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(54) **SUSPENSION AEROSOL FORMULATIONS OF PHARMACEUTICAL PRODUCTS**

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(57) **ABSTRACT**

Pharmaceutical preparations for producing powder aerosols using propellant gases which use TG 227, and possibly also TG 11, TG 12, TGH 114, propane, butane, pentane or DME.

SUSPENSION AEROSOL FORMULATIONS OF PHARMACEUTICAL PRODUCTS

[0001] The invention relates to new propellent gases which contain as a typical ingredient 1,1,1,3,3,3,3-heptafluoropropane (TG 227), the use of these propellent gases in pharmaceutical preparations suitable for producing aerosols, and these pharmaceutical preparations themselves.

[0002] Aerosols of powdered (micronised) drugs are used widely in therapy, e.g. in the treatment of obstructive diseases of the respiratory tract. If such aerosols are not produced by atomizing the pharmaceutical powder or by spraying solutions, suspensions of the drugs in liquefied propellent gases are used. The latter consist primarily of mixtures of TG 11 (trichlorofluoromethane), TG 12 (dichlorodifluoromethane) and TG114 (1,2-dichloro-1,1,2,2-tetrafluoroethane), optionally with the addition of lower alkanes such as butane or pentane, or with the addition of DME (dimethylether). Mixtures of this kind are knows for example from German Patent 11178975.

[0003] Owing to their harmful effect on the earth's atmosphere (destruction of the ozone layer, Greenhouse effect) the use of chlorofluorocarbons has become a problem, with the result that the search is on for other propellent gases or propellent gas mixtures which do not have the above-mentioned harmful effects or, at least, have them to a lesser degree.

[0004] However, this search has come up against major problems, since propellent gases for therapeutic use have to satisfy numerous criteria which cannot easily be reconciled, e.g. in terms of toxicity, stability, vapour pressure, density and solubility characteristics.

[0005] As has now been found, TG 227 (1,1,1,2,3,3,3-heptafluoropropane, optionally in admixture with one of more propellent gases from the group comprising TG 11 (trichlorofluoromethane), TG 12 (dichlorodifluoromethane), TG 114 (1,2-dichloro-1,1,2,2-Tetrafluoroethane), propane, butane, pentane, and DME (dimethylether) is particularly suitable for use in therapeutic preparations.

[0006] The compounds to be used in addition to TG 227 are added if the properties of the propellent gas are to be modified, e.g. if the liquefied propellent gas is to have a different density, different pressure or different solubility characteristics. Pharmaceutical preparations based on the propellent gas contain an active substance in finely divided form, usually as a suspension, and generally also contain surface-active substances, e.g. a phospholipids (such as lecithin), an ester of a polyalcohol (such as sorbitol) with higher saturated or unsaturated fatty acids (e.g. stearic, palmitic or oleic acid), such as sorbitan trioleate, or a polyethoxysorbitan ester of a higher, preferably unsaturated fatty a acid. The adjuvant may be present in the mixture in dissolved or undissolved form. In some cases, the suspensions produced with the new propellent gas have a tendency to separate out. However, it has been found that the separated suspensions can easily be uniformly distributed again in the suspension medium simply by shaking.

[0007] The ratios of quantities of the individual ingredients of the propellent gas mixtures may be varied within wide limits. The proportion (in percent by weight) is 10 to 100% in the case of TG 227. The mixture may also contain up to 50% propane and/or butane and/or pentane and/or DME and/or RG and/or TG 11 and/or TG 12 and/or 114. Within the limits specified the ingredients are chosen to add up to 100%. Propellent gas mixtures which contain 30 to 100% TG 227 are preferred.

[0008] The proportion of suspended drug in the finished preparation is between 0.001 and 5%, preferably between 0.005 to 3%, more particularly between 0.01 and 2%. The surface-active substances are added in amounts of from 0.01 to 10%, preferably 0.05 to 5%, more particularly 0.1 to 3% (here, as in the case of the pharmaceutical substances, the percentage by weight of the finished preparation is given). The pharmaceutical substances used in the new preparations may be any of the substances suitable for use by inhalation or possibly for intranasal administration. They include, steroids, antiallergics, PAF-antagonists and combinations of these active substances.

[0009] The following are given as specific examples:

Examples of Betamimetics

[0010] Bambuterol
[0011] Bitolterol
[0012] Carbuterol
[0013] Clenbuterol
[0014] Fenoterol
[0015] Hexoprenalin
[0016] Ibuterol
[0017] Pirbuterol
[0018] Procaterol
[0019] Reproterol
[0020] Salbutamol
[0021] Salmeterol
[0022] Sulfonterol
[0023] Terbutalin
[0024] Tulobuterol
[0025] 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol
[0026] erythro-5'-hydroxy-8'-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one
[0027] 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-ter.-butylamino)ethanol
[0028] 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl-2-(tert.-butylamino)ethanol.

Examples of Anticholinergics:

[0029] Ipratropium bromide
[0030] Oxitropium bromide
[0031] Trospium chloride
[0032] Benzilic acid-N-β-fluoroethylnortropine ester
[0033] methobromide

Examples of Steroids:

[0034] Budesonide
[0035] Beclomethasone (or the 17,21-dipropionate thereof)
[0036] Dexamethason-21-isonicotinate
[0037] Flunisolide

Examples of Anti-Allergics:

[0038] Disodium cromoglycate
[0039] Nedocromil

Examples of PAF-Antagonists:

[0040] 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.

[0041] 3-(Morpholin-4-yl-carbonyl)-5-(2-chlorphenyl)-10-methyl-7H-cyclopental[4.5]thieno-[3.2-f][1.2.4]triazolo[4.3-a][1.4]diazepine

[0042] 3-(Di-n-propylamincarbonyl)-5-(2-chlorphenyl)-10-methyl-7H-cyclopental[4.5]thieno-[3.2-f][1.2.4]triazolo[4.3-a][1.4]diazepine

[0043] The active substances may also be combined, e.g., betamimetics plus anticholinergics or betamimetics plus antiallergics.

[0044] Examples of preparations according to the invention (amounts given in percent by weight):

1)	0.10%	Oxitropium bromide
	0.01%	Soya lecithin
	4.0%	Pentane
	95.89%	TG 227
2)	0.3%	Fenoterol
	0.1%	Soyalecithin
	10.0%	Pentane
	70.0%	TG 227
	19.6%	TG 134a
3)	0.1%	Ipratropium bromide
	0.1%	Soya lecithin
	20.0%	Pentane
	20.0%	Butane
	49.8%	TG 11
4)	0.3%	Fenoterol
	0.1%	Soya lecithin
	30.0%	TG 11
	69.6%	TG 227
5)	1.5%	Disodium cromoglicate
	0.1%	Tween 20
	98.4%	TG 227
	1.4%	Butane
6)	0.3%	Salbutamol
	0.2%	Span 85
	20.0%	Pentane
	60.0%	TG 227
	19.5%	TG 12
7)	0.15%	Fenoterol
	0.06%	Ipratropium bromide
	0.10%	Soya lecithin
	40.00%	TG 11
	19.69%	Propane
	40.00%	TG 227
8)	0.1%	Ipratropium bromide
	0.1%	Soya lecithin
	15.3%	Propane
	30.5%	TG 11
	54.0%	TG 227

1. Propellent gases characterised in that they contain TG 227, in admixture with one or more propellent gases from the group comprising TG 11, TG 12, TG 114, propane, butane, pentane and DME.

2. Propellent gases according to claim **1**, characterised in that they additionally contain at least one surface-active substance.

3. Propellent gases according to claim **2**, characterised in that the surface-active substance is a prospholipid, a sorbitan ester with a higher saturated or unsaturated fatty acid or a polyethoxysorbitan ester of a higher, preferably unsaturated fatty acid.

4. Propellent gases according to claim **2**, characterised in that the surface-active substance is a lecithin, a polyethoxyethylenesorbitan oleate or sorbitan trioleate.

5. Pharmaceutical preparations for producing powder aerosols based on propellent gases according to claim **1** characterised in that they contain as active substance a betamimetic, an anticholinergic, a steroid, an antiallergic or a PAF-antagonist or a combination of such compounds.

6. Pharmaceutical preparations according to claim **5**, characterised in that the betamimetic used is selected from the group consisting of Bambuterol, Bitolterol, Carbuterol, Clenbuterol, Fenoterol, Hexoprenalin, Ibuterol, Pirbuterol, Procaterol, Reproterol, Salbutamol, Salmeterol, Sulfonterol, Terbutalin, Tulobuterol, 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.-butylamino)ethanol and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol

the anticholinergic used is selected from the group consisting of Ipratropium bromide, Oxitropium bromide, Trospium chloride, Benzilic acid-N-β-fluoroethylnortropine ester, and methobromide;

the steroid used is selected from the group consisting Budesonide, Beclomethasone or the 17,21-dipropionate thereof, Dexamethason-21-isonicotinate, and Flunisolide;

the antiallergic agent is selected from the group consisting of Disodium cromoglycate and Nedocromil; and

the PAF-antagonist is selected from the group consisting of 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, 3-(Morpholin-4-yl-carbonyl)-5-(2-chlorphenyl)-10-methyl-7H-cyclopental[4.5]thieno-[3.2-f][1.2.4]triazolo[4.3-a][1.4]diazepine, and 3-(Di-n-propylamincarbonyl)-5-(2-chlorophenyl)-10-methyl-7H-cyclopental[4.5]thieno-[3.2-f][2.4]triazolo[4.3-a][1.4]diazepine.

7.-**10**. (canceled)

11. Process for preparing pharmaceutical preparations according to claim **5**, characterised in that pharmaceutically active substances micronised by conventional methods are suspended in a liquefied propellent gas mixture optionally with the addition of surface-active substances.

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