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(54) STABLE SOLUTIONS OF ERGOT ALKALOIDS

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to solutions of ergot alkaloids and their synthetic derivatives including their hydrogenated derivatives and salt forms thereof.

Solutions of such compounds in predominantly aqueous media have the disadvantage that the concentration of the active species decreases on storage, for example because of oxidation reactions. For this reason it is normal practice to pass inert gas through the solution during filling of the vessels in which the solution is to be sold, and to protect the contents from air, light and high temperatures.

It has now been found that solutions of certain ergot alkaloids have improved stability when pharmacologically acceptable organic solvents are used in place of aqueous media.

The present invention provides a stable hydrogenated ergopeptide alkaloid solution consisting essentially of

(a) a hydrogenated ergopeptide alkaloid or a pharmaceutically acceptable acid addition salt thereof or mixture thereof,

(b) a pharmacologically acceptable monofunctional alcohol having up to 18 carbon atoms or mixture thereof,

(c) a polyfunctional alcohol having up to 6 carbon atoms and 6 hydroxy groups or a polymeric polyfunctional alcohol having a molecular weight of from 200 to 20,000 or mixture thereof, and

(d) up to 40% by weight of the solution of water, the weight ratio of component (b) to component (c) being 1:01 to 1:100.

By the term 'hydrogenated ergopeptide alkaloids' is included hydrogenated natural or synthetic ergopeptide alkaloids, and also their salt forms. The expression "consisting essentially of" is to be interpreted as meaning that the compositions do not contain any pharmaceutically active species other than component (a).

The pharmacologically acceptable monofunctional alcohols having up to 18 carbon atoms preferably have up to 10 carbon atoms and most preferably up to 3 carbon atoms. An especially preferred solvent of this type is ethanol. The polyfunctional alcohols having up to 6 carbon atoms and up to 6 hydroxy groups preferably have 2 or 3 carbon atoms and 2 or 3 hydroxy groups. Especially preferred are glycerol and propylene glycol. The polyfunctional alcohols may also be used in polymeric form, for example polyalkylene glycols, especially polyethylene glycol, polypropylene glycol or their copolymers, having a molecular weight from 200 to 20,000, preferably from 200 to 600. A particularly suitable polyalcohol is polyethylene glycol with a molecular weight of approximately 400.

The above mono- and polyfunctional alcohols are used according to the invention in the form of mixtures in which the monofunctional and the polyfunctional alcohol are present in a ratio of from 1:0.1 to 1:100 by weight, preferably in a ratio of from 1:1 to 1:4, more preferably of 1:2 by weight. A mixture of ethanol and propylene glycol is particularly preferred.

The solutions may of course contain a mixture of several mono- and/or polyfunctional alcohols.

Furthermore, the compositions according to the invention may further contain, as additional solvents, pharmacologically acceptable organic esters and ethers, particularly those formed from the above-mentioned mono- and polyfunctional alcohols and fatty acids having from 12—18 carbon atoms, for example stearic acid, palmitic acid and oleic acid; or fatty

alcohols having from 12 to 18 carbon atoms, for example lauryl alcohol, cetyl alcohol and stearyl alcohol.

The compositions may contain minor amounts of water, but the water content must not exceed 40% by weight of the composition.

Hydrogenated natural and synthetic ergopeptide alkaloids which may be stabilised in solution by the process of the invention include dihydroergotamine, dihydroergocristine, dihydroergocryptine, dihydroergocornine and mixtures thereof, particularly a mixture of dihydroergocristine, dihydroergocryptine and dihydroerocornine in 1:1:1 ratio. Suitable salt forms are salts of pharmacologically acceptable acids, for example the methanesulphonate, maleate and tartrate.

Although the concentration of the hydrogenated ergopeptide alkaloids in the solutions is not critical, it is preferred to use solutions with a concentration of active species of from 0.1 to 1% by weight, preferably from 0.1 to 0.5% by weight. It is to be understood that the concentration to be used will depend upon the application for which the solution is intended.

The solutions may in addition contain further solubilising additives for example acids, particularly methanesulphonic acid, maleic acid and tartaric acid.

The preparation of the compositions according to the invention is carried out by dissolving the hydrogenated ergopeptide alkaloids in one of the described organic solvent mixtures by stirring, suitably under an atmosphere of inert gas, e.g. nitrogen, and suitably with exclusion of daylight and at room temperature (15—25°C).

The preparation of solvent mixtures is carried out in conventional manner, and where one of the solvent components is solid at room temperature, mixing is suitably carried out at higher temperatures, e.g. at up to 80°C. Ethanol may advantageously be used as co-solvent.

Compositions according to the invention are useful as pharmaceuticals in the same way as corresponding aqueous solutions of the same active species. They may be administered orally, and may for this purpose be made up in vessels designed to dispense unit dosages, for example dropper bottles; or parenterally, in which case the solutions will normally be sterilized and may be sealed in ampoules of unit dosage.

EXAMPLE 1

A mixture of 50.0 g propylene glycol and 41.9 g 94% ethanol was prepared and in this mixture was dissolved, by stirring at room temperature under a nitrogen atmosphere, 0.1 g of a mixture of dihydroergocristine, dihydroergocryptine and dihydroergocornine (1:1:1). After filtration under pressure, the solution was used to fill dropper bottles.

EXAMPLE 2

A mixture of 40.0 g propylene glycol, 34.0 g 94% ethanol and 25.0 g anhydrous glycerol was prepared and in this mixture was dissolved, by stirring at room temperature under a nitrogen atmosphere, 0.1 g of a mixture of dihydroergocristine, dihydroergocryptine and dihydroergocornine (1:1:1). After filtration under pressure, the solution was used to fill dropper bottles.

EXAMPLE 3

A mixture of 50.0 g propylene glycol and 41.9 g 94% ethanol was prepared and in this mixture was dissolved, by stirring at room temperature under a nitrogen atmosphere, 0.1 g of dihydroergotamine methanesulphonate. After filtration under pressure, the solution was used to fill dropper bottles.

WHAT WE CLAIM IS:—

1. A stable hydrogenated ergopeptide alkaloid solution consisting essentially of

a) a hydrogenated ergopeptide alkaloid as herein defined,

b) a pharmacologically acceptable monofunctional alcohol having up to 18 carbon atoms,

c) a polyfunctional alcohol having up to 6 carbon atoms and 6 hydroxy groups or a polymeric polyfunctional alcohol having a molecular weight of from 200 to 20,000, and

d) up to 40% by weight of the solution of water, the weight ratio of component b) to component c) being 1:0.1 to 1:100.

2. A solution as claimed in Claim 1 in which the concentration of component a) is from 0.1 to 1 per cent by weight.

3. A solution as claimed in Claim 2 in which the concentration of component a) is from 0.1 to 0.5 per cent by weight.

4. A solution as claimed in any one of Claims 1—3 in which component b) has up to 10 carbon atoms and the ratio of component b) to component c) is 1:1 to 1:10.

5. A solution as claimed in Claim 4 in which component b) has up to 3 carbon atoms and component c) is a polyhydroxy alcohol of 2 to 3 carbon atoms and 2 or 3 hydroxy groups or a polymeric polyhydroxy alcohol having a molecular weight of 200 to 600 and the ratio of component b) to component c) is 1:1 to 1:4.

6. A solution as claimed in Claim 5 in which the ratio of component b) to component c) is 1:1 to 1:2.

7. A solution as claimed in Claim 5 in which the ratio of component b) to component c) is 1:2.

8. A solution as claimed in any one of the

alcohols having from 12 to 18 carbon atoms, for example lauryl alcohol, cetyl alcohol and stearyl alcohol.

The compositions may contain minor amounts of water, but the water content must not exceed 40% by weight of the composition.

Hydrogenated natural and synthetic ergopeptide alkaloids which may be stabilised in solution by the process of the invention include dihydroergotamine, dihydroergocristine, dihydroergocryptine, dihydroergocornine and mixtures thereof, particularly a mixture of dihydroergocristine, dihydroergocryptine and dihydroerocornine in 1:1:1 ratio. Suitable salt forms are salts of pharmacologically acceptable acids, for example the methanesulphonate, maleate and tartrate.

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The preparation of solvent mixtures is carried out in conventional manner, and where one of the solvent components is solid at room temperature, mixing is suitably carried out at higher temperatures, e.g. at up to 80°C. Ethanol may advantageously be used as co-solvent.

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4. A solution as claimed in any one of Claims 1—3 in which component b) has up to 10 carbon atoms and the ratio of component b) to component c) is 1:1 to 1:10.

5. A solution as claimed in Claim 4 in which component b) has up to 3 carbon atoms and component c) is a polyhydroxy alcohol of 2 to 3 carbon atoms and 2 or 3 hydroxy groups or a polymeric polyhydroxy alcohol having a molecular weight of 200 to 600 and the ratio of component b) to component c) is 1:1 to 1:4.

6. A solution as claimed in Claim 5 in which the ratio of component b) to component c) is 1:1 to 1:2.

7. A solution as claimed in Claim 5 in which the ratio of component b) to component c) is 1:2.

8. A solution as claimed in any one of the

preceding claims in which component a) is ethanol and component b) is propylene glycol or glycerol or a mixture thereof.

9. A solution as claimed in any one of the preceding claims in which the hydrogenated ergopeptide alkaloid is dihydroergotamine, dihydroergocristine, dihydroergocryptine, dihydroergocornine or pharmaceutically acceptable salts thereof or mixtures thereof.

10. A solution as claimed in Claim 9 in which the hydrogenated ergopeptide alkaloid is a 1:1:1 mixture of dihydroergocristine, dihydroergocryptine and dihydroergocornine or pharmaceutically acceptable salts thereof.

11. A sterilized, sealed ampoule containing essentially a solution as claimed in any one of the preceding claims.

12. A dropper bottle containing essentially a solution as claimed in any one of the preceding claims.

13. A method of preparing a stable hydrogenated ergopeptide alkaloid solution according to Claim 1 which comprises dissolving a hydrogenated ergopeptide alkaloid or a pharmaceutically acceptable acid addition salt thereof or mixture thereof in a solvent consisting essentially of; a) a pharmacologically acceptable monofunctional alcohol having up to 18 carbon atoms or mixture thereof; b) a polyfuctional alcohol having up to 6 carbon atoms and 6 hydroxy groups or a polymeric polyfunctional alcohol having a molecular weight of from 200 to 20,000 or mixture thereof; and c) up to 40% by weight of the solution of water, the weight ratio of component b) to component c) being 1:0.1 to 1:100, under an atmosphere of inert gas with the exclusion of daylight and at a temperature of 15 to 25°C.

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