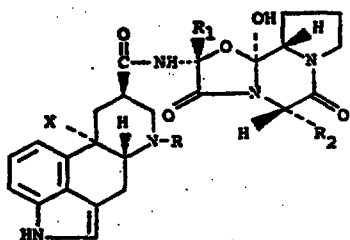


SPECIFICATION

Stable solutions of hydrogenated ergotalkaloids

5 The present invention relates to pharmaceutical compositions in the form of stable solutions and comprising as active ingredients a combination of

a) a compound of formula I,



wherein R is hydrogen or C₁₋₄alkyl,

R₁ is methyl, ethyl or isopropyl,

R₂ is isopropyl, sec.-butyl, isobutyl or benzyl, and

X is hydrogen or methoxy,

or a pharmaceutically acceptable acid addition salt thereof; and

b) heparin or a pharmaceutically acceptable salt thereof.

Previous attempts to prepare pharmaceutical compositions in solution form comprising mixtures of active ingredients a) and b) as aforesaid (for example of dihydroergotamine and dihydroergovaline or their salts, e.g. the methane sulphonate, or of 6-nor-6-isopropyl-9,10-dihydro-2'β-methyl-5'α-benzyl-ergopeptine or its salts, e.g. the maleate, and of heparin or its salts, e.g. the sodium salt) have not met with success. First the individual ingredients are themselves unstable in solution. Secondly when combined in solution, the ingredients a) and b) react to form difficultly soluble salts which precipitate out of the solution. The obtained solutions accordingly possess very low stability. They cannot be kept in reserve for periods of more than a few hours and are thus of little practical value.

Various proposals have been made to surmount this problem. Thus it has been suggested to use e.g. the methane sulphonate salt of dihydroergotamine in the form of a solid solution employing polyvinyl-pyrrolidone. Salt formation can be delayed in this manner, but only for a relatively limited period of time. More recently lyophilised preparations have been developed for use in the preparation of injectable solutions.

As an alternative, individually stabilized solutions comprising components a) and b) separately, have been developed. The individually stabilized solutions are then brought into admixture shortly before administration.

Clearly none of these proposals provides a satisfactory, practical answer to the problem. The development of stabilized solution forms comprising ingredients a) and b) in combination, having a prolonged shelf-life, capable of transport and storage and ready for use as and when required has remained a major objective.

In accordance with the present invention it has now surprisingly been found that the above problems may be overcome and clear solutions of component a) and b) in combination obtained, which are stable over prolonged periods of time, e.g. for two years and more, employing a carrier medium comprising.

c) water;

d) a pharmaceutically acceptable mono- or poly-alcohol;

e) an acetanilide anaesthetic or a pharmaceutically acceptable acid addition salt thereof; and

f) urea and/or mono-calcium di-sodium ethylenediaminetetra-acetate.

Accordingly the present invention provides, in a first aspect, a pharmaceutical composition in stable solution form comprising as active ingredients a combination of a component a) and a component b) as hereinbefore defined and a carrier medium comprising components c), d), e) and f) as hereinbefore defined.

Preferably the compositions according to the invention have a pH of from 4 to 6.

Suitable pharmaceutically acceptable acid addition salt forms of the compounds of formula I,

include e.g. the methane sulphonates, maleates and tartrates. Suitable pharmaceutically acceptable salts of heparin include e.g. the sodium, potassium and calcium salt.

Preferred ingredients a) are dihydroergotamine or a pharmaceutically acceptable acid addition salt thereof, in particular the methane sulphonate, dihydroergovaline or a pharmaceutically acceptable acid addition salt thereof, in particular the methane sulphonate and 6-nor-6-isopropyl-9,10-dihydro-2'β-methyl-5'α-benzyl-ergotepiptine and the pharmaceutically acceptable acid salts thereof, in particular the maleate. When b) is present in pharmaceutically acceptable salt form this is preferably the sodium salt.

The ingredients a) and b) are preferably present in a ratio of 1 mg compound of formula I: 500 to 70,000 I.U., more preferably 2,000 to 20,000 I.U. heparin. When ingredient a) and/or b) is present in pharmaceutically acceptable salt form the equivalent amount of salt form giving the stated ratios for the free compound is employed.

Components c) and d) are preferably present in an amount of 45 to 72% and 28 to 55% respectively based on the total volume of the composition.

Preferred components d) are ethanol, propylene glycol, polyethylene glycol having an average molecular weight of 400, diethylene glycol and glycerol, as well as mixtures thereof. More preferably component d) comprises a mixture of (i)

ethanol and (ii) triethylene glycol or of (iii) glycerol and (iv) propylene glycol. In such mixtures (i) and (ii) are preferably present in a ratio of from 1:6 to 10, more preferably 1:8 parts by weight and (iii) and (iv) are preferably present in a ratio of from 1:8 to 12, more preferably 1:10 parts by weight.

By the term "acetanilide anaesthetic" as used in respect of component e) is meant any member of the class of physiologically acceptable acetanilide derivatives having anaesthetic activity, including the



various known anaesthetically active 2 - amino - N - phenyl - acetanilide derivatives. Preferred acetanilide anaesthetics are 2 - (diethylamino) - N - (2,6 - dimethyl - phenyl) - acetamide (also known as

5 Lidocaine), 2 - (butylamino) - N - (2 - chloro - 6 - methyl - phenyl) - acetamide (also known as Hostacain) and 2 - (2 - diethylaminoacetamido) - m - toluic acid methyl ester (also known as Baycain). Apart from their clearly advantageous anaesthetic properties e.g. when the compositions are administered by injection, it has surprisingly been found that the presence of ingredient e) is essential in contributing to the long-term stability properties of the inventive compositions.

15 Preferably ingredient e) is present in an amount of 1 to 2% by weight based on the total weight of the composition. Ingredient f) is preferably present in an amount of 2 to 5 mg based on an amount of 5,000 I.U. to 2,500 I.U. heparin, or an amount of 5 to 10 mg based on an amount of 2,500 I.U. heparin.

20 The compositions according to the invention may contain further additives, e.g. stabilizing agents, preserving agents, colouring agents and surfactants, as known in the art. Suitable preserving agents include e.g. chlorocresol or trichloro-tert.-butanol, suitably present in an amount of from 0.2 to 1% based on the total weight of the composition.

The compositions of the invention are suitably put up in unit dosage form, e.g. in the form of ampoules for injection, including e.g. throw-away syringes containing a predetermined amount of the composition. Such unit dosage forms preferably contain 0.5 mg of the compound of formula I and/or 2,500 or 5,000 I.U. heparin per unit dosage.

35 In addition to the foregoing the present invention also provides a process for the preparation of pharmaceutical compositions in accordance with the invention, which process comprises bringing an active ingredient a) and an active ingredient b) as hereinbefore defined into solution in a carrier medium comprising components c), d), e) and f) as hereinbefore defined.

Preferably the process is carried out step-wise in a procedure comprising

- 45 1) preparing a solution of an active ingredient a) in a solvent medium comprising components d) and e);
- 2) preparing a solution of an active ingredient b) in a solvent medium comprising components c) and f);
- 50 3) combining the solutions obtained via steps 1) and 2); and
- 4) optionally adding additional component c) and/or d).

55 The process of the invention is preferably carried out with protective gassing, e.g. CO₂-gassing, of the solutions. If the pH of the obtained solution is outside the range pH 4 to 6, it is preferably adjusted to within this range e.g. by the addition of an appropriate quantity of a pharmaceutically acceptable acid e.g. an organic acid. When an acid addition salt of a compound of formula I is employed as ingredient a), the added acid will preferably correspond to the salt form employed. Thus when ingredient a) is in methane sulphonate salt form, any

adjustment of the pH necessary will preferably be effected by addition of methane sulphonic acid.

The obtained composition may be put-up in unit dosage form as hereinbefore described, e.g. by filling into ampoules after filtration, preferably with protective, e.g. CO₂, gassing.

The solutions according to the invention may be used for therapeutic treatment or prophylaxis as known in the art; for example as anti-thrombotic agents particularly in the prophylaxis of post-operative thrombosis as described in e.g. U.K. Patent Specification No. 1,557,331 (= NZ Patent Specification No. 182797).

The following examples are illustrative of the present invention:

Example I

Preparation of a 5,000 I.U. heparin/0.5 mg Dihydroergotamine injectable solution:

1) 18.4 kg of propylene glycol and 1.84 kg of anhydrous glycerol are poured into a 50 litres stirring vessel, and the mixture stirred for 10 minutes with CO₂-gassing. 0.0286 kg of dihydroergotamine methane sulphonate and 0.426 kg of lidocain hydrochloride are dissolved in the mixture with stirring and CO₂-gassing over a period of a further 30 minutes.

2) 18.4 kg of water (suitable for injection) are poured into a 30 litre stirring vessel and stirred for 10 minutes with CO₂-gassing. 1.896 kg of heparin sodium salt (= circa 285.7 million I.U.) and 0.114 kg of mono-calcium di-sodium ethylenediaminetetraacetate (commercially available under the name Calcium titriplex®) are then dissolved in the water with stirring and CO₂-gassing over a further 30 minutes.

3) The solution obtained via step 2) above is added with stirring and CO₂-gassing to the solution obtained via step 1). The vessel in which solution 2) is obtained is then washed out with 1 kg of water (suitable for injection) and is also added to the step 1) solution. The combined solutions are stirred for a further 10 minutes with CO₂-gassing. The pH of the solution is ca. 5.7.

4) The solution is made up to a weight of 42.810 kg (= 40 litres) by the addition of water (suitable for injection).

5) The obtained solution is pre-filtered using a membrane-filter (0.2 µm: Ultipor nm. Pall) and then passed via a sterilized pressure-filtration apparatus having a membrane filter (0.2 µm: Ultipor nm. Pall) at 1.7 bar with CO₂ directly into an ampoule-filling machine. The solution is filled in 0.7 ml dosages into 1 ml ampoules under sterile conditions.

Example II

Steps 1)-4) of example I are repeated precisely using the following quantities of ingredients:

Step 1) Propylene glycol	15.30 kg
Anhydrous glycerol	1.53 kg
Dihydroergotamine-methane sulphonate	0.03 kg
Lidocain-HCl. H ₂ O	0.32 kg
Step 2) Water(for injection)	12.00 kg
Heparin-Na salt	0.997 kg (= 150 million I.U.)
mono-Calcium di-sodium ethylenediaminetetraacetate (hexahydrate)	0.12 kg

Step 3)

No change

Step 4)

- The solution is made up to a weight of 32.040 kg =
5 30 litres by the addition (for injection).

Step 5)

The resultant solution is filled into 1 ml ampoules
in 0.5 ml dosages.

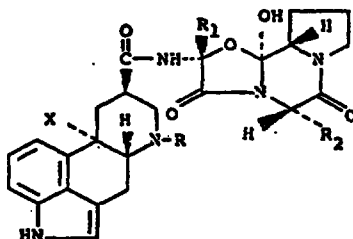
Example III

- 10 i) The method of example I is repeated using an
equivalent quantity of a 1:10 (parts by weight)
mixture of ethanol and triethylene glycol in
place of propylene glycol and glycerol in step 1).
ii) The method of example I is repeated using an
15 equivalent quantity of hostacain in place of
lidocain in step 2).
iii) The method of example I is repeated using an
equivalent quantity of Baycain in place of lido-
cain in step 2).

20 CLAIMS

1. A pharmaceutical composition in stable solu-
tion form comprising as active ingredient a combina-
tion of

- a) a compound of formula I,



- 25 wherein R is hydrogen or C₁₋₄alkyl,
R₁ is methyl, ethyl or isopropyl,
R₂ is isopropyl, sec.-butyl, isobutyl or ben-
zyl, and
X is hydrogen or methoxy,
30 or a pharmaceutically acceptable acid salt thereof;
and
b) heparin or a pharmaceutically acceptable salt
thereof, and a carrier medium comprising
c) water;
35 d) a pharmaceutically acceptable mono- or poly-al-
cohol;
e) an acetanilide anaesthetic or a pharmaceutically
acceptable acid addition salt thereof; and
f) urea and/or mono-calcium di-sodium ethylene-
40 diaminetetraacetate.
2. Composition according to Claim 1, having a
pH of from 4 to 6.
3. Composition according to Claim 1 or 2, where-
in the compound of formula I is dihydroergotamine.
45 4. Composition according to Claim 1 or 2, where-
in the compound of formula I is dihydroergovaline.
5. Composition according to Claim 3 or 4, where-
in the compound of formula I is in the form of the
methane sulphonate.
50 6. Composition according to Claim 1 or 2 where-
in the compound of formula I is 6 - nor - 6 - isopropyl
- 9,10 - dihydro - 2'β - methyl - 5'α - benzyl -

ergopeptine.

7. Composition according to Claim 6, wherein
55 the compound of formula I is in the form of the
maleate.

8. Composition according to any one of Claims 1
to 7 wherein the heparin is in the form of the sodium
salt.

- 60 9. Composition according to any one of Claims 1
to 8 wherein the compound of formula I and heparin
are present in a ratio of 1 mg:500 to 70,000 I.U.

10. Composition according to Claim 9 wherein
the ratio is 1 mg:2,000 to 20,000 I.U.

- 65 11. Composition according to any one of Claims
1 to 10 wherein component c) is present in an
amount of from 45 to 72% based on the total volume
of the composition.

12. Composition according to any one of Claims
70 1 to 11 wherein component d) is present in an
amount of from 28% to 55% based on the total
volume of the composition.

13. Composition according to any one of Claims
1 to 12 wherein component d) is selected from the
group consisting of ethanol, propylene glycol,
75 polyethylene glycol of average mol. wt. ca. 400,
diethyleneglycol, glycerol and mixtures thereof.

14. Composition according to Claim 13 wherein
component d) comprises either (i) ethanol and (ii)
80 triethylene glycol or (iii) glycerol and (iv) propylene
glycol.

15. Composition according to Claim 14 wherein
(i) and (ii) are present in a ratio of from 1:6 to 10
parts by weight or (iii) and (iv) are present in a ratio
85 of from 1:8 to 12 parts by weight.

16. Composition according to Claim 15 wherein
(i) and (ii) are present in a ratio of from 1:8 parts by
weight or (iii) and (iv) are present in a ratio of from
1:10 parts by weight.

17. Composition according to any one of Claims
90 1 to 16 wherein the acetanilide anaesthetic is
selected from the group consisting of o-Lidocain,
Hostacain and Baycain.

18. Composition according to any one of Claims
95 1 to 17 wherein the acetanilide anaesthetic is present
in an amount of from 1 to 2% based on the total
weight of the composition.

19. Composition according to any one of Claims
1 to 18 wherein component f) is present in an
100 amount of 2 to 5 mg based on an amount of 5,000
I.U. to 2,500 I.U. heparin.

20. Composition according to any one of Claims
1 to 19 wherein component f) is mono-calcium
di-sodium ethylenediaminetetraacetate.

- 105 21. Composition according to Claim 20 wherein
component f) is in the form of the hexahydrate.

22. Composition according to any one of Claims
1 to 19 in unit dosage form.

23. Composition according to any one of Claims
110 1 to 22 in ampoule form for injection and containing
0.5 mg of compound of formula I and/or 2,500 or
5,000 I.U. heparin.

24. Process for the preparation of a phar-
maceutical composition according to any one of
115 Claims 1 to 23 which process comprises bringing an
active ingredient a) and an active ingredient b) into
solution in a carrier medium comprising compo-



Step 3)
No change

Step 4)
The solution is made up to a weight of 32.040 kg =
5 30 litres by the addition (for injection).

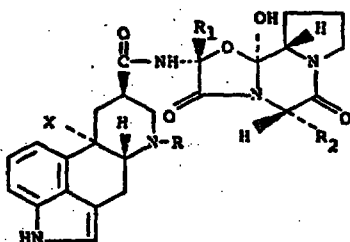
Step 5)
The resultant solution is filled into 1 ml ampoules
in 0.5 ml dosages.

Example III

- 10 i) The method of example I is repeated using an equivalent quantity of a 1:10 (parts by weight) mixture of ethanol and triethylene glycol in place of propylene glycol and glycerol in step 1).
- 15 ii) The method of example I is repeated using an equivalent quantity of hostacain in place of lidocain in step 2).
- iii) The method of example I is repeated using an equivalent quantity of Baycain in place of lidocain in step 2).

20 CLAIMS

1. A pharmaceutical composition in stable solution form comprising as active ingredient a combination of
a) a compound of formula I,



- 25 wherein R is hydrogen or C₁₋₄alkyl,
R₁ is methyl, ethyl or isopropyl,
R₂ is isopropyl, sec.-butyl, isobutyl or benzyl, and
X is hydrogen or methoxy,
- 30 or a pharmaceutically acceptable acid salt thereof; and
b) heparin or a pharmaceutically acceptable salt thereof, and a carrier medium comprising
c) water;
- 35 d) a pharmaceutically acceptable mono- or poly-alcohol;
e) an acetanilide anaesthetic or a pharmaceutically acceptable acid addition salt thereof; and
f) urea and/or mono-calcium di-sodium ethylene-
- 40 diaminetetraacetate.
2. Composition according to Claim 1, having a pH of from 4 to 6.
3. Composition according to Claim 1 or 2, wherein the compound of formula I is dihydroergotamine.
- 45 4. Composition according to Claim 1 or 2, wherein the compound of formula I is dihydroergovaline.
5. Composition according to Claim 3 or 4, wherein the compound of formula I is in the form of the methane sulphonate.
- 50 6. Composition according to Claim 1 or 2 wherein the compound of formula I is 6 - nor - 6 - isopropyl - 9,10 - dihydro - 2'β - methyl - 5'α - benzyl -

ergopeptine.

7. Composition according to Claim 6, wherein
55 the compound of formula I is in the form of the maleate.

8. Composition according to any one of Claims 1 to 7 wherein the heparin is in the form of the sodium salt.

60 9. Composition according to any one of Claims 1 to 8 wherein the compound of formula I and heparin are present in a ratio of 1 mg:500 to 70,000 I.U.

10. Composition according to Claim 9 wherein the ratio is 1 mg:2,000 to 20,000 I.U.

65 11. Composition according to any one of Claims 1 to 10 wherein component c) is present in an amount of from 45 to 72% based on the total volume of the composition.

70 12. Composition according to any one of Claims 1 to 11 wherein component d) is present in an amount of from 28% to 55% based on the total volume of the composition.

13. Composition according to any one of Claims 1 to 12 wherein component d) is selected from the group consisting of ethanol, propylene glycol, polyethylene glycol of average mol. wt. ca. 400, diethyleneglycol, glycerol and mixtures thereof.

14. Composition according to Claim 13 wherein component d) comprises either (i) ethanol and (ii) triethylene glycol or (iii) glycerol and (iv) propylene glycol.

80 15. Composition according to Claim 14 wherein (i) and (ii) are present in a ratio of from 1:6 to 10 parts by weight or (iii) and (iv) are present in a ratio of from 1:8 to 12 parts by weight.

85 16. Composition according to Claim 15 wherein (i) and (ii) are present in a ratio of from 1:8 parts by weight or (iii) and (iv) are present in a ratio of from 1:10 parts by weight.

90 17. Composition according to any one of Claims 1 to 16 wherein the acetanilide anaesthetic is selected from the group consisting of o-Lidocain, Hostacain and Baycain.

95 18. Composition according to any one of Claims 1 to 17 wherein the acetanilide anaesthetic is present in an amount of from 1 to 2% based on the total weight of the composition.

19. Composition according to any one of Claims 1 to 18 wherein component f) is present in an amount of 2 to 5 mg based on an amount of 5,000 I.U. to 2,500 I.U. heparin.

20. Composition according to any one of Claims 1 to 19 wherein component f) is mono-calcium di-sodium ethylenediaminetetraacetate.

105 21. Composition according to Claim 20 wherein component f) is in the form of the hexahydrate.

22. Composition according to any one of Claims 1 to 19 in unit dosage form.

23. Composition according to any one of Claims 110 1 to 22 in ampoule form for injection and containing 0.5 mg of compound of formula I and/or 2,500 or 5,000 I.U. heparin.

24. Process for the preparation of a pharmaceutical composition according to any one of
115 Claims 1 to 23 which process comprises bringing an active ingredient a) and an active ingredient b) into solution in a carrier medium comprising compo-



nents c), d), e) and f).

25. Process according to Claim 24, which comprises the individual steps of

- 5 1) preparing a solution of an active ingredient a) in a solvent medium comprising components d) and e);
- 2) preparing a solution of an active ingredient b) in a solvent medium comprising components c) and f);
- 10 3) combining the solutions obtained via steps 1) and 2); and
- 4) optionally adding additional component c) and/or d).

26. Process according to Claim 24 or 25 conducted with inert gassing during solution.

27. Process according to any one of Claims 24 to 26 wherein the obtained solution is adjusted to pH 4 to 6.

28. Process according to Claim 24, substantially as herein before described with reference to the accompanying examples.

29. A pharmaceutical composition whenever prepared by a process as claimed in any one of Claims 24 to 28.