Solid Medicament Formulation containing Nifedipine

The invention relates to special solid medicament formulations containing nifedipine, a process for their preparation and use of nifedipine in the preparation of such formulations for the treatment of cardiovascular or coronary diseases.

It has already been disclosed that the compound nifedipine has potent cardiovascular effect, especially coronary and antihypertensive effects (see GB-A-1 173 862). By reason of the poor solubility and high sensitivity to light of nifedipine, relatively severe difficulties occur in pharmaceutical processing, as is obvious from numerous publications and patent applications on special formulations of this active compound. For example, to utilise the coronary effect of nifedipine, gelatin capsules which contain nifedipine in dissolved form and which ensure a rapid onset of action have been produced (see US-A-3 784 684). The rapid onset of action necessary for coronary disease is ensured by this capsule formulation. A disadvantage of this formulation with a rapid onset of action is its short duration of action. The concentration of nifedipine in the plasma decreases only 3 hours after administration to about 1/10 of the maximum initial concentration. Thus, for long-term treatment of coronary and hypertensive patients, it is necessary to administer the capsules repeatedly at short intervals.

Solid nifedipine formulations which are described and claimed in, for example, GB-A-1 456 618 ("solid solution in polyethylene glycol") or in EP-A-0 001 247 also have the same disadvantage of a short duration of action. In addition, an attempt is made in DE-A-2 822 882 to compensate for the poor solubility of nifedipine, using certain solubilisers and surface-active substances. All these formulations of nifedipine have the disadvantage of a short duration of action. The use

of additional auxiliaries, such as solubilisers, surface-active substances and porous vehicles, frequently leads to forms for administration which are very bulky and can be taken by the patient only with difficulty.

Furthermore, it is desirable to keep the number and the amount of the auxiliaries and vehicles as low as possible, since, when comparing two medicament preparations, preference is always given to that preparation which contains as few auxiliaries as possible in addition to the active compound, in order substantially to avoid undesired biological effects.

Attempts have also been made to produce nifedipine formulations having a longer duration of action. These contain nifedipine in a crystalline form (see DE-A- 3 039 919). In this reference, an attempt is made, by selecting a particular crystal size, to improve the release of nifedipine in aqueous media and thus to increase the absorbability and bioavailability on oral administration. It is true that the resulting tablets have a markedly longer action, which persists for more than 8 hours, but they have the disadvantage that the onset of action is considerably delayed. An onset of action after a few minutes is desirable for the treatment of acute coronary disease.

In order to utilise as completely as possible the advantageous properties of nifedipine, a need has long existed to make available a homogeneous formulation which

a) has a very rapid onset of action, particularly for the treatment of acute coronary disease;

b) has a long duration of action, particularly for the treatment of hypertension and for long-term therapy;

c) can be produced without an elaborate pharmaceutical process;

d) is in a small form for administration having a high

content of active compound, which can reliably and easily be taken by the patient.

The present invention provides a solid medicament formulation comprising a mixture of:

a) a nifedipine coprecipiate comprising a solid solution of non-crystalline nifedipine in a coprecipitate former; and b) a proportion of crystalline nifedipine.

The formulation may be in the form of tablets, coated tablets, capsules or sachets, and are preferably in the form of tablets, coated tablets or hard gelatin capsules.

Preferably the nifedipine coprecipitate comprises 1 part by weight of non-crystalline nifedipine and from 1 to 10, in particular 2 to 6, parts by weight of coprecipitate former. The formulation preferably comprises one part of non-crystalline nifedipine and from 1 to 5 parts by weight of crystalline nifedipine.

Suitable and preferable as the coprecipitate former are polyvinylpyrrolidone (PVP), methylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, especially PVP.

Nifedipine crystals which have a mean particle diameter of 10 to 1 μm, or nifedipine crystals which have a specific surface area of 0.5 to 6 m^2/g, in particular 1.0 to 4 m^2/g, are preferably employed as the crystalline nifedipine in the present formulations.

The present invention also provides a process for the preparation of a formulation as defined above, comprising:

a) dissolving nifedipine and a coprecipitate former in an organic solvent;

b) removing the organic solvent;

c) mixing the coprecipitate thus formed with crystalline nifedipine; and

d) converting the mixture into a solid form for administration.

The nifedipine coprecipitate is prepared by dissolving nifedipine and the coprecipitate former in a suitable organic solvent. Examples of suitable solvents are

chlorinated hydrocarbons having one to three carbon atoms, such as methylene chloride and chloroform, acetone and lower aliphatic alcohols having one to four carbon atoms such as ethanol or isopropanol, or mixtures thereof. After solution is complete, the solvent is removed by means of a suitable drying process (for example vacuum drying or spray drying) and the remaining solid coprecipitate is then comminuted.

In addition, in a variant of this process, it is possible immediately to granulate further the solution of nifedipine and coprecipitate former in the organic solvent with suitable pharmaceutical auxiliaries and vehicles, and then to remove the organic solvent from the granules or powders by, for example, drying.

Examples of auxiliaries and vehicles which may be mentioned are: water, vegetable oils (for example groundnut/sesame oil), alcohols (for example ethyl alcohol and glycerol), glycols (for example propylene glycol and polyethylene glycol), solid vehicles, such as ground natural minerals (for example kaolins, clays, talc, chalk and calcium phosphate), ground synthetic minerals (for example highly disperse silicic acid and silicates), sugars (for example sucrose, lactose and glucose), emulsifying agents, such as non-ionic and anionic emulsifiers (for example polyoxyethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, alkylsulphonates and arylsulphonates), dispersing agents, for example celluloses or cellulose derivatives such as methylcellulose, sodium carboxymethylcellulose, starch, lactose, PVP and crosslinked PVP, and lubricants (for example magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

Preferably the auxiliary is crystalline cellulose, starch or crosslinked PVP.

The crystalline nifedipine to be used in formulations according to the invention is prepared by milling the nifedipine crystals obtained on synthesis. This milling is preferably carried out with hammer mills or pinned disc mills, it being possible to obtain the desired particle size by varying the speed of rotation of the mill, the amount of product being introduced and/or the milling time.

It is advantageous for the preparation of particularly fine nifedipine crystals (particle diameter about 1 µm) to employ air jet mills.

The particle size is determined by measuring the specific surface area by the gas adsorption method

(see S. Brunauer: The absorption of gases and vapours, Princeton (1945)).

Knowing the state of the art and knowing the need, which has existed for years, to find a formulation which has both a rapid onset of action and a long duration of action of the active compound nifedipine, which is difficult to formulate, it is extremely surprising that a very simple and effective pharmaceutical arrangement, which places the specialist in the position of being able to utilise the coronary and hypotensive effects of nifedipine to an optimal extent, has been found in the formulation according to the invention. The investigations which follow show that the formulation according to the invention combines at the same time the known advantageous properties of the nifedipine gelatin capsule (rapid mobilisation of the active compound) with the retard effect lasting several hours (long-lasting levels in the blood plasma).

One tablet according to Example 1, containing 10 mg of non-crystalline nifedipine in a coprecipitate and 20 mg of crystalline nifedipine, was administered orally to each of five healthy male subjects. Table 1 shows the concentrations (µg/l) of nifedipine in the plasma over a period of 8 hours .

Table 1 Plasma concentration (µg/l) after administration of the two-phase tablet (according to Example 1)

Subj.	0.00 h	0.25 h	0.50 h	0.75 h	1.00 h	1.50 h	2.00 h	3.00 h	4.00 h	8.00 h
1	< 2	< 2	6.43	9.07	41.49	100.35	121.35	73.79	58.98	23.81
2	< 2	2.81	56.03	103.42	101.42	102.10	93.87	87.85	59.00	20.83
3	< 2	< 2	19.14	76.74	90.96	97.76	95.36	80.12	52.68	21.83
4	< 2	< 2	16.54	51.03	115.36	133.08	126.55	92.77	80.76	33.86
5	< 2	9.32	95.06	128.20	150.22	142.00	118.46	86.52	60.78	28.33
$\bar{X}$	< 2	3.03	38.64	73.69	99.89	115.06	111.12	84.21	62.44	25.73

Table 2 Plasma concentration (µg/l) after administration of a tablet containing 20 mg of crystalline nifedipine

Subj.	0.00 h	0.50 h	1.00 h	2.00 h	3.00 h	4.00 h	8.00 h	24.00 h
1	< 2	10.73	16.15	16.55	28.19	29.29	11.93	7.02
2	< 2	8.11	24.75	27.34	26.84	24.04	16.62	3.20
3	< 2	10.92	31.16	25.14	18.83	16.03	11.02	6.41
4	5.21	11.42	17.73	18.93	56.48	27.75	17.32	8.91
5	2.11	21.35	28.25	19.84	20.84	27.95	11.67	6.71
X	2.06	12.51	23.61	21.57	30.24	25.01	13.70	6.45

The same group of five healthy subjects received orally a tablet which contained 20 mg of crystalline nifedipine. The plasma concentrations show a delayed onset of action and overall lower plasma concentrations (Table 2, see page 7).

The comparison experiments above show that the formulation according to the invention combines the advantages of various formulations hitherto known without having their specific disadvantages. By having this formulation, the specialist is placed in a position of being able to utilise the valuable coronary and hypotensive properties of the active compound nifedipine. The formulation according to the invention permits simple, reliable and easy administration, and is an enrichment of pharmacy.

Medicament formulations according to the invention which may be mentioned as being preferred are: tablets, coated tablets, granules, capsules, suppositories, sachets and other solid medicament formulations. In certain cases, it can also be advantageous to combine the formulation according to the invention with other active compounds (for example with beta-blockers).

An advantageous method of preparation comprises initially preparing a nifedipine coprecipitate in the form of granules (granules I) and in a second step, preparing granules II which contain crystalline nifedipine and then mixing granules I and II in the ratio of amounts according to the invention and compressing to produce a suitable form for administration, such as tablets or coated tablets, or filling into hard gelatin capsules.

The present invention also provides a formulation as defined above for use in the treatment of cardiovascular or coronary diseases and use of nifedipine in the preparation of a formulation as defined above for the treatment of cardiovascular or coronary diseases.

The exemplary embodiments which follow illustrate the invention.

Example 1

Granules I:

10 g of nifedipine and 40 g of polyvinylpyrrolidone (PVP) 25 are dissolved in 60 g of acetone, and this

solution is granulated with a mixture of 105 g of microcrystalline cellulose, 20 g of maize starch and 10 g of crosslinked PVP. The composition is dried in vacuo, and then screened and mixed with 20 g of maize starch, 14.6 g of crosslinked PVP and 0.4 g of magnesium stearate.

Granules II:

20 g of crystalline nifedipine, 34.8 g of microcrystalline cellulose, 12 g of maize starch and 10 g of lactose are mixed and granulated with a paste of 2 g of maize starch in water with the addition of 1 g of polyoxyethylene sorbitan monooleate (Tween 80®). The moist composition is dried and screened and mixed with 0.2 g of magnesium stearate.

Granules I and II are mixed and an amount of 300 mg is filled into hard gelatin capsules or compressed to produce tablets.

Example 2

Granules I:

50 g of nifedipine and 100 g of PVP 25 are dissolved in 350 g of acetone, and this solution is granulated with a mixture of 420 g of microcrystalline cellulose, 99.5 g of maize starch and 25 g of crosslinked PVP. The composition is dried and screened.

Granules II:

150 g of crystalline nifedipine are mixed with 150 g of microcrystalline cellulose and 180 g of maize starch and granulated with a paste of 22.5 g of maize starch in water. The moist composition is dried and screened.

Granules I and II are mixed with 100 g of crosslinked PVP and 3 g of magnesium stearate, and an amount of 130 mg is fil into hard gelatin capsules or compressed to produce tablets.

Example 3

Granules I:

100 g of nifedipine and 400 g of PVP 25 are dissolved in 750 g of acetone, and this solution is

granulated with a mixture of 800 g of microcrystalline cellulose, 161 g of maize starch and 200 g of crosslinked PVP. The composition is dried and screened.

Granules II:

100 g of crystalline nifedipine are mixed with 100 g of microcrystalline cellulose and 120 g of maize starch and granulated with a paste of 14 g of maize starch in water with the addition of 1 g of polyoxyethylene sorbitan monooleate. The moist composition is dried and screened.

Granules I and II are mixed with 200 g of crosslinked PVP and 4 g of magnesium stearate, and an amount of 220 mg is filled into hard gelatin capsules or compressed to produce tablets.

Example 4

Granules I:

100 g of nifedipine and 1,000 g of hydroxypropylmethylcellulose are dissolved in 800 g of a solvent mixture comprising methylene chloride and ethanol. The solvent is removed in vacuo and the remaining material is comminuted.

Granules II:

200 g of crystalline nifedipine are mixed with 400 g of microcrystalline cellulose and 240 g of maize starch and granulated with a paste of 30 g of maize starch in water. The moist composition is dried and screened.

Granules I and II are mixed with 126 g of crosslinked PVP and 4 g of magnesium stearate, and an amount of 210 g is filled into hard gelatin capsules.

In a variant of this example, 210 g of this mixture of granules I and II are compressed to produce tablets.

Example 5

Granules I:

100 g of nifedipine and 600 g of hydroxypropylmethylcellulose are dissolved in 500 g of a solvent mixture comprising methylene chloride and ethanol. The

solvent is removed in vacuo and the remaining material is comminuted.

Granules II:

300 g of crystalline nifedipine are mixed with 400 g of microcrystalline cellulose, 360 g of maize starch and 100 g of lactose and granulated with a paste of 40 g of maize starch in water. The moist composition is dried and then screened.

Granules I and granules II are mixed with 96 g of sodium carboxymethylcellulose and 4 g of magnesium stearate, and an amount of 200 g is filled into hard gelatin capsules or compressed to produce tablets.

Example 6

Granules I:

50 g of nifedipine and 150 g of PVP 25 are dissolved in 400 g of acetone, and this solution is granulated with a mixture of 500 g of microcrystalline cellose, 160 g of maize starch and 40 g of crosslinked PVP. The composition is dried and screened.

Granules II:

200 g of crystalline nifedipine are mixed with 200 g of microcrystalline cellulose and 240 g of maize starch and granulated with a paste of 30 g of maize starch in water. The moist composition is dried and screened. Granules I and granules II are mixed with 126 g of crosslinked PVP and 4 g of magnesium stearate, and an amount of 170 mg is filled into hard gelatin capsules or compressed to produce tablets.

Example 7

Granules I:

50 g of nifedipine and 200 g of PVP 25 are dissolved in 400 g of acetone, and this solution is granulated with a mixture of 350 g of microcrystalline cellulose, 40 g of maize starch and 25 g of crosslinked PVP. The composition is dried and screened.

Granules II:

The preparation of granules II is carried out in the same manner as in Example 2.

Granules I and II are mixed with 129.5 g of crosslinked PVP and 3 g of magnesium stearate, and the mixture is compressed to produce tablets each weighing 130 mg.

CLAIMS

1. A solid medicament formulation comprising a mixture of:
a) a nifedipine coprecipiate comprising a solid solution of non-crystalline nifedipine in a coprecipitate former; and
b) a proportion of crystalline nifedipine.

2. The formulation of claim 1, wherein the nifedipine coprecipitate comprises one part of non-crystalline nifedipine and from one to ten parts of coprecipitate former.

3. The formulation of claim 1 or claim 2, wherein the nifedipine coprecipitate comprises one part of non-crystalline nifedipine and from two to six parts of coprecipitate former.

4. The formulation of any one of claims 1 to 3, wherein the coprecipitate former is polyvinylpyrrolidone, methylcellulose, hydroxypropyl cellulose of hydroxypropyl methylcellulose.

5. The formulation of any one of claims 1 to 4, wherein the coprecipitate former is polyvinylpyrrolidone.

6. The formulation of any one of claims 1 to 5, comprising one part of non-crystalline nifedipine and from one to five parts of crystalline nifedipine.

7. The formulation of any one of claims 1 to 6, wherein the mean particle diameter of the crystals of the crystalline nifedipine is from one to ten micrometres.

8. The formulation of any one of the claims 1 to 7, wherein the specific surface area of the crystalline nifedipine is from one to four square meters per gram.

9. The formulation of any one of claims 1 to 8, in the form of tablets, coated tablets or hard gelatin capsules.

10. A process for the preparation of a formulation according to any one of claims 1 to 9, comprising:
a) dissolving nifedipine and a coprecipitate former in an organic solvent;
b) removing the organic solvent;
c) mixing the coprecipitate thus formed with crystalline nifedipine; and
d) converting the mixture into a solid form for administration.

11. The process of claim 10, wherein, prior to removing the organic solvent, the nifedipine solution is granulated with suitable pharmaceutical auxilaries and vehicles.

12. The process of claim 11, wherein the auxiliary is crystalline cellulose, starch or crosslinked polyvinylpyrrolidone.

13. The process of any one of claims 10 to 12, wherein the organic solvent is a chlorinated hydrocarbon having one to three carbon atoms, acetone, a lower aliphatic alcohol having one to four carbon atoms or a mixture therof.

14. The formulation of any one of claims 1 to 9 for use in the treatment of cardiovascular or coronary diseases.

15. Use of nifedipine in the preparation of a formulation according to any one of claims 1 to 9 for the treatment of cardiovascular or coronary diseases.