stabilising agents to stabilise the suspended particles against physical changes. The benefit of this is that the particle size will remain pharmaceutically acceptable even over lengthy periods, e.g. during storage. Preferred particle sizes are up to 20 µm, whilst particularly preferred particle sizes are between 5 and 15 µm, best of all not exceeding 10 µm. The advantage of these particle sizes is that the particles are small enough to penetrate deeply into the lungs but not so small as to be breathed out again with the exchanged air.

Suitable surfactants and suspension-stabilising agents include all pharmacologically acceptable substances which have a lipophilic hydrocarbon group and one or more functional hydrophilic groups, especially C_{5-20} fatty alcohols, C_{5-20} fatty acids, C_{5-20} fatty acid esters, lecithin, glycerides, propyleneglycol esters, polyoxyethylenes, polysorbates, sorbitan esters and/or carbohydrates. C_{5-20} fatty acids, propyleneglycol diesters and/or triglycerides and/or sorbitans of the C_{5-20} fatty acids are preferred, whilst oleic acid and sorbitan mono-,

di- or trioleates are particularly preferred. Alternatively, toxicologically and pharmaceutically acceptable polymers and block-polymers can be used as suspension-stabilising agents. The surfactants used are either non-fluorinated or partially fluorinated or perfluorinated, the term fluorinated referring to the exchange of hydrogen radicals bound to the carbon for fluorine radicals. The quantity of surfactant may be up to 1:1 based on the proportion by weight of the suspended active substances; amounts of 0.0001:1 to 0.5:1 are preferred, whilst amounts of from 0.0001:1 to 0.25:1 are particularly preferred.

A further advantage of the above surfactants is that they can also be used as valve lubricants. Therefore, one embodiment relates to formulations in which said surfactants are added as valve lubricants.

In another embodiment the solubility of at least one active substance to be dissolved is increased by the addition of one or more co-solvents. This has the advantage that the active substance or substances to be dissolved can be formulated in higher concentrations. The addition of co-solvent must not exceed the critical threshold of polarity of the liquid phase at which one of the disadvantages described above begins to affect the suspended particles of active substance.

Suitable co-solvents are pharmacologically acceptable alcohols such as ethanol, esters or water or mixtures thereof; ethanol is preferred. The concentration of the co-solvent in relation to the total formulation may be from 0.0001 to 50 wt.-%, preferably 0.0001 to 25 wt.-%. In another embodiment a concentration of 0.0001 to 10 wt.-% is preferred whilst particularly preferred embodiments are those wherein just enough alcohol is added

to dissolve the active substance which has to be dissolved.

In another embodiment, other common propellants are added to the HFC propellant. These added propellants may be, beside other HFCs, saturated lower hydrocarbons such as propane, butane, isobutane or pentane provided that the mixture is pharmacologically acceptable.

In one embodiment, stabilisers are added to the formulation, with a beneficial effect on the pharmaceutical stability of the active substances even over lengthy periods, e.g. during storage. In the context of the invention, stabilisers denotes those substances which prolong the durability and usability of the pharmaceutical preparation by preventing or delaying chemical changes in the individual ingredients, particularly the active substances, e.g. caused by subsequent reactions or degradation, or those which prevent biological contamination. Stabilisers which are preferred for this purpose are those which influence the pH of the liquid phase, such as acids and/or the salts thereof, particularly suitable substances are hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, ascorbic acid, citric acid and the salts thereof. In addition, preferred bactericides, fungicides etc. are benzalkonium chloride or ethylene diamine tetraacetate. Citric acid is most preferred. The concentration of the stabilisers may be up to 1000 ppm, preferably up to 100 ppm and most preferably 20 to 40 ppm.

One particularly preferred embodiment comprises suspended salbutamol sulphate (albuterol sulphate), dissolved ipratropium bromide, ethanol as co-solvent and citric acid as stabiliser.

Examples

Example 1

In a solution of liquefied 89.96 g (1 mol, 89.71 wt.-%) of TG 134a and 10.03 g (218 mmol, 10.00% by weight) of ethanol are dissolved 37 mg (0.09 mmol, 0.037 wt.-%) of ipratropium bromide and 4 mg (20 µmol, 0.004% by weight) of citric acid and 210.5 mg (0.88 mmol, 0.21% by weight) of salbutamol sulphate (albuterol sulphate) are suspended together with 0.05% by weight of surfactant (e.g. 50 mg (177 mmol) of oleic acid).

Example 2

Analogous to Example 1 using TG 227 as the propellant gas instead of TG 134a.

Example 3

Disodium chromoglycate is suspended in liquefied P134 and a small amount of ethanol and fenoterol hydrobromide is dissolved therein.

Example 4

Analogous to Example 3 using TG 227 as propellant gas instead of TG 134a.

Patent Claims

1. Pharmaceutical preparation for propellant driven metered dose inhalers having a fluorohydrocarbon (HFC) as propellant, which contains a combination of two or more active substances characterised in that at least one active substance selected from ipratropium, Fenoterol and salts thereof is present in dissolved form by the use of a co-solvent together with at least one other active substance in the form of suspended particles selected from salbutamol, cromoglycinic acid and salts thereof.

2. Pharmaceutical preparation according to claim 1, characterised in that the combination of active substances consists of two active substances.

3. Pharmaceutical preparation according to claim 1, characterised in that the combination of active substances consists of ipratropiumbromide and salbutamol sulphate.

4. Pharmaceutical preparation according to any of claims 1 to 3, characterised in that the propellant is TG 134a and/or TG 227.

5. Pharmaceutical preparation according to any of claim 1 to 4, characterised in that the co-solvent is present in a concentration of 0.0001 to 50% by weight, based on the quantity of liquefied propellant.

6. Pharmaceutical preparation according to any of claim 1 to 4, characterised in that the co-solvent is present in a concentration of up to 25% by weight, based on the quantity of liquefied propellant.

7. Pharmaceutical preparation according to any of claim 1 to 4, characterised in that the co-solvent is present in a concentration of up to 10% by weight, based on the quantity of liquefied propellant.

8. Pharmaceutical preparation according to any of claim 1 to 7, characterised in that the co-solvent is selected from the group of pharmacologically tolerable alcohols, a pharmacologically tolerable ester, water or a mixture thereof.

9. Pharmaceutical preparation according to any of claim 1 to 7, characterised in that the co-solvent is ethanol.

10. Pharmaceutical preparation according to any of claims 1 to 9, characterised in that the composition is stabilised by a stabiliser.

11. Pharmaceutical preparation according to claim 10, characterised in that the stabiliser contains one or more acids and/or salts.

12. Pharmaceutical preparation according to claim 10, characterised in that the stabiliser is selected from the group of hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, ascorbic acid, citric acid, benzalkonium chloride and/or ethylene diamine tetraacetic and/or a salt thereof.

13. Pharmaceutical preparation according to claim 10, characterised in that the stabiliser is citric acid.

14. Pharmaceutical preparation according to any of claims 10 to 13, characterised in that the stabiliser is present in an amount of up to 100 ppm.

15. Pharmaceutical preparation according to any of claims 10 to 13, characterised in that stabiliser is present in an amount of up to 40 ppm.

16. Pharmaceutical preparation according to any of claims 1 to 15, characterised in that the preparation contains a surfactant or suspension-stabilising agent.

17. Pharmaceutical preparation according to claim 16, characterised in that the surfactant is selected from the group of C_{5-20} fatty alcohols, C_{5-20} fatty acids, C_{5-20} fatty acid esters, lecithin, glycerides, propyleneglycol esters, polyoxyethanes, polysorbates, sorbitan esters and/or carbohydrates.

18. Pharmaceutical preparation according to claim 16, characterised in that the surfactant is selected from the group of C_{5-20} fatty acids and/or the esters thereof.

19. Pharmaceutical preparation according to claim 16, characterised in that the surfactant is selected from the group of oleic acid and/or sorbitan mono-, di- or trioleate.

20. Pharmaceutical preparation according to claim 16, characterised in that the surfactant contains oleic acid.

21. Pharmaceutical composition according to claim 16 characterised in that the surfactant or suspension-stabilising agent comprises a toxicologically acceptable polymer and/or block-polymer.

22. Pharmaceutical composition according to any of claims 1 to 21 characterised in that the composition comprises ipratropiumbromide, salbutamol sulphate, ethanol, citric acid, TG 227.

23. Pharmaceutical composition according to any of claims 1 to 21 characterised in that the composition comprises ipratropiumbromide, salbutamol sulphate, ethanol, citric acid, TG 134a.

24. Use of a pharmaceutical composition according to any claims 1 to 23 for the manufacture of a medicament for treating asthmatic diseases or COPD.