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New stable pharmaceutical preparation for producing propellant-free aerosols

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The present invention relates to pharmaceutical preparations in the form of stable ethanolic solutions of active substances for producing propellant-free aerosols.

In the last 20 years, the use of metering aerosols has become an established component of the treatment of obstructive lung diseases, particularly asthma. Usually, fluorochlorohydrocarbons have been used as propellant gases. Since the ozone-damaging potential of these propellant gases was recognised, more and more efforts have been made to develop alternatives. One alternative is the development of nebulisers in which aqueous solutions of pharmacologically-active substances are sprayed under high pressure so as to produce a mist of inhalable particles. The advantage of these nebulisers is that there is no need to use any propellant gases whatsoever.

Some nebulisers are described, for example, in PCT Patent Application WO91/14468, the contents of which are referred to hereinafter. In the nebulisers described therein, solutions of defined volumes containing active substances are sprayed, using high pressures through small nozzles so as to produce inhalable aerosols with a preferred particle size of between 1 and 10, preferably between 2 and 5 micrometres.

Hitherto, it has been assumed that, with conventional metering aerosols containing propellant gas, the optimum level of lung-bound particles is obtained in the aerosol. It has now been found, surprisingly, that by

using ethanolic active substance solutions in combination with, for example, the above-mentioned nebulisers it is possible to generate a significantly better spectrum of inhalable particles than is usually the case with metering aerosols which contain propellant gas.

Suitable solvents for the pharmaceutical preparation within the scope of the present inventions are solutions containing at least 70% (v/v) of ethanol; solutions containing at least 85% (v/v) are preferred whilst solutions having an ethanol content of more than 95% (v/v) are particularly preferred. The concentration is given in percent by volume (v/v), the remainder being water. Most particularly preferred is ethanol which already contains small amounts of water, e.g. 96% ethanol, so that it is no longer hygroscopic and evaporates azeotropically.

Apart from water, the solvent may include other cosolvents and the pharmaceutical preparation may also contain flavourings and other pharmacological excipients. Examples of cosolvents are those which contain hydroxyl groups or other polar groups, e.g. alcohols, especially isopropyl alcohol, glycols, particularly propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol, polyoxyethylene alcohols and esters of polyoxyethylene fatty acids. Cosolvents are suitable for increasing the solubility of the excipients and possibly the active substances.

The proportion of dissolved pharmaceutical substance in the finished pharmaceutical preparation is between 0.001 and 5%, preferably between 0.05 and 3%, most particularly 0.01 to 2%, where the figures refer to the percentage by weight. The maximum concentration of pharmaceutical substance depends on the solubility in

the solvent and on the dosage required to achieve the desired therapeutic effect.

As pharmaceutically active agent in the new preparations, it is possible to use any substances which are suitable for administration by inhalation and which are soluble in the solvent specified. These may include, in particular, betamimetics, anticholinergics, antiallergics, PAF-antagonists and particularly steroids and combinations of active substances thereof.

The following are mentioned specifically by way of example:

Tiotropium bromide, 3-[(hydroxydi-2-thienylacetyl)oxy]-8,8-dimethyl-8-azoniabicyclo[3,2,1]oct-6-en-bromide

As betamimetics:

Bambuterol	Bitolterol	Carbuterol	Formoterol
Clenbuterol	Fenoterol	Hexoprenaline	Procaterol
Ibuterol	Pirbuterol	Salmeterol	Tulobuterol
Reproterol	Salbutamol	Sulfonterol	Terbutaline

1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol,
erythro-5'-hydroxy-8'-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one,
1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butyl-amino)ethanol,
1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol.

As anticholinergics:
Ipratropium bromide
Oxitropium bromide
Trospium chloride
N-β-fluorethylnortropine benzilate methobromide

As steroids:
Budesonide
Beclomethasone (or the 17,21-dipropionate)
Dexamethasone-21-isonicotinate
Flunisolide

As antiallergics:
Disodium cromoglycate
Nedocromil
Epinastin

As PAF-antagonists:
WEB 2086 (4-(2-chlorophenyl)-9-methyl-2-[3-(4-morpholinyl)-3-propanon-1-yl]-6H-thieno-[3,2-f][1,2,4]-triazolo[4,3-a][1,4]diazepine)
WEB 2170
(6-(2-chlorophenyl)-8,9-dihydro-1-methyl-8-[(4-morpholinyl)carbonyl]-4H,7H-cyclopenta[4,5]thieno-[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine)

The pharmaceutical preparations according to the invention may contain other excipients such as soya lecithin or surface-active substances.

Surprisingly, it has also been found that the addition of an organic or inorganic acid, preferably in conjunction with a complex forming agent, leads to an improvement in the stability (shelf life) of steroid-containing preparations. This has been found particularly useful for pharmaceutical preparations which contain as active substance Flunisolide or the hydrate or hemihydrate thereof or Budenoside, and which contain ethanol as solvent.

Examples of inorganic acids include, for example: hydrochloric acid, sulphuric acid or phosphoric acid; examples of organic acids include ascorbic acid, malic acid, citric acid, tartaric acid, maleic acid, succinic

acid, fumaric acid, acetic acid, formic acid, propionic acid, etc.

The amount of acid in the finished pharmaceutical preparation is in every case selected so that the pH of the solution is between 2.0 and 7.0, especially between 3.0 and 4.0.

In a preferred embodiment, the pharmaceutical preparation also contains a complex forming agent. Examples of complex forming agents include EDTA, citric acid, nitrilo triacetic acid and the salts thereof. The quantity of complex forming agent is between 0.1 and 3 mg/100 ml, preferably between 0.2 and 2 mg/100 ml, particularly between 0.9 and 1.1 mg/100 ml, based on the finished pharmaceutical preparation.

The preferred complex forming agent is EDTA (ethylene diamine tetraacetic acid or a salt thereof, such as the disodium salt). A preferred pharmaceutical preparation according to the present invention contains 1.667% Flunisolide in the ethanol (96% v/v) as solvent, which contains 0.01% (v/v) EDTA as complex forming agent and is adjusted by the addition of acid to a pH of between 3.0 and 4.0.

Examples of steroids which may be used as an active substance in the pharmaceutical preparation according to the invention are:

Seratrodast	Mycophenolate mofetil
Pranlukast	Zileuton
Butixocort	Budesonide
Deflazacort	
Fluticasone	Promedrol
Mometasone furoate	Tipredane
Beclomethasone, Douglas	Icomethasone enbutate

Ciclometasone	Cloprednol
Fluocortin butyl	Halometasone
Deflazacort	Alclometasone
Ciclometasone	Alisactide
Prednicarbate	Hydrocortisone butyrate
Tixocortol pivalate	Alclometasone dipropionate
Lotrisone	Canesten-HC
Deprodone	Fluticasone propionate
Methylprednisolone-Aceponate	Halopredone acetate
Mometasone	Mometasone furoate
Hydrocortisone aceponate	Mometasone
Ulobetasol propionate	Aminoglutethimide
Triamcinolone	Hydrocortisone
Meprednisone	Fluorometholone
Dexamethasone	Betamethasone
Medrysone	Fluclorolone acetonide
Fluocinolone acetonide	Paramethasone acetate
Deprodone Propionate	Aristocort diacetate
Fluocinonide	Mazipredone
Difluprednate	Betamethasone valerate
Dexamethasonisonicotinate	Beclomethasone dipropionate
Fluocortoloncapronate	Formocortal
Triamcinolon hexacetonide	Cloprednol
Formebolone	Clobetason
Endrisone	Flunisolide
Halcinonide	Fluazacort
Clobetasol	Hydrocortisone-17-butyrate
Diflorasone	Flucortin
Amcinonide	Betamethasone dipropionate
Cortivazol	Betamethasone adamantoate
Fluodexan	Triiostane
Budesonide	Clobetasone
Demetex	Trimacinolon Benetonide

9α-chloro-6α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxo-1,4-androstadiene-17β-carboxylic acid methylester-17-propionate.

Table 1 shows a comparison of a deposition study which was carried out on the one hand with a standard commercial metering aerosol Inhacort® (Flunisolide, dichloromethane, trichlorofluoromethane, cryofluoran, sorbitane triolate) = MDI, and on the other hand with the pharmaceutical preparation according to the invention containing Flunisolide in 96% (v/v) ethanol, which was carried out with a nebuliser as in the above-mentioned PCT Application WO 91/14468 (BINEB®; technical data: volume of drug preparation administered 15 µl, pressure approx. 300 bar, 2 jets squeezed out of two nozzle openings measuring 5 x 8 µm).

Table 1

Table 1: Deposition study

	BINEB®	MDI
Lung (%)	39.7 (9.9)	15.3 (5.1)
Mouthpiece (%)	39.9 (9.4)	66.9 (7.1)
Exhaled part (%)	10.4 (4.9)	1.4 (1.3)
Central lung region (%)	10.7 (2.5)	4.5 (1.8)
Middle lung region (%)	14.9 (3.6)	5.4 (1.9)
Peripheral lung region (%)	14.1 (4.3)	5.4 (1.4)
Peripheral zone/central zone ratio	1.3 (0.2)	1.3 (0.2)

The Table clearly shows the advantage of the pharmaceutical preparation according to the invention which was administered with the nebuliser described.

Examples:

Flunisolide hemihydrate-6α-fluoro-11β,16α,17α,21-tetrahydropregna-1,4-diene-3,20-16 acetonide hemihydrate has a molecular weight of 442.5. When used in BINEB, 250 µg of Flunisolide are dissolved, per dose, in 15 µl of solution so as to give a concentration of 1.667% (g/100 ml).

96% ethanol is used as solvent. In addition, the finished pharmaceutical preparation contains 1 mg/100 ml of disodium-EDTA. The pH value of the pharmaceutical preparation is adjusted to pH 4 using 0.1N HCl.

Analogously to the above experiment, formulations were prepared containing Budesonide as active substance.

The following mixtures of pharmaceutical preparations were made up, containing Flunisolide-hemihydrate as active substance.

Table II

Experiment No.	Combination	Ethanol content (v/v) %	pH	Quantity of disodium EDTA in mg/100 ml
1	1	85	3.6	0
2	A	96	3.6	0
3	B	85	7.0	0
4	AB	96	7.0	0
5	C	85	3.6	1
6	AC	96	3.6	1
7	BC	85	7.0	1
8	ABC	96	7.0	1

The Flunisolide-hemihydrate content was 1,666.7 mg/100 ml. The pH of the solution was adjusted using 1N HCl and was determined using a pH meter, pH 1162 Radiometer Copenhagen. The samples were transferred into 5 ml glass ampoules and stored at 80°C away from light. The combination AC showed the lowest amount of decomposition product after 30 days' storage.

Further examples of formulations which additionally contain disodium EDTA as complex forming agent are shown in Table III.

Table III

Ingredients	I Amount in mg/100 ml	II Amount in mg/100 ml	III Amount in mg/100 ml	IV Amount in mg/100 ml
Flunisolide hemihydrate	1667	1667	1667	1667
Disodium EDTA	1	1	1	1
0.1 N HCl	ad pH 3.6	ad pH 3.2	ad pH 4.0	ad pH 3.6
Menthol	-	-	-	667
Ethanol 96%	ad 100 ml	ad 100 ml	ad 100 ml	ad 100 ml

The adjuvant menthol was added in order to mask the bitter flavour of the steroid where necessary.

The formulations described above were packaged in 5 ml glass ampoules and stored at 80°C. The preferred preparation, on account of the small amount of decomposition product, is preparation III.

Table IV shows some examples of formulations for Budenoside.

Table IV

Ingredients	I Amount in mg/100 ml	II Amount in mg/100 ml	III Amount in mg/100 ml	IV Amount in mg/100 ml	V Amount in mg/100 ml
Budesonide	1333	1333	1333	1333	1333
Disodium EDTA	1	-	1	1	-
0.1N HCl ad pH	3.2	3.2	3.6	4.0	4.0
Ethanol 96% ad	100	100	100	100	100

After 3 months' storage at 80°C in sealed glass ampoules the amount of decomposition product was determined by HPLC. Formulations IV and V showed the smallest amount of decomposition product.

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Claims

1. A pharmaceutical preparation for use in producing propellant-free aerosols which comprises a pharmacologically active substance, and if necessary, pharmacologically-harmless adjuvants and/or flavourings, characterised in that the pharmaceutical preparation contains at least 70% (v/v) ethanol as a solvent.

2. A pharmaceutical preparation according to claim 1, characterised in that it contains 96% (v/v) ethanol as a solvent.

3. A pharmaceutical preparation according to claim 1 or 2, characterised in that the active substance is suitable for administration by inhalation and is selected from the group comprising betamimetics, anticholinergics, antiallergics and/or PAF-antagonists.

4. A pharmaceutical preparation according to claims 1 to 3, characterised in that the proportion of dissolved pharmaceutical product in the pharmaceutical preparation is between 0.001 and 5.0 percent by volume.

5. A pharmaceutical preparation for the production of propellant-free aerosols, comprising a steroid and, if necessary, pharmacologically-harmless adjuvants and/or flavourings, characterised in that the pharmaceutical preparation contains at least 85% (v/v) ethanol as a solvent, and if necessary, a complex forming agent.

6. A pharmaceutical preparation according to claim 5, characterised in that the solvent is 96% (v/v) ethanol.

7. A pharmaceutical preparation according to claim 6, characterised in that the complex forming agent is EDTA or a salt thereof.

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8. A pharmaceutical preparation according to claim 5 or claim 7, characterised in that the quantity of complex forming agent is between 0.1 and 5 mg/100 ml of solution.

9. A pharmaceutical preparation according to one of claims 5 to 8, characterised in that the pH value of the preparation is adjusted to a level between 3.2 and 4.5.

10. A pharmaceutical preparation according to one of claims 5 to 9, characterised in that the active substance is Flunisolide or Budesonide.

11. A pharmaceutical preparation according to one of claims 1 to 6, characterised in that the active substance is Tiotropium or an acid addition salt thereof.

12. A pharmaceutical preparation according to one of claims 1 to 6, characterised in that the active substance is 3-[(hydroxydi-2-thienylacetyl)oxy]-8,8-dimethyl-8-azoniabicyclo[3,2,1]oct-6-ene or an acid addition salt thereof.

13. A pharmaceutical preparation for use in producing a propellant-free metering aerosol containing, per 100 ml of 96% (v/v) ethanol, 1.667 g of Flunisolide hemihydrate and 1 mg of disodium EDTA, the pH value of the pharmaceutical preparation being adjusted to 4.0.

14. A pharmaceutical preparation for use in producing a propellant-free metering aerosol containing, per 100 ml of 90% (v/v) ethanol, 1.667 g of Flunisolide hemihydrate and 1 mg of disodium EDTA, the pH value of the pharmaceutical preparation being adjusted to 4.0.

15. A pharmaceutical preparation for use in producing a propellant-free metering aerosol containing, per 100 ml

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of 96% (v/v) ethanol, 1.333 g of Budesonide and 1 mg of disodium EDTA, the pH value of the pharmaceutical preparation being adjusted to 4.0.

16. A pharmaceutical preparation for use in producing a propellant-free metering aerosol containing, per 100 ml of 90% (v/v) ethanol, 1.333 g of Budesonide and 1 mg of disodium EDTA, the pH value of the pharmaceutical preparation being adjusted to 4.0.

17. Use of a pharmaceutical preparation comprising a pharmacologically active substance in a solution containing at least 79% ethanol by volume in the preparation of a propellant-free composition for administration by inhalation.

18. Use of a pharmaceutical preparation as defined in one of claims 1 to 16 as a propellant-free composition for administration by inhalation.

19. A process for preparing a pharmaceutical preparation as defined in claim 1 which comprises dissolution of a pharmacologically active substance in at least 70% v/v.

20. A delivery system for a pharmacologically active substance which comprises a preparation as defined in any one of claims 1 to 16 in combination with a propellant-free nebuliser.

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