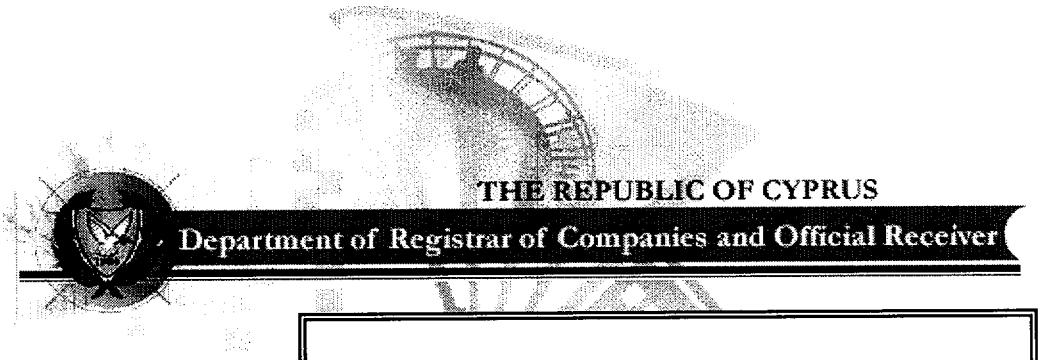

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

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(54) Pharmaceutical compositions comprising hydrogenated ergot alkaloids and heparin

(57) Novel pharmaceutical compositions comprising i) an hydrogenated ergot alkaloid having vaso-constrictor activity, for example dihydroergotamine, or a pharmaceutically acceptable acid addition salt thereof and ii) a low molecular weight heparin or pharmaceutically acceptable salt thereof, and process for their production. Components ii) suitably have an average molecular weight of less than 10,000. The compositions are especially useful in the prevention of post-operative thrombosis.

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SPECIFICATION

Pharmaceutical compositions comprising an hydrogenated ergot alkaloid and heparin

The present invention relates to novel pharmaceutical compositions useful in thrombosis prophylaxis, in particular for the prevention of post-operative thrombosis as well as to processes for the production of said compositions.

Heparin is a highly sulfated, dextro-rotatory mucopolysaccharide, having specific anti-coagulant properties and commonly employed *inter al.* in the prevention of post-operative thrombosis. It occurs as a natural constituent of various tissues, especially liver and lung, in a variety of mammalian species and preparations isolated from differing sources are available commercially, both in free and in pharmaceutically acceptable salt form, e.g. in the form of various alkaline and alkaline-earth metal salts.

Whole heparin, i.e. as commonly isolated directly from source, comprises polymer units of non-uniform molecular weight commonly ranging from between 6,000 and 20,000 and with an average molecular weight of from 14,000 to 18,000, in which the basic polymer chain is composed of D-glucosamine and D-glucuronic acid residues. The specific chemical and physical constitution, e.g. the precise degree of sulfation and the molecular weight characteristics vary according to the source, i.e. the animal material from which it is obtained, as well as the precise means of isolation. As further discussed hereinafter, various techniques are also known and described in the art for the obtention of heparin preparations of lower average molecular weight than is found in whole heparin preparations, e.g. as otherwise directly obtained from the animal source.

It is also known that administration of heparin together with hydrogenated ergot alkaloids having vaso-constrictor activity, in particular dihydroergotamine, is of especial advantage in relation to thrombosis prophylaxis, especially the prevention of post-operative thrombosis — see e.g. U.K. patent specification no. 1,557,331 — and heparin/dihydroergotamine therapy is now a valued and commonly employed treatment for patients at risk of thrombosis, in particular following major surgery. Administration is generally parenteral, e.g. by intravenous injection, and various formulations, e.g. having improved stability characteristics as compared with simple solutions, for use in this manner are known in the literature or are commercially available (see e.g. U.S. Patent No. 4,402,949).

In accordance with the present invention it has now surprisingly been found that where combined therapy as described above is applied, especially advantageous results are obtained if the heparin component is a heparin of low molecular weight. In particular it has been found that by using a low molecular weight heparin in conjunction with hydrogenated ergot alkaloids having vaso-constrictor activity, in particular dihydroergotamine, in place of conventionally employed whole heparin preparations, therapeutic effectiveness, e.g. duration of anti-thrombotic activity, is dramatically increased, whereby the daily dosage of both the heparin and hydrogenated ergot alkaloid component required for effective prophylactic therapy may be correspondingly reduced.

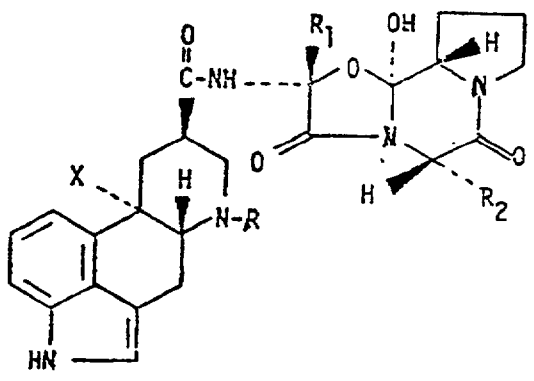
The present invention therefore has the very important advantage of enabling significant reduction of the daily medication required for patient treatment. In that, as already noted, treatment is generally by means of i.v. injection, the present invention further provides the concommitant advantage of enabling reduction of the required daily injection rate and hence substantial reduction of patient discomfort. This is of especial importance in relation to patients undergoing and recovering from major surgery.

In accordance with the foregoing the present invention provides a pharmaceutical composition comprising:

i) an hydrogenated ergot alkaloid having vaso-constrictor activity, or pharmaceutically acceptable acid addition salt thereof,
and

ii) a low molecular weight heparin, or pharmaceutically acceptable salt thereof.

Component i) of the compositions of the invention is suitably: a hydrogenated ergot alkaloid of formula I



I

wherein R is hydrogen or C_{1-4} alkyl,

R_1 is methyl, ethyl or iso-propyl,
R_2 is iso-propyl, sec.-butyl, iso-butyl or benzyl and
X is hydrogen or methoxy,
or a pharmaceutically acceptable acid addition salt thereof.

Preferably component i) is dihydroergotamine, 6-nor-isopropyl-9,10-dihydro-2′β-methyl-5′α-benzyl-ergopeptine or dihydroergovaline or a pharmaceutically acceptable acid addition salt thereof, dihydroergotamine and its pharmaceutically acceptable acid addition salts being most preferred. Suitable pharmaceutically acceptable acid addition salts are e.g. the methanesulfonates, maleinates and tartrates, and, in the case of dihydroergotamine the methanesulfonate in particular.

By the term "a low molecular weight heparin" is meant a heparin prepared, e.g. by isolative procedures or depolymerisation such as hereinafter described, so as to achieve significant reduction of average molecular weight as compared with whole heparin preparations.

Components ii) for use in accordance with the present invention preferably have an average molecular weight of ca. 10,000 or less, more preferably of ca. 8,000 or less. Preferably however the average molecular weight is not less than ca. 4,000, more preferably not less than ca. 5,000, most preferably not less than ca. 6,000. Especially preferred components ii) accordingly have an average molecular weight of from ca. 10,000 to ca. 4,000 in particular from ca. 8,000 to ca. 5,000, e.g. of ca. 7,000 ± 1,000 or of ca. 6,000 ± 1,000. It is further preferred that components ii) should be of relatively uniform molecular weight, e.g. with at least 60%, more preferably 80% of polymer units having a molecular weight within the above defined average molecular weight limits, e.g. having a molecular weight of 10,000 or less.

Suitable pharmaceutically acceptable salts of low molecular weight heparins as component ii) are e.g. the calcium and potassium and, in particular, the sodium salt.

The low molecular weight heparin or pharmaceutically acceptable salt thereof employed as component ii) may be obtained in accordance with methods known in the art, e.g. by isolation of low molecular weight fractions from whole heparin preparations, e.g. by fractional precipitation and filtration, for example as described in German Offenlegungsschrift No. 29 45 591, or by depolymerisation of high molecular weight fractions of whole heparin e.g. by chemical cleavage, for example as described in Belgian Patent No. 888,864 or European Patent Publication No. 27,089. Alternatively components ii) may be obtained by a combination of such techniques, e.g. by separation of low molecular weight heparin from whole heparin preparations, followed by depolymerisation of remaining higher molecular weight heparin fractions to yield further low molecular weight heparin and, optionally, combination of the two low molecular weight heparin preparations thus obtained.

Where low molecular weight heparin is prepared by chemical cleavage, individual chain residues may undergo a measure of chemical modification in particular de-sulfatisation. Where this occurs, for use in accordance with the present invention, components ii) initially produced may, if desired, subsequently be reconstituted or otherwise appropriately modified in accordance with known techniques, for example analogously to the techniques disclosed in French patent specification No. 888,864.

Where low molecular weight heparin preparations obtained by chemical cleavage are used in the compositions of the invention, these will preferably be preparations which have undergone no, or substantially no additional chemical modification.

Components i) and ii) are suitably present in a ratio of 1 mg of component i): 300 to 70,000, (e.g. 500 to 70,000), preferably 300 to 35,000 IU of component ii). More preferably components i) and ii) are present in a ratio of 1 mg of component i): 1,000 to 20,000, (e.g. 2,000 to 20,000) most preferably 1,000 to 10,000 IU of component ii). When component i) and/or ii) is present in pharmaceutically acceptable salt form, the equivalent amount of salt form providing the indicated ratios is employed.

As previously indicated the compositions of the invention will generally be administered by injection. For direct application they will accordingly be in liquid form. Although e.g. simple aqueous or aqueous/alcoholic solutions are possible, these are generally not preferred since, in the absence of stabilizing means, components i) and ii) will react to form difficulty soluble salts which precipitate out of solution. Simple solutions accordingly can not be kept in reserve for periods of more than a few hours and are thus of limited practical value.

Preferred compositions in accordance with the present invention are stabilized solutions of the type described in the aforementioned U.S. Patent No. 4,402,949 employing e.g., as an additional component iii) a pharmaceutically acceptable calcium or magnesium salt of ethylenediaminetetraacetic acid (EDTA) as a stabilizing agent. For such solutions the solvent medium preferably comprises iv) water and v) a pharmaceutically acceptable mono- or poly-alcohol.

Indicated magnesium and calcium salts of EDTA as component iii) are the mono-magnesium and mono-calcium salts including the pharmaceutically acceptable poly-metal salts incorporating magnesium and, preferably, calcium together with mono-valent metal ions, e.g. sodium or potassium ions. The preferred salt of EDTA for use in accordance with the invention is the mono-calcium-bis-sodium salt ($CaNa_2$ EDTA) also known as calcium titriplex. The mono-magnesium-bis-potassium salt (MgK_2 EDTA) may also be mentioned.

Component iii) is preferably present in a range of from about 1 to about 50 mg, more preferably 1

to 25 mg, most preferably 1 to 10 mg based on an amount of 5,000 IU of component ii).

When the solvent medium comprises components iv) and v) i.e. as diluent or carrier, these 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 v) are ethanol, propylene glycol, polyethylene glycol (suitably having an average molecular weight of ca. 400), diethylene glycol, triethylene glycol and glycerol, as well as mixtures thereof. More preferably v) comprises a mixture of a) ethanol and b) triethylene glycol or of c) glycerol and d) propylene glycol. In such mixtures a) and b) are preferably present in a ratio of from 1:6 to 10, more preferably 1:8 parts by weight and c) and d) are preferably present in a ratio of from 1:8 to 12, more preferably 1:10 parts by weight.

In a preferred embodiment, such solutions as aforesaid also comprise as a further component vi), a physiologically acceptable anaesthetic. Anaesthetic components vi) are preferably "acetanilide anaesthetics" by which 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 and their pharmaceutically acceptable salts. Preferred acetanilide anaesthetics are 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide (also known as 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). Commonly employed pharmaceutically acceptable salts of such acetanilide anaesthetics include e.g. their hydrochlorides. When present, component vi) is preferably present in an amount of from 1 to 2% by weight based on the total weight of the composition.

Solutions, e.g. for injection, in accordance with the present invention suitably have a pH of from 4 to 6.

It will of course be appreciated that while solutions, e.g. as described above, will generally be most convenient and preferred, the present invention also includes other appropriate forms of composition comprising components i) and ii), such as lyophylised preparations e.g. for putting up in solution or other suitable liquid form, prior to administration. The compositions of the invention may contain any further desired additives, e.g. carriers, diluents, stabilizing agents, preserving agents, colouring agents, and surfactants as known in the art.

Compositions of the invention are indicated for use for the prophylaxis of thrombosis, in particular for use in the prevention of post-operative thrombosis.

The advantageous properties of compositions of the invention as compared with compositions previously employed in the art may, for example, be demonstrated in clinical trials, e.g. employing the I^{125}-fibrinogen uptake test of K. H. Frey *et al.* [Med. Klin., *70* (1975, pp. 1553—1558)], in which radiation from I^{125}-fibrinogen, which is selectively concentrated in thrombotic material in leg veins, is measured externally in patients.

In this test, patients undergoing major surgery, for example total hip replacement, receive 100 uci of I^{125}-fibrinogen parenterally the day before surgery and their legs are scanned for I^{125} radiation each day for between 2 and 3 weeks thereafter. The fibrinogen injection is repeated 8 to 10 days after initial administration if the count rate remains low. A Logic 121 counter/ratemeter is used for recording radioactivity, counting being performed according to the technique of Kakkar et al. [Lancet, 1 (1970), p 540]. Deep vein thrombosis (DVT) is diagnosed if the count at any site differs by 20% or more from those at an adjacent point on the same leg or the same position on the opposite leg, and if this difference persists or increases in the subsequent 24 hours.

In one such clinical trial subjects are divided into two groups. Group 1 receives 0.5 mg dihydroergotamine methanesulfonate and 2,500 IU low molecular weight sodium heparinate (average molecular weight ca. 7,000 ± 1,000) administered in the form of a stabilised solution i.v. 1 × daily. Group 2 receives 0.5 mg dihydroergotamine methanesulfonate and 5,000 IU whole sodium heparinate also administered in the form of a stabilised solution i.v. 2× daily. Results for group 1 receiving composition in accordance with the present invention are compared with those for group 2 receiving conventional therapy. Reduction of the incidence of DVP in both groups is found to be equivalent.

Comparable results to those obtained in the above clinical trial with daily injection of a single dosage comprising 0.5 mg dihydroergotamine methane sulfonate and 2,500 IU low molecular weight sodium heparinate (7,000 ± 1,000) may also be obtained when the low molecular weight heparin dosage is reduced to 1,500 IU.

A suitable indicated daily dosage for the compositions of the invention, will accordingly be of the order of 1/3 of daily dosages employed using known compositions comprising whole heparin or a pharmaceutically acceptable salt thereof, with further reduction of the conventional heparin dosage, e.g. down to 1,500 IU daily being possible. Thus an indicated daily dosage for component i) will be of the order of from ca. 0.2 to ca. 1.5 mg, e.g. ca. 0.5 mg and for component ii) ca. 1,000 to ca. 10,000 IU e.g. ca. 1,500 to ca. 5,000 IU. If desired the daily dosage may be administered in divided dosages e.g. 2 to 4× daily. Preferably however it is administered as a single dosage 1 × daily e.g in unit dosage form. Alternatively components i) and ii) may, if desired, be administered separately.

Suitable unit dosage forms for the compositions of the invention e.g. for stabilized injection solutions as hereinbefore described comprising e.g components iii), iv), v) and, optionally, vi), include

injection ampoules and throw-away syringes containing a pre-determined amount of the composition. Such unit dosage forms suitably contain from ca. 0.2 to ca. 1.5 mg, preferably ca. 0.5 mg, of component i) and from ca. 1,000 (e.g. ca. 1,500), to ca. 10,000 IU, preferably ca. 1,500 IU (e.g. ca. 2,500), to ca. 5,000 IU of component ii). Most preferably they contain ca. 0.5 mg of component i) and ca. 1,500, ca. 2,500 or ca. 5,000 IU of component ii).

In addition to the foregoing the present invention also provides a process for the preparation of a pharmaceutical composition in accordance with the invention, which process comprises, bringing a component i) into intimate admixture with a component ii) for example, bringing a component i) together with a component ii) into solution in a pharmaceutically acceptable solvent medium. Where solutions are prepared comprising additional components iii), iv) and v) and, optionally, vi) as hereinbefore described, the process is suitably carried out by a step-wise procedure comprising

1) preparation of a solution of component i) and, optionally, component vi) in a solvent medium comprising component v);
2) preparation of a solution of component ii) and component iii) in a solvent medium comprising component iv);
3) combination of the solutions obtained via steps 1) and 2), and
4) optional addition of further component iv) and/or v).

For the preparation of solutions, the process of the invention is preferably carried out with protective gassing, e.g. CO_2-gassing of the solution(s). 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. a pharmaceutically acceptable organic acid. When a pharmaceutically acceptable acid addition salt is employed as component i), added acid will preferably correspond to the salt form employed. Thus when component i) is in methane sulfonate salt form, any adjustment of pH necessary will preferably be effected by addition of methane sulfonic acid.

The obtained composition may be put-up in unit dosage form as hereinbefore described, e.g. in the case of injectible solutions, by filling into ampoules after filtration, preferably with protective, e.g. CO_2 gassing.

In a further aspect the present invention also provides a method for the prophylactic treatment of thrombosis, in particular for the prevention of post-operative thrombosis, in a subject in need of such treatment, which method comprises administering to said subject an amount of a component i) as hereinbefore defined and of a component ii) as hereinbefore defined, sufficient to effect thrombosis prophylaxis, in particular to prevent occurrence of post-operative thrombosis.

Suitable daily dosages of components i) and ii) for use in the above method are as hereinbefore described. Preferably components i) and ii) are administered concommitantly in the form of a pharmaceutical composition as hereinbefore described.

In a yet further aspect the present invention also provides a pack or dispenser-device adapted for substantially concommitant presentation or administration of a component i) as hereinbefore defined and of a component ii) as hereinbefore defined, said components i) and ii) being contained in said pack or dispenser device apart. Conveniently the components i) and ii) are each contained in the pack or dispenser device in unit dosage form, the quantities of components i) and ii) in each unit dosage being e.g. as hereinbefore described, i.e. with individual dosage forms most preferably comprising ca. 0.5 mg of component i) and 1,500, 2,500 or 5,000 IU of component ii). Preferably the pack or dispenser-device bears directions for the concommitant administration of a predetermined amount of each of components i) and ii).

Suitable dispenser-devices in accordance with the present invention include multiple-, e.g. twin-chambered syringes in which components i) and ii) are contained in separate chambers thereof and which are adapted for concommitant or immediately consecutive administration of the contained components by injection. Such multiple-chambered syringes are known in the art.

The following examples are illustrative of processes for the production of compositions in accordance with the present invention.

EXAMPLE 1

Process for the preparation of low molecular weight sodium heparinates having an average molecular weight of from ca. 6,000 to ca. 9,000

1,000 g whole sodium heparinate having an average molecular weight of 15,000 are dissolved in 6.66 litres distilled water, the pH adjusted to 2.7 by the addition of ca. 145 ml 25% HCl, and the whole passed through a 520 b 1/2 (0 320 mm) folded filter from the company Schleicher and Schüll. The obtained filtrate is pumped through a molecular filtration membrane having a nominal molecular weight exclusion limit of 10,000, (Pellicon filter-cassette: catalogue no. PT GC 00001 of the Millipore company) at room temperature and with the exclusion of light. The following conditions are employed:

Entry pressure:	3.2×10^5 Pa.
Pressure at the residue side:	1.2×10^5 Pa.

Total through-flow:	ca. 200 ml/min.
Residue flow:	ca. 196 ml/min.
Filtrate flow:	ca. 4 ml/min.

After pumping for 1 hour, the filtrate flow is lead into a separate container and collected. Filtration is stopped after ca. 24 hours. The filtrate (ca. 1000—1200 ml) is readjusted to the pH value of the original whole sodium heparinate solution (ca. pH 7) by the addition of ca. 3 ml 30% aqueous NaOH. This solution is FRACTION I.

The residue is adjusted to pH 3.5 by the addition of ca. 10 ml 30% aqueous NaOH and re-filtered for ca. 24 hours under the same conditions as set forth above. The filtrate (ca. 800 ml) is adjusted to the pH value of the original whole sodium heparinate solution (ca. pH 7) by the addition of aqueous NaOH. This solution is FRACTION II.

The residue is adjusted to pH 4.2 by the addition of ca. 60 ml 30% aqueous NaOH and re-filtered for ca. 24 hours, again under the same conditions as set forth above. The filtrate (ca. 500 ml) is adjusted to the pH value of the original whole sodium heparinate solution (ca. pH 7). This solution is FRACTION III.

The three fractions are each separately further processed as follows:

The sodium-heparinate is first precipitated by the addition of 1.1 x the volume of acetone, the oily, viscous precipitate allowed to settle overnight and the solvent decanted off. The residue is covered with ca. 3x the volume of methanol and the whole stirred thoroughly at ca. 1000 r.p.m. The sodium heparin subsequently precipitates as a whitish precipitate which is granulated in a mortar under methanol. The obtained suspension is filtered off and the residue dried at 60° at a pressure of ca. 200 Pa. In the event that the NaCl content is greater than 0.5% re-precipitation in accordance with the same technique will be required.

The three fractions thus obtained have the following characteristics:

ELEMENTARY ANALYSIS	FRACTION I	FRACTION II	FRACTION III
C	23.7%	24.9%	24.4%
H	3.3%	3.1%	3.2%
N	2.9%	2.4%	2.7%
O	47.1%	45.9%	46.8%
S	11.7%	11.9%	11.6%
Na	12.3%	11.8%	11.3%
Activity (PTT-Test), based on WHO-Standard III	ca. 75±5 IU/mg	ca 80±5 IU/mg	ca. 90±5 IU/mg
Anti Xa-activity	ca. 150±10 U/mg	ca. 155±10 U/mg	ca. 160±10 U/mg
Average mol. wt.	ca. 6,000±1,000	ca. 8,000±1,000	ca. 9,000±1,000
NaCl content	<0.5%	<0.5%	<0.5%

EXAMPLE 2

Preparation of a 1,500 IU low molecular weight heparin/0.5 mg dihydroergotamine injectible solution

1) 18.4 kg propylene glycol and 1.84 kg anhydrous glycerol are poured into a 50 litre stirring vessel and the mixture stirred for 10 minutes with CO_2 gassing. 0.0286 kg dihydroergotamine methane sulfonate and 0.426 kg lidocain hydrochloride are dissolved in the mixture with stirring and CO_2 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 ca. 10 mins. with CO_2 gassing. 85.71 million IU (= ca. 1.7 to 2.5 kg) sodium heparinate having an average molecular weight of 6,000 ± 1,000 and 0.114 kg of $CaNa_2$ EDTA hexahydrate (commercially available under the name calciumtitriplex) are then dissolved in the water with stirring and Co_2 gassing over a further 30 minutes.

3) The solution obtained via step 2) above is added with stirring and CO_2 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 CO_2 gassing. The pH of the solution is ca. 5.5.

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

5) The obtained solution is pre-filtered using a membrane-filter (0.2 um: Ultipor nm. Pall) and then passed via a sterilised pressure-filtration apparatus having a membrane filter (0.2 um: Ultipor nm Pall) at 1.7 bar with CO_2 directly into an ampoule-filling machine. The solution is filled in 0.8 ml dosages into 1 ml ampoules under sterile conditions.

EXAMPLE 3

Preparation of injectible solutions comprising 0.5 mg dihydroergotamine and i) 2,500 and 5,000 IU low molecular weight heparin.

The procedure of example 2 is repeated employing the same relative quantities of all ingredients except that in a first run 1 and 2/3 and in a second run 3 and 1/3 the relative proportion of sodium heparinate (average molecular weight = 6,000 ± 1,000) is used.

EXAMPLE 4

Preparation of injectible solutions comprising dihydroergotamine and low molecular weight heparin of average molecular weight = i) 7,000 ± 1,000 and ii) 8,000 ± 1,000.

The procedures of examples 2 and 3 are repeated but replacing the sodium heparinate of average molecular weight = 6,000 ± 1,000 with 1) sodium heparinate of average molecular weight = 7,000 ± 1,000 or 2) sodium heparinate of average molecular weight = 8,000 ± 1,000. In each case the relative proportions of all ingredients remain the same as in example 2. The relative proportions of sodium heparinate employed, are respectively ca. 3,000, ca. 5,000 and ca. 10,000 IU/1 mg dihydroergotamine methane sulfonate.

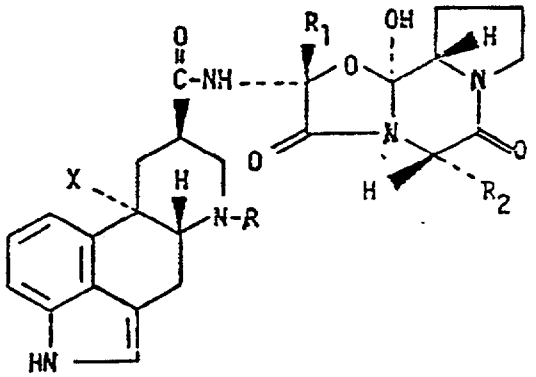
CLAIMS

1. A pharmaceutical composition comprising

i) an hydrogenated ergot alkaloid having vaso-constrictor activity, or pharmaceutically acceptable acid addition salt thereof, and

ii) a low molecular weight heparin, or pharmaceutically acceptable salt thereof.

2. A composition according to claim 1 wherein component i) is a hydrogenated ergot alkaloid of formula I



I

wherein R is hydrogen or C_{1-4}alkyl,
R_1 is methyl, ethyl or iso-propyl,
R_2 is iso-propyl, sec.-butyl, iso-butyl or benzyl
and
X is hydrogen or methoxy,
or a pharmaceutically acceptable acid addition salt thereof.

3. A composition according to claim 2, wherein component i) is dihydroergotamine or a pharmaceutically acceptable acid addition salt thereof.

4. A composition according to claim 2, wherein component i) is 6-nor-6-iso-propyl-9,10-dihydro-2'β-methyl-5'α-benzoergopeptine, or dihydroergovaline, or a pharmaceutically acceptable acid addition salt thereof.

5. A composition according to any one of claims 1 to 4, wherein component i) is the methane sulfonate, maleinate or tartrate of the anti-thrombotically active ergot alkaloid.

6. A composition according to any one of claims 1 to 5, wherein component ii) has an average molecular weight of ca. 10,000 or less.

7. A composition according to claim 6, wherein component ii) has an average molecular weight of ca. 8,000 or less.

8. A composition according to any one of claims 1 to 7, wherein component ii) has an average molecular weight of not less than ca. 4,000.

9. A composition according to claim 8, wherein component ii) has an average molecular weight of not less than ca. 5,000.

10. A composition according to claim 9, wherein component ii) has an average molecular weight of not less than ca. 6,000.

11. A composition according to any one of claims 6 to 10 wherein at least 60% of polymer units in component ii) have a molecular weight of 10,000 or less.

12. A composition according to any one of claims 1 to 11, wherein component ii) is the sodium, potassium or calcium salt of a low molecular weight heparin.

13. A composition according to any one of claims 1 to 12, wherein components i) and ii) are present in a ratio of 1 mg component i): 300 to 70,000 IU component ii).

14. A composition according to claim 13, wherein the ratio is 1 mg component i): 300 to 35,000 IU component ii).

15. A composition according to claim 14, wherein the ratio is 1 mg component i): 1,000 to 20,000 IU component ii).

16. A composition according to claim 15, wherein the ratio is 1 mg component i): 1,000 to 10,000 IU component ii).

17. A composition according to any one of claims 1 to 16 in the form of a solution in a pharmaceutically acceptable solvent medium and additionally comprising iii) a pharmaceutically acceptable calcium or magnesium salt of EDTA.

18. A composition according to claim 17, wherein iii) is $CaNa_2$ EDTA.

19. A composition according to claim 17 or 18, wherein iii) is present in a range of from about 1 to about 50 mg based on an amount of about 5,000 IU of iii).

20. A composition according to claim 20, wherein the range is from about 1 to about 25 mg.

21. A composition according to claim 20, wherein the range is from about 1 to about 10 mg.

22. A composition according to any one of claims 17 to 21, wherein the solvent medium comprises:

iv) water and

v) a pharmaceutically acceptable mono- or poly-alcohol.

23. A composition according to claim 22, wherein component iv) is present in an amount of from 45 to 72% based on the total volume of the composition.

24. A composition according to claim 22 or 23, wherein component v) is present in an amount of from 28 to 55% based on the total volume of the composition.

25. A composition according to any one of claims 21 to 22, wherein component v) comprises either a) ethanol and b) triethylene glycol, or c) glycerol and d) propylene glycol.

26. A composition according to claim 25, wherein a) and b) are present in a ratio of from 1:6 to 10 parts of weight, or wherein c) and d) are present in a ratio of from 1:8 to 12 parts by weight.

27. A composition according to claim 26, wherein a) and b) are present in a ratio of from 1:8 parts by weight, or wherein c) and d) are present in a ratio of from 1:10 parts by weight.

28. A composition according to any one of claims 1 to 27, additionally comprising vi) a physiologically acceptable anaesthetic.

29. A composition according to claim 28, wherein component vi) is an acetanilide anaesthetic or a pharmaceutically acceptable acid addition salt thereof.

30. A composition according to claim 28 or 29, wherein component vi) is present in an amount of from 1 to 2% by weight based on the total weight of the composition.

31. A composition according to any one of claims 1 to 30 in unit dosage form.

32. A composition according to claim 31 in ampoule form for injection.

33. A composition according to claim 31 or 32 comprising from ca. 0.2 to ca. 1.5 mg of i) and from ca. 1,000 to ca. 10,000 IU of ii).

34. A composition according to claim 33 comprising ca. 0.5 mg of i) and from ca. 1,500 to ca. 5,000 IU of ii).

35. A process for the preparation of a pharmaceutical composition according to any one of claims 1 to 34, which process comprises, bringing component i) into intimate admixture with component ii) for example bringing component i) together with component ii) into solution in a pharmaceutically acceptable solvent medium.

36. A method for the prophylactic treatment of thrombosis, in particular for the prevention of post-operative thrombosis, in a subject in need of such treatment, which method comprises administering to said subject an amount of a component i) as defined in any one of claims 1 to 12 and of a component ii) as defined in any one of claims 1 to 12 sufficient to effect thrombosis prophylaxis, in particular to prevent occurrence of post-operative thrombosis.

37. A method according to claim 36, wherein components i) and ii) are administered in the form of a composition as defined in any one of claims 1 to 33.

38. A method according to claim 36 or 37, wherein component i) is administered at a daily dosage rate of from ca. 0.2 to ca. 1.5 mg and component ii) is administered at a daily dosage rate of from ca. 1,000 to ca. 10,000 IU.

39. A method according to claim 38, wherein component i) is administered at a daily dosage rate of ca. 0.5 mg and component ii) is administered at a daily dosage rate of ca. 1,500 to ca. 5,000 IU.

40. A pack or dispenser-device adapted for substantially concommitant presentation or administration of a component i) as defined in any one of claims 1 to 12 and of a component ii) as defined in any one of claims 1 to 12, said components i) and ii) being contained in said pack or dispenser-device apart.

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