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# Medicinal aerosol formulation

The present invention relates to medicinal aerosol formulations which are free from chlorofluorocarbons.

Medicinal aerosol formulations are suitable especially for buccal, nasal and topical administration. They have gained particular importance e.g. in the administration of bronchodilators via the patients' respiratory system.

In general, medicinal aerosol formulations contain the active ingredient, surface-active substances and a propellant gas liquefied under pressure. They are marketed in a pressurized container, usually made of metal or glass, which is provided with a valve device for discharging the contents. The purpose of the surface-active substances is to create a stable suspension of uniformly distributed, fine particles of active ingredient in the propellant and at the same time to lubricate the valve device.

The propellants used are inert gases liquefied under pressure. Hitherto, medicinal aerosol formulations have generally used mixtures of trichlorofluoromethane (R 11) and dichlorodifluoromethane (R 12) or of dichlorodifluoromethane (R 12) and 1,2-dichlorotetrafluoroethane (R 114), on account of their non-flammability, chemical and physical stability, substantial physiological/-toxicological safety and favorable propellant and solvent properties. The pressures, densities, viscosities and stability of the aerosol formulations could be adjusted to the desired values according to the composition of the mixtures.

Because of their high stability to biotic and abiotic degradation, these chlorofluorocarbons, which are released into the atmosphere, are not prevented from reaching the stratosphere, where they are photolyzed by

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the penetrating solar UV radiation and lose chlorine radicals. These chlorine radicals can react with the ozone in a complex reaction sequence and can thus result in a weakening of the ozone layer, which acts as a protective screen against UV rays. Attempts are therefore being made to find suitable propellants which are incapable of degrading ozone but which nevertheless have the above-mentioned favorable properties of the chlorofluorocarbons used hitherto.

European patent application A-0 384 371 describes aerosol propellants composed of 2-hydroheptafluoropropane liquefied under pressure, or a mixture thereof with propane and/or n-butane and/or i-butane and/or dimethyl ether and/or 1,1-difluoroethane liquefied under pressure. As fields of application for these propellants, there may be mentioned aerosol products which contain only these propellants and are used e.g. for cleaning camera lenses, and aerosol products which contain these propellants together with a filling product, such as an insecticide spray, room spray, deodorant spray, perfume spray, shampoo, shower foam, shaving foam or anti- sunburn foam. In Examples of a body deodorant spray and a perfume spray, the filling product contains ethanol as a solvent for the active ingredients.

In medicinal aerosols, replacement of the chlorofluorocarbons used hitherto is particularly critical. On the one hand, the alternative propellants must be physiologically/toxicologically safe. On the other hand, they should be as similar as possible to the propellants used hitherto, in respect of non-flammability, pressure, density, viscosity, compatibility and stabilization of the active ingredient formulation, so that the previous active ingredient formulations, whose physiological compatibility is proven, can be used unchanged. Furthermore, they must have a good compatibility with the elastomers of the valve devices.

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European patent application A-0 372 777 has disclosed medicinal aerosol formulations in which the propellant used is 1,1,1,2-tetrafluoroethane (R 134a) to which at least one compound of higher polarity than 1,1,1,2-tetrafluoroethane is added. As compounds of higher polarity than 1,1,1,2-tetrafluoroethane, there may be mentioned alcohols such as ethanol, isopropanol and propylene glycol, hydrocarbons such as propane, butanes and pentanes, other propellants selected from the group comprising the chlorofluorocarbons and 1,2-difluoroethane (R 152a), and dimethyl ether. It is indicated that, together with R 134a, these adjuvants give a propellant system which has comparable properties to those of the propellant systems based on chlorofluorocarbons, so that it is possible to use the surface- active substances and additives used hitherto in pharmaceutical formulations, as well as conventional valve components. As regards the effects of the adjuvants, specific reference is made to the possibility of decreasing and increasing the pressure and modifying the density, viscosity and interfacial tension. The use of R 134a on its own, without adjuvants, is described as unsuitable.

The object of the present invention is to provide a medicinal aerosol formulation with an improved propellant system.

To achieve this object, a medicinal aerosol formulation is proposed which contains at least one medicinal active ingredient, at least one surface-active substance and heptafluoropropane liquefied under pressure.

Heptafluoropropane (R 227), which is to be understood as meaning both 2-hydroheptafluoropropane and 1-hydroheptafluoropropane, is surprisingly far more suitable than R 134a as a replacement for the propellant mixtures R 11/12 and R 12/114 frequently used hitherto in medicinal aerosol formulations.

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Thus R 227 has a considerably more favorable vapor pressure profile than R 134a. At 50°C, R 134a has a vapor pressure of 13.2 bar, which is above the 12 bar demanded for compressed gas packs by the Guidelines of the Technical Regulations for Compressed Gases 300. The predominantly used aluminum cans, for example, are permitted for pressures up to 12 bar. For this very reason, R 134a can only be used in combination with pressure-lowering components. By contrast, R 227 has a vapor pressure of 9.2 bar at 50°C, so pressure-lowering components are not needed. Moreover, R 227 has pressure/density profiles which correspond far better to those of the propellant mixtures used hitherto than do the profiles of R 134a. Furthermore, the compatibility with elastomers and the solubilizing action on the surface-active substances which can be used in medicinal aerosols are better in some cases and the stability of the formulations is also better as a result.

This all enables the propellant mixtures used hitherto to be replaced with the non-flammable R 227 without too great a change in the previous medicinal aerosol formulations, so the proven combinations of active ingredients and surface-active substances can be retained.

Compounds of higher polarity than R 227 can be added to the aerosol formulation according to the invention. Suitable compounds are lower hydrocarbons such as propane, butanes and pentanes, aliphatic ethers such as dimethyl ether, and aliphatic alcohols. It is preferable to use monohydric alcohols with a low boiling point and high volatility. Ethanol and isopropanol are particularly preferred.

These compounds are added if the pressure has to be reduced. Because, for reasons of cost, aluminum cans are sometimes replaced with tin-plate cans, for which the

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permitted pressure is restricted to 8 bar at 50°C, it is necessary to lower the pressure. However, it is preferable to add these compounds even if it is not necessary to lower the pressure. They serve as solubilizers for the solubility of surface-active substances in R 227 or mixtures thereof with other propellants, so the stability of the formulations can frequently be increased as well.

The weight ratio of R 227 to the compound of higher polarity is chosen so that the pressure in the pressurized container holding the aerosol formulation preferably does not fall below 3 bar at room temperature. When using alcohols, especially ethanol and isopropanol, the weight ratio of R 227 to alcohol is at least 70:30. The weight ratio is particularly preferably in the range from 85:15 to 96:4.

The aerosol formulation according to the invention can contain another propellant apart from R 227. Suitable propellants are especially fluorocarbons selected from the group $C_aH_bF_c$, in which b + c = 2a + 2, a is 1 to 3, b is 0 to 4 and c is 2 to 8. Examples of particularly suitable propellants from this group are difluoromethane (R 32), pentafluoroethane (R 125), 1,1,2,2-tetrafluoroethane (R 134), 1,1,2-trifluoroethane (R 143), 1,1,1-trifluoroethane (R 143a), 1,1-difluoroethane (R 152a), octafluoropropane (R 218), hexafluoropropane (R 236) and pentafluoropropane (R 245). These propellants can be added in any desired amounts provided the vapor pressure and density profiles of R 227, or R 227 in combination with the above-mentioned compounds of higher polarity than R 227, remain substantially unchanged. The aerosol formulation according to the invention preferably contains 50 to 95% by weight of heptafluoropropane.

As medicinal active ingredients, the aerosol formulations according to the invention can contain e.g. betamimetics,

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steroids, cromoglycates, nedocromil, anticholinergics, antihistamines, potassium channel openers, e.g. of the chroman type, receptor antagonists, e.g. bradykinin antagonists, and chloride channel modulators, e.g. furosemide. The content of the medicinal active ingredient in the aerosol formulation according to the invention is generally in the range from 0.01 to 5% by weight, preferably in the range from 2 to 5% by weight. The particle size of the active ingredients is generally less than 20 μm and should be as small as possible, preferably less than 6 μm.

As surface-active substances, the aerosol formulations according to the invention contain those which are toxicologically safe. Purely by way of example, reference is made to some of the conventional substances which are suitable, such as polyoxyethylene sorbitan fatty acid esters, e.g. polyoxyethylene(20) sorbitan monolaurate and polyoxyethylene(20) sorbitan monooleate, sorbitan fatty acid esters, e.g. sorbitan trioleate, glycerol fatty acid esters, oleic acid, polyalkylene glycol based on ethylene oxide and propylene oxide, quaternary ammonium compounds of the alkylbenzyldimethylammonium chloride type with $C_8H_{17}$ to $C_{18}H_{37}$ alkyl radicals, and lecithins, e.g. the lecithin Epikuron. The content of surface-active substances in the aerosol formulations according to the invention is conventionally up to 5% by weight. The amount depends on the surface-active substance, the particular active ingredient and the particular amount of active ingredient in the formulation.

The invention is illustrated in greater detail with the aid of the Figures and Examples.

Figure 1 shows the density as a function of the temperature for two chlorofluorocarbon mixtures, R 11/12 and R 12/114, used hitherto in medicinal aerosol formulations, for R 134a and for the R 227 used according

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to the invention;
Figure 2 shows the gas pressure as a function of the temperature for the same gases or gas mixtures as in Figure 1, liquefied under pressure, and also for R 12;
Figure 3 shows the pressure as a function of the mixing ratio of ethanol and R 134a liquefied under pressure, at 20°C and 50°C;
Figure 4 shows the pressure as a function of the mixing ratio of ethanol and the R 227 used according to the invention, liquefied under pressure, at 20°C and 50°C;
Figure 5 shows the pressure as a function of the mixing ratio of isopropanol and R 134a liquefied under pressure, at 20°C and 50°C; and
Figure 6 shows the pressure as a function of the mixing ratio of isopropanol and the R 227 used according to the invention, liquefied under pressure, at 20°C and 50°C.

2-Hydroheptafluoropropane was used in each case as R 227 in the measurements of the curves shown in the Figures, and in the Examples.

Figures 1 and 2 show that the profiles of the pressure/density curves of R 227 correspond far better to those of the chlorofluorocarbon mixtures used hitherto than do the profiles of R 134a.

Example 1

The compatibility of R 134a and R 227 with elastomers was studied by cold extraction according to DIN 8944. The results are collated in Table 1 below.

Table 1

| Polymer | R 134a | | R 227 | |
|---|---|---|---|---|
| | Change in weight (%) | Change in length (%) | Change in weight (%) | Change in length (%) |
| Butyl rubber | -1.1 | 0 | -0.6 | 0 |
| Acrylonitrile/ butadiene rubber | -0.4 | 0 | -0.2 | 0 |

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| | | | | |
|---|---|---|---|---|
| Chloroprene rubber | -0.6 | 0 | -0.4 | 0 |
| Fluorinated rubber | 7.3 | 10.8 | 2.3 | 0.5 |
| Natural rubber | -0.6 | 0 | -0.4 | 0 |
| Polyamide | 0 | 0.1 | 0 | 0.16 |

These values show that the compatibility of R 227 with elastomers is for the most part better than that of R 134a.

Example 2

Either ethanol (99.8%) or isopropanol was weighed into 175 ml aluminum cans, the evacuated cans were closed by means of the appropriate precision valve and R 134a or R 227 was introduced in varying amounts under pressure so as to produce different mixing ratios of alcohol to R 134a and alcohol to R 227. The excess pressure was always measured after storage for 1 h at temperatures of 20°C and 50°C. The results are collated in Tables 2 to 5 below and shown as curves in Figures 3 to 6. The Tables also indicate the measured densities.

Table 2

| Ethanol % by weight | R 134a % by weight | Excess pressure (bar) at 20°C | Density (kg/l) | Excess pressure (bar) at 50°C | Density (kg/l) |
|---|---|---|---|---|---|
| 0 | 100 | 4.7 | 1.226 | 12.2 | 1.103 |
| 10 | 90 | 4.3 | 1.182 | 10.9 | 1.069 |
| 20 | 80 | 4.2 | 1.139 | 10.4 | 1.035 |
| 30 | 70 | 4.0 | 1.095 | 9.8 | 1.001 |
| 40 | 60 | 3.7 | 1.051 | 8.8 | 0.967 |
| 50 | 50 | 3.4 | 1.008 | 7.8 | 0.933 |
| 60 | 40 | 3.0 | 0.964 | 6.8 | 0.899 |
| 70 | 30 | 2.4 | 0.920 | 5.5 | 0.865 |
| 80 | 20 | 1.3 | 0.876 | 3.7 | 0.831 |
| 90 | 10 | 0.3 | 0.833 | 2.0 | 0.797 |
| 100 | 0 | 0 | 0.789 | 0 | 0.763 |

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Table 3

| Ethanol % by weight | R 227 % by weight | Excess pressure (bar) at 20°C | Density (kg/l) at 20°C | Excess pressure (bar) at 50°C | Density (kg/l) at 50°C |
|---|---|---|---|---|---|
| 0 | 100 | 3.4 | 1.417 | 8.1 | 1.265 |
| 10 | 90 | 3.0 | 1.354 | 7.1 | 1.215 |
| 20 | 80 | 2.8 | 1.291 | 6.5 | 1.165 |
| 30 | 70 | 2.5 | 1.229 | 5.9 | 1.114 |
| 40 | 60 | 2.2 | 1.166 | 5.2 | 1.064 |
| 50 | 50 | 1.9 | 1.103 | 4.2 | 1.014 |
| 60 | 40 | 1.4 | 1.040 | 3.3 | 0.964 |
| 70 | 30 | 0.9 | 0.977 | 2.4 | 0.914 |
| 80 | 20 | 0.5 | 0.915 | 1.6 | 0.863 |
| 90 | 10 | 0.1 | 0.852 | 0.7 | 0.813 |
| 100 | 0 | 0 | 0.789 | 0 | 0.763 |

Table 4

| Isopropanol % by weight | R 134a % by weight | Excess pressure (bar) at 20°C | Density (kg/l) at 20°C | Excess pressure (bar) at 50°C | Density (kg/l) at 50°C |
|---|---|---|---|---|---|
| 0 | 100 | 4.7 | 1.226 | 12.2 | 1.103 |
| 10 | 90 | 4.7 | 1.182 | 10.3 | 1.069 |
| 20 | 80 | 4.7 | 1.138 | 9.9 | 1.034 |
| 30 | 70 | 4.5 | 1.094 | 9.4 | 1.000 |
| 40 | 60 | 4.0 | 1.050 | 7.9 | 0.966 |
| 50 | 50 | 4.2 | 1.006 | 7.9 | 0.932 |
| 60 | 40 | 3.7 | 0.961 | 6.8 | 0.897 |
| 70 | 30 | 2.5 | 0.917 | 4.9 | 0.863 |
| 80 | 20 | 1.7 | 0.873 | 3.5 | 0.829 |
| 90 | 10 | 0.7 | 0.829 | 1.8 | 0.794 |
| 100 | 0 | 0 | 0.785 | 0 | 0.760 |

Table 5

| Isopropanol % by weight | R 227 % by weight | Excess pressure (bar) at 20°C | Density (kg/l) at 20°C | Excess pressure (bar) at 50°C | Density (kg/l) at 50°C |
|---|---|---|---|---|---|
| 0 | 100 | 3.4 | 1.417 | 8.1 | 1.265 |
| 10 | 90 | 3.0 | 1.354 | 7.1 | 1.222 |
| 20 | 80 | 2.2 | 1.291 | 5.1 | 1.165 |
| 30 | 70 | 2.0 | 1.227 | 4.6 | 1.114 |
| 40 | 60 | 1.8 | 1.164 | 4.2 | 1.063 |
| 50 | 50 | 1.4 | 1.101 | 3.4 | 1.013 |
| 60 | 40 | 1.1 | 1.038 | 2.8 | 0.962 |
| 70 | 30 | 0.5 | 0.975 | 1.8 | 0.912 |
| 80 | 20 | 0.2 | 0.911 | 1.2 | 0.861 |
| 90 | 10 | 0 | 0.848 | 0.6 | 0.811 |
| 100 | 0 | 0 | 0.785 | 0 | 0.760 |

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As can be seen from the pressure values in the above Tables and Figures 3 to 5, R 227 is suitable for aluminum cans (up to 12 bar) even without additives. If small amounts of alcohol are added, a pressure is attained which permits use in tin-plate cans. By contrast, R 134a cannot be used without additives. For use in tin-plate cans, large amounts of alcohols have to be added.

Example 3

Different amounts of the surface-active substances indicated below were weighed with an analytical balance into 80 ml glass aerosol bottles according to the desired mixing ratio and the bottles were closed with the appropriate AR valves (Deutsche Aerosol-Ventil GmbH) so as to prevent diffusion. R 134a or R 227 was introduced into the glass bottles under pressure with the aid of an adapter, the weight being monitored. The mixtures were then shaken for 30 min, then left to stand undisturbed for 12 h at room temperature and then tested and accordingly assessed for any separation of the surface-active substances. The results are collated in Table 6. The following surface-active substances were studied:

SS 1 Polyoxyethylene(20) sorbitan monolaurate (Tween 20®)
SS 2 Polyoxyethylene(20) sorbitan monooleate (Tween 80®)
SS 3 Sorbitan trioleate (Span 85®)
SS 4 Glycerol fatty acid ester Arlacel 186®
SS 5 Oleic acid
SS 6 Benzododecinium chloride
SS 7 Epikuron

The tested mixtures were assessed as follows:

| | |
|---|---|
| Precipitation of the surface-active substances in solid form | PS |
| Separation of large drops | +++ |

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| | |
|---|---|
| Separation of small drops | ++ |
| Separation of isolated drops | + |
| No separation | o |

Table 6

| Surface-active substance | Propellant | % by weight of surface-active substance in propellant 0.05 | 0.15 | 0.25 | 0.5 | 0.75 | 1.0 |
|---|---|---|---|---|---|---|---|
| SS 1 | R 134a | o | o | + | ++ | +++ | +++ |
| SS 1 | R 227 | o | o | o | o | o | o |
| SS 2 | R 134a | + | ++ | ++ | ++ | ++ | +++ |
| SS 2 | R 227 | o | o | o | o | + | ++ |
| SS 3 | R 134a | +++ | +++ | +++ | +++ | PS | PS |
| SS 3 | R 227 | + | ++ | ++ | +++ | +++ | PS |
| SS 4 | R 134a | + | ++ | +++ | +++ | PS | PS |
| SS 4 | R 227 | + | + | ++ | +++ | +++ | +++ |
| SS 5 | R 134a | ++ | ++ | +++ | +++ | PS | PS |
| SS 5 | R 227 | + | ++ | ++ | +++ | +++ | +++ |
| SS 6 | R 134a | | | PS | PS | | |
| SS 6 | R 227 | | | ++ | +++ | | |
| SS 7 | R 134a | | | PS | PS | | |
| SS 7 | R 227 | | | + | ++ | | |

These results show that R 227 has a better solubilizing power than R 134a for some surface-active substances conventionally used in medicinal aerosols, and therefore gives more stable aerosol formulations.

Example 4

To make a further study of the aerosol formulations prepared in Example 3 with the surface-active substances SS 1 and SS 2, the corresponding mixtures were stored for a further 12 h at 6°C and 23°C after the initial twelve-hour storage period, and then assessed. The results are collated in Table 7 below.

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Table 7

| Surface-active substance | Propellant | Storage temp. (°C) | % by weight of surface-active substance in propellant 0.05 | 0.15 | 0.25 | 0.5 | 0.75 | 1.0 |
|---|---|---|---|---|---|---|---|---|
| SS 1 | R 134a | 6 | o | o | + | + | ++ | +++ |
| SS 1 | R 134a | 23 | o | o | + | ++ | +++ | +++ |
| SS 1 | R 227 | 6 | o | o | o | o | o | o |
| SS 1 | R 227 | 23 | o | o | o | o | o | o |

Example 5

In this Example, the stability of aerosol formulations containing ethanol in addition to R 227 (weight ratio of R 227 to ethanol 4:1) was tested. To do this, different amounts of some of the surface-active substances defined above were weighed with an analytical balance into 80 ml glass aerosol bottles according to the desired mixing ratio and ethanol was added. The glass bottles were closed with the appropriate AR valves so as to prevent diffusion. R 227 was then introduced into the glass bottles under pressure with the aid of an adapter, the weight being monitored. The mixtures were then shaken for 30 min, left to stand undisturbed for 12 h and then assessed as described in Example 3. The results in Table 8 below show that the solubilizing power for the tested surface-active substances was improved, and the stability therefore increased, by the addition of ethanol.

Table 8

| Surface-active substance | % by weight of surface-active substance in R 227 0.05 | 0.15 | 0.25 | 0.5 | 0.75 | 1.0 |
|---|---|---|---|---|---|---|
| SS 1 | o | o | o | o | o | o |
| SS 2 | o | o | o | o | o | o |
| SS 3 | o | o | o | + | + | + |
| SS 4 | o | o | o | o | o | o |
| SS 5 | o | o | o | o | o | o |

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WHAT IS CLAIMED IS:

1. A medicinal aerosol formulation which contains at least one medicinal active ingredient, at least one surface-active substance and heptafluoropropane liquefied under pressure.

2. The medicinal aerosol formulation as claimed in claim 1, which additionally contains a compound of higher polarity than heptafluoropropane.

3. The medicinal aerosol formulation as claimed in claim 2, wherein the compound of higher polarity than heptafluoropropane is an alcohol.

4. The medicinal aerosol formulation as claimed in claim 3, wherein the alcohol is ethanol.

5. The medicinal aerosol formulation as claimed in claim 3, wherein the alcohol is isopropanol.

6. The medicinal aerosol formulation as claimed in one of claims 2 to 5, wherein the weight ratio of heptafluoropropane to the compound of higher polarity is chosen so that the pressure in the pressurized container holding the aerosol formulation is at least 3 bar at room temperature.

7. The medicinal aerosol formulation as claimed in one of claims 3 to 5, wherein the weight ratio of heptafluoropropane to the alcohol is at least 70:30.

8. The medicinal aerosol formulation as claimed in claim 7, wherein the weight ratio of heptafluoropropane to the alcohol is in the range from 85:15 to 96:4.

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9. The medicinal aerosol formulation as claimed in one of claims 1 to 8, which additionally contains a propellant selected from the group $C_aH_bF_c$, in which b + c = 2a + 2, a is 1 to 3, b is 0 to 4 and c is 2 to 8.

10. The medicinal aerosol formulation as claimed in claim 9, which contains 50 to 95% by weight of heptafluoropropane.

11. The medicinal aerosol formulation as claimed in one of claims 1 to 10, which contains 2 to 5% by weight of the medicinal active ingredient.

12. The medicinal aerosol formulation as claimed in one of claims 1 to 11, which contains 2-hydroheptafluoropropane.