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**New aqueous pharmaceutical preparation for the production of propellant-free aerosol**

The present invention relates to pharmaceutical preparations in the form of aqueous solutions for the production of propellant-free aerosols.

In the last 20 years, the use of dosage aerosols has become a strong part of the therapy of obstructive lung diseases, especially asthma. Usually, fluorochlorohydrocarbons are used as propellant gases. Following the recognition of the ozone damaging potential of these propellant gases, attempts to develop alternatives have increased. One alternative is the development of nebulisers, where aqueous solutions of pharmacologically active substance are sprayed under high pressure so that a mist of inhalable particles results. The advantage of these nebulisers is that they completely dispense with the use of propellant gases.

Such nebulisers are, for example, described in PCT Patent Application WO91/14468, herein incorporated by reference. With the nebulisers described here, active ingredients solutions in defined volumes are sprayed through small jets under high pressure, so that inhalable aerosols with a mean particle size of between 3 and 10 micrometers result. A further developed embodiment of the aforementioned nebuliser is described in PCT/EP96/04351. The nebuliser portrayed in Figure 6 carries the trade mark Respimat®.

Usually, pharmaceuticals intended for inhalation are dissolved in an aqueous or ethanolic solution, and according to the solution characteristics of the active

substances, solvent mixtures of water and ethanol may also be suitable.

Other components of the solvent are, apart from water and/or ethanol, optionally other cosolvents, and also the pharmaceutical preparation may also additionally contain flavourings and other pharmacological additives. Examples of cosolvents are those which contain hydroxyl groups or other polar groups, for example alcohols - especially isopropylalcohol, glycols - especially propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. Cosolvents are suitable for increasing the solubility of adjuvant materials and, if necessary, active ingredients.

The proportion of dissolved pharmaceutical in the finished pharmaceutical preparation is between 0.001 and 30% - preferably between 0.05 and 3%, especially 0.01 to 2%. The maximum concentration of pharmaceutical is dependent on the solubility in solvent and on the dosage required to achieve the desired therapeutical effect.

All substances which are suitable for application by inhalation and which are soluble in the specified solvent can be used as pharmaceuticals in the new preparations. Pharmaceuticals for the treatment of diseases of the respiratory passages are of especial interest. Therefore, of especial interest are betamimetics, anticholinergics, antiallergics, antihistamines and steroids, as well as combinations of these active ingredients.

It was found, in a series of examinations, that the nebuliser described above can feature spraying anomalies when using aqueous pharmaceutical solutions. These

spraying anomalies represent an alteration of the spraying pattern of the aerosol, with the consequence that in extreme cases an exact dose can no longer be guaranteed to the patient as a result of the altered mean droplet size distribution (alteration to the lung accessible part of the aerosol). These spraying anomalies especially occur when the nebuliser is used at intervals, for example with breaks of approximately 3 or more days between utilisation. It is possible that these spraying anomalies, which in extreme cases can lead to a dysfunction of the nebuliser, are as a result of microscopic deposits in the area of the jet opening.

Surprisingly, it was discovered that these spraying anomalies no longer occur when the aqueous pharmaceutical preparations which are to be sprayed contain a defined effective quantity of a complexing agent, especially of EDTA (ethylenediamine tetraacetic acid) or salts thereof. The aqueous pharmaceutical preparations according to the invention contain water as a solvent, but if necessary ethanol can be added to increase the solubility up to 70% (by volume), preferably between 30 and 60% (by volume).

Other pharmacological adjuvants such as preservatives, especially benzalkonium chloride, can be added. The preferred quantity of preservative, especially benzalkonium chloride, is between 8 and 12 mg/100 ml solution.

Suitable complexing agents are those which are pharmacologically acceptable, especially those which are already approved by medical regulating authorities. EDTA, nitrilotriacetic acid, citric acid and ascorbic acid and their salts are especially suitable. The disodium salt of ethylenediamtetraacetic acid is especially preferred.

The quantity of complexing agent is selected so that an effective quantity of complexing agent is added to prevent further occurrence of spraying anomalies.

The effective quantity of the complexing agent Na-EDTA is between 10 and 1000 mg/100 ml solution. The preferred range of the quantity of complexing agent is between 25 and 100 mg/100 ml solution.

The following named compounds can principally be used as active ingredients, singly or in combination, in the aqueous pharmaceutical preparation according to the invention. In individual cases, it may be required to add a higher quantity of ethanol or a solution mediator to improve solubility.

Tiotropium bromide, 3-[(hydroxydi-2-thienylacetyl)oxy]-8,8-dimethyl-8-azoniabicyclo[3.2.1]oct-6-ene-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-fluoroethylene nortropine benzylate methobromide

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

As antiallergics:
Disodium cromoglycate
Nedocromil
Epinastine

Examples of steroids which can be used as active ingredients in the pharmaceutical preparations according to the invention:

| | |
|---|---|
| Seratrodast | Mycophenolate mofetil |
| Pranlukast | Zileutone |
| Butixocort | Budesonide |
| Deflazacort | |
| Fluticasone | Promedrol |
| Mometasone furoate | Tipredane |
| Beclomethasone, Douglas | Icomethasone enbutate |
| Ciclometasone | Cloprednol |
| Fluocortin butyl | Halometasone |
| Deflazacort | Alclometasone |
| Ciclometasone | Alisactide |
| Prednicarbate | Hydrocortisone-butyrate propionate |
| Tixocortol-pivalate | Alclometasone-dipropionate |
| Lotrisone | Canesten-HC |
| Deprodone | Fluticasone-propionate |
| Methylprednisolone- | Halopredone-acetate |

Aceponate

| | |
|---|---|
| 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 |
| Dexamethasone isonicotinate | Beclomethasone-Dipropionate |
| Fluocortolone capronate | Formocortal |
| Triamcinolone-Hexacetonide | Cloprednol |
| Formebolone | Clobetasone |
| Endrisone | Flunisolide |
| Halcinonide | Fluazacort |
| Clobetasol | Hydrocortisone-17-Butyrate |
| Diflorasone | Fluocortin |
| Amcinonide | Betamethasone Dipropionate |
| Cortivazol | Betamethasone adamantoate |
| Fluodexane | Trilostane |
| Budesonide | Clobetasone |
| Demetex | Trimacinolon Benetonide |

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

Other especially suitable active ingredients for the production of aqueous pharmaceutical preparations for applications by inhalation are:

β-Sympatico-mimetics;
e.g. Fenoterol, Salbutamol, Formoterol, Terbutalin;
Anticholinergics;

e.g. Ipatropium, Oxitropium, Thiotropium;
Steroids;
e.g. Beclomethasone dipropionate, Budesonide, Flunisolide;
Peptides;
e.g. insulin;
Pain killers;
e.g. Fentanyl.

In the following text, the advantage of the pharmaceutical preparation according to the invention will be explained more clearly with Examples.

As a pharmaceutical solution, Ipratropium bromide solution (c = 333 mg/100 ml) with a pH value of 3.4, and the preservative benzalkonium chloride (c = 10 mg/100 ml) was used. The tested solutions either contained no EDTA or EDTA in a concentration of c = 0.1 mg, 1 mg, 50 mg and 75 mg/100 ml as a disodium salt.

Unused Respimat® nebulisers were used for the test (technical data: volumes of the applied pharmaceutical preparation approximately 15 µl, pressure approximately 300 bar, 2 streams impacting from two jet openings of size 5 x 8 µm). The operation mode for the test is set so that the units are used 5 times, are left to stand for 3 days, and then are used again 5 times, this pattern being repeated. 15 units were examined in each series of measurements, the results with regard to spray anomalies are shown in Table 1.

Table 1

| Test No. | Concentration of EDTA in mg/100 ml | Number of nebulisers with spray anomalies | Duration of test in days |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 1 | 0 mg/100 ml | 2 | 20 |
| 2 | 0 mg/100 ml | 5 | 9 |
| 3 | 0.1 mg/100 ml | 5 | 6 |
| 4 | 1 mg/100 ml | 6 | 6 |
| 5 | 50 mg/100 ml | 0 | 200 |
| 6 | 50 mg/100 ml | 0 | 200 |
| 7 | 75 mg/100 ml | 0 | 200 |
| 8 | 75 mg/100 ml | 0 | 200 |

Formulation Examples (for Fenoterol and Ipatropium bromide)

| **Components** | **Composition in mg/100 ml** |
|---|---|
| Fenoterol | 833.3 mg |
| Benzalkonium chloride | 10.0 mg |
| EDTA* | 50.0 mg |
| HCl (1n) | ad pH 3.2 |

| **Components** | **Composition in mg/100 ml** |
|---|---|
| Ipatropium bromide | 333.3 mg |
| Benzalkonium chloride | 10.0 mg |
| EDTA* | 50.0 mg |
| HCl (1n) | ad pH 3.4 |

In analogy to the above Examples, the following solutions were produced.

| Active ingredient | Concentration mg/100 ml | Benzalkonium chloride | EDTA* | Solvent |
|---|---|---|---|---|
| Berotec | 104-1.667 | 10 mg | 50 mg | Water |
| Atrovent | 83-1.333 | 10 mg | 50 mg | Water |
| Berodual (Atrovent) | 41-667 | 10 mg | 50 mg | Water |

| | | | | |
|---|---|---|---|---|
| (Berotec) | 104-1.667 | 10 mg | 50 mg | Water |
| Salbutamol | 104-1.667 | 10 mg | 50 mg | Water |
| Combivent<br>(Atrovent)<br>(Salbutamol) | <br>167-667<br>833-1.667 | <br>10 mg<br>10 mg | <br>50 mg<br>50 mg | <br>Water<br>Water |
| Ba 679 Br | 4-667 | 10 mg | 50 mg | Water |
| BEA 2108 Br | 17-833 | 10 mg | 50 mg | Water |
| Oxivent | 416-1.667 | 10 mg | 50 mg | Water |

* In the form of the disodium salt

A concentration range from 10 mg to 20,000 mg/100 ml is conceivable for the active ingredients, depending on the dose per operation and their solubility. The specified doses are calculated based on a therapeutically effective single dose of approximately 12 microlitres per operation. The active ingredient concentrations of the pharmaceutical preparations can alter when the volume of the individual dose is altered.

The concentration range for the complexing agents (for example DiNa-EDTA) is between 10 and 1000 mg/100 ml (dependent on the pH value of the solution). The preferred range is between 25 mg and 100 mg/100 ml.

The quantity of benzalkonium chloride should be in the range of 8 to 12 mg/100 ml.

The solutions are set to a pH of 3.2 to 3.4 with 0.1 or 1N HCl. All concentrations relate to 100 ml of finished active ingredient solution.

* C L M S *

**Claims**

1. An aqueous pharmaceutical preparation in the form of a solution for the production of propellant-free aerosols comprising a pharmacologically active ingredient, characterised in that the pharmaceutical preparation contains a complexing agent.

2. A pharmaceutical preparation according to claim 1, characterised in that the active ingredient is intended for application by inhalation, especially for the treatment of respiratory passage diseases.

3. A pharmaceutical preparation according to claim 2, characterised in that the active ingredient is selected from the group betamimetics, anticholinergics, antiallergics and/or antihistamines.

4. A pharmaceutical preparation according to claims 1, 2 or 3, characterised in that the active ingredient is selected from the group

Fenotrol, Ipatropium bromide, Berotec, Atrovent, Berodual, Salbutamol, Combivent, Ba 679 Br, BEA 2108 Br, Oxivent.

5. A pharmaceutical preparation according to any one of claims 1 to 4, characterised in that the complexing agent is nitrilotriacetic acid, citric acid, ascorbic acid or salts thereof.

6. A pharmaceutical preparation according to any one of claims 1 to 4, characterised in that the complexing agent is EDTA or a salt thereof.

7. A pharmaceutical preparation according to any one of claims 1 to 6, characterised in that the concentration of

the complexing agent is between 10 and 1000 mg/100 ml solution.

8. A pharmaceutical preparation according to claim 7 characterised in that the concentration of the complex former is between 25 and 100 mg/100 ml solution, preferably 50 mg.

9. A pharmaceutical preparation according to one of claims 1 to 8, characterised in that the adjuvant is a preservative.

10. A pharmaceutical preparation according to claim 9, characterised in that the preservative is Benzalkonium chloride.

11. A pharmaceutical preparation according to any one of the previous claims, characterised in that the pharmaceutical preparation contains up to 70% (by volume) ethanol.

12. A pharmaceutical preparation according to one of the previous claims, characterised in that it contains the active ingredient in a concentration of 0.001 to 2 g/100 ml solution.

13. A pharmaceutical preparation according to any one of the previous claims, characterised in that it contains pharmacologically acceptable adjuvant and flavouring substances.