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(54) Titre : NOUVELLES COMPOSITIONS MEDICAMENTEUSES STABLES UTILES POUR GENERER DES AEROSOLS SANS GAZ PROPULSEURS

(54) Title: NEW STABLE PHARMACEUTICAL PREPARATION FOR PRODUCING PROPELLANT-FREE AEROSOLS

(57) Abrégé/Abstract:
Ethanol-containing medicinal compositions are disclosed for generating propellant-free aerosols.

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(54) Bezeichnung: NEUE STABILE ARZNEIMITTELZUBEREITUNG ZUR ERZEUGUNG TREIBGASFREIER AEROSOLE

(57) Abstract

Ethanol-containing medicinal compositions are disclosed for generating propellant-free aerosols.

(57) Zusammenfassung

Die Erfindung betrifft ethanolhaltige Arzneimittelzubereitungen zur Erzeugung von treibgasfreien Aerosolen.

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New stable pharmaceutical preparation for producing propellant-free aerosols

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

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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

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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™
Fluocortin butyl™
Deflazacort™
Ciclometasone™
Prednicarbate™
Tixocortol pivalate™
Lotrisone™
Deprodone™
Methylprednisolone-Aceponate
Mometasone™
Hydrocortisone aceponate
Ulobetasol propionate
Triamcinolone™
Meprednisone™
Dexamethasone™
Medrysone™
Fluocinolone acetonide
Deprodone Propionate
Fluocinonide™
Difluprednate™
Dexamethasonisonicotinate™
Fluocortoloncapronate™
Triamcinolon hexacetonide
Formebolone™
Endrisone™
Halcinonide™
Clobetasol™
Diflorasone™
Amcinonide™
Cortivazol™
Fluodexan™
Budesonide™
Demetex™

Cloprednol™
Halometasone™
Alclometasone™
Alisactide™
Hydrocortisone butyrate
Alclometasone dipropionate
Canesten-HC™
Fluticasone propionate
Halopredone acetate

Mometasone furoate
Mometasone™
Aminoglutethimide™
Hydrocortisone™
Fluorometholone™
Betamethasone™
Fluclorolone acetonide
Paramethasone acetate
Aristocort diacetate
Mazipredone™
Betamethasone valerate
Beclomethasone dipropionate
Formocortal™
Cloprednol™
Clobetason™
Flunisolide™
Fluazacort™
Hydrocortisone-17-butyrate
Flucortin™
Betamethasone dipropionate
Betamethasone adamantoate
Triiostane™
Clobetasone™
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

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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 producing propellent gas-free inhalable aerosols for administering into the lungs in the form of a solution of active substance, wherein one or more active substance selected from among a betamimetic, an anticholinergic, an antiallergic, a PAF-antagonist, and a steroid, in an amount of 0.001 to 5.0 percent by weight, is dissolved in a solvent free from propellent gas which consists of at least 70 percent by volume of ethanol, the remainder being water.

2. The pharmaceutical preparation according to claim 1, wherein the one or more active substance together with a flavouring is dissolved in the solvent.

3. The pharmaceutical preparation according to claim 1, wherein the one or more active substance together with a flavouring and a pharmacologically acceptable carrier is dissolved in the solvent.

4. The pharmaceutical composition according to claim 1, wherein the one or more active substance together with a pharmacologically acceptable carrier is dissolved in the solvent.

5. The pharmaceutical preparation according to any one of claims 1 to 4, wherein the solvent consists of 70 percent by volume of ethanol, the remainder being water and cosolvents.

6. The pharmaceutical preparation according to any one of claims 1 to 5, wherein the active substance is selected from among a betamimetic, an anticholinergic and an antiallergic.

7. The pharmaceutical preparation according to any one of claims 1 to 6, wherein the solvent consists of at least 85 percent by volume of ethanol.

8. The pharmaceutical preparation according to any one of claims 1 to 7, wherein the solvent consists of at least 95 percent by volume of ethanol.

9. The pharmaceutical preparation according to any one of claims 1 to 8, wherein the solvent contains, in addition to the active substance, one or more pharmacologically acceptable adjuvants.

10. The pharmaceutical preparation according to any one of claims 1 to 7, wherein the solvent contains at least 85% by volume of ethanol and the pharmaceutical preparation contains a complexing agent.

11. The pharmaceutical preparation according to claim 10, wherein the solvent contains at least 96% by volume of ethanol and the complexing agent is EDTA or a salt thereof.

12. The pharmaceutical preparation according to any one of claims 1 to 11, wherein the active substance is tiotropium bromide or an acid addition salt thereof.

13. The pharmaceutical preparation according to any one of claims 1 to 11, wherein 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.

14. The pharmaceutical preparation according to any one of claims 1 to 9, wherein the active substance is ipratropium bromide, oxitropium bromide or trospium chloride.

15. The pharmaceutical preparation according to any one of claims 1, 2, 3, 4, 5, 7, 8 or 9, wherein the active substance is a steroid and the pharmaceutical preparation contains an organic or inorganic acid.

16. The pharmaceutical preparation according to claim 15, wherein the solvent contains at least 96% by volume of ethanol.

17. The pharmaceutical preparation according to claim 15 or 16, wherein the pharmaceutical preparation contains a complexing agent.

18. The pharmaceutical preparation according to claim 17, wherein the complexing agent is EDTA or a salt thereof.

19. The pharmaceutical preparation according to claim 17 or 18, wherein the quantity of complexing agent is between 0.1 and 5 mg/100 ml of solvent.

20. The pharmaceutical preparation according to any one of claims 15 to 19, wherein the pH of the solution is adjusted to between 3.2 and 4.5.

21. The pharmaceutical preparation according to any one of claims 15 to 20, wherein the active substance is flunisolide or budesonide.

22. A pharmaceutical preparation for producing propellent gas-free inhalable aerosols in the form of a solution of active substance which contains as solvent 96 percent by volume of ethanol and 4 percent by volume of water, and which contains, per 100 ml of solvent, 1.667 g of flunisolide-hemihydrate and 1 mg of disodium EDTA and the pH of which is adjusted to 4.0.

23. A pharmaceutical preparation for producing propellent gas-free inhalable aerosols in the form of a solution of active substance which contains as solvent 90 percent by volume of ethanol and 10 percent by volume of water, and which contains, per 100 ml of solvent, 1.667 g of flunisolide-hemihydrate and 1 mg of disodium EDTA and the pH of which is adjusted to 4.0.

24. A pharmaceutical preparation for producing propellent gas-free inhalable aerosols in the form of a solution of active substance and a solvent, the solvent of which consists of 96 percent by volume of ethanol and 4 percent by volume of water, and which contains, per 100 ml of solvent, 1.333 g of budesonide and 1 mg of disodium EDTA and the pH of which is adjusted to 4.0.

25. A pharmaceutical preparation for producing propellent gas-free inhalable aerosols in the form of a solution of active substance and a solvent, the solvent of which consists of 90 percent by volume of ethanol and 10 percent by volume of water, and which contains, per 100 ml of solvent, 1.333 g of budesonide and 1 mg of disodium EDTA and the pH of which is adjusted to 4.0.

26. Use of a pharmaceutical preparation according to any one of claims 1 to 25, for directly producing a propellent gas-free inhalable aerosol for pulmonary application.

27. Use of a pharmaceutical preparation according to any one of claims 11 to 25, for pulmonary application.

28. Use according to claim 26 or 27, wherein the pharmaceutical preparation is used in an inhaler which nebulises the solution under high pressure in two jets, squirted out through two small nozzle openings, thereby

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generating an inhalable propellent gas-free aerosol with particle sizes from 1 to 10 microns.

29. Aerosol consisting of inhalable particles, with sizes from 1 to 10 microns, which is produced by nebulising a pharmaceutical preparation according to any one of claims 1 to 25, through an inhaler which nebulises the solution under high pressure in two jets squirted out through two small nozzle openings.

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