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# Pharmaceutical formulations with controlled release of the active substance

This invention relates to pharmaceutical formulations with controlled release of active substances having an influence on blood circulation, including the heart and isa4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate ester, especially Darodipine and isradipine.

Darodipine is the generic name of diethyl-4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.
It is disclosed in the British Patent GB 2.037766 B. For pharmaceutical use Darodipine is used as the free base.

The pharmacological and clinical properties have been extensively reviewed. Darodipine is a potent calcium antagonist on isolated coronary arteries and other peripheral blood vessels. Haemodynamic studies in healthy subjects show a reduction in total peripheral resistance and arterial blood pressure.

Darodipine is indicated for the treatment of angina pectoris, of hypertension, of stroke and of cerebral vasospasms.

Usual oral daily dosages are e.g. for the treatment of angina pectoris 75 to 300 mg, preferably given in 3 divided doses and for the treatment of hypertension 37.5 to 150 mg, given in 2 to 3 divided doses.

Isradipine is the generic name of isopropyl methyl-4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate.
It is generally administered as the free base.
It is disclosed in the British Patent GB 2.037.766 B.

The pharmacological and clinical properties of Isradipine have been extensively investigated. It is a potent calcium antagonist and influences in particular the coronary and the peripheral arteries. The drug is especially indicated for the treatment of e.g. hypertension, angina pectoris and cerebral insufficiency.
Usual oral daily dosages are 10 to 20 mg, preferably divided into smaller dosages of 5 to 10 mg two times a day.

The administration of the active substances mentioned above can occasionally be associated with adverse side effects, e.g. headaches in case of Darodipine and headache, flush, palpitation and

tachycardia, when Isradipine is administered.

We have now found it is preferred to keep the concentration of the active substance at a therapeutically active level between narrow limits and to avoid the usual drug burst just after administration of non-controlled release preparations, which leads to temporary high blood levels and to proportionately strong adverse effects.

Therapy can be improved by administering two or three times a day smaller doses, the sum of which equals the total daily dosage. However, this manner is cumbersome and still does not meet the requirement of providing blood levels of active substance only between narrow limits.

The present invention provides a controlled release formulation of the active substances having a prolonged action of the active substance to reduce the number of times the active substance has to be administered each day and to reduce certain adverse reactions. Additionally the present formulations provide under the test conditions excellent bioavailability in food interaction studies, e.g. as described hereinafter.

The present invention accordingly provides a controlled release formulation for oral administration comprising an active substance which is

a 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro 2,6 -dimethyl-3,5-pyridine dicarboxylate ester

- a pharmaceutically acceptable hydrophilic swellable substance and

- a pharmaceutically acceptable inert fatty material.

In a further aspect the present invention provides a controlled release formulation for oral administration and containing Isradipine, and having a relative bioavailability of more than 65% compared with a non controlled release oral Isradipine formulation on administration to a subject in the fasted state.

Conveniently the controlled release formulation for oral administration comprises an active substance which is a 4-(2,1,3-bezoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate ester), having bioavailability differences on administration to a subject in the fasted state and to a subject in the unfasted state of at most 20%.

Preferred amounts of Darodipine in unit dosage form are from 10 to 200 mg, especially 20 to 150, e.g. 100 mg.
Preferred amounts of Isradipine in unit dosage form are from 5 to 40 mg, especially 10 to 20 mg.

Preferred swellable substance is a cellulose compound, which in water turns into a colloid.

Hydrophilic swellable substances that are preferred include one or more natural, partially or totally synthetic, anionic or, preferably, nonionic hydrophilic gums, modified cellulose substances or protein aceous substances such as, for example, acacia, gum tragacanth, locust bean gum, guar gum, karaya gum, agar, peptin, carrageen, soluble and insoluble alginates, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, sodiumcarboxymethylcellulose, carboxypolymethylene, gelatin.

Preferred are cellulose hydrocolloids which include methylcellulose, hydroxypropylcellulose and especially hydroxypropylmethylcellulose and sodium carboxymethylcellulose.

Preferably the weight ratio of Darodipine to swellable substance is from 1:0.2 to 1:2, especially from 1:0.5 to 1,
and of Isradipine to swellable substance from 1:2 to 1:20, especially from 1:4 to 1:10.

Suitable pharmaceutically acceptable inert fatty materials include beeswax; fatty acids; long chain fatty alcohols, such as, for example, cetyl alcohol, myristyl alcohol, stearyl alcohol, esters, e.g. glycerides such as glyceryl esters of fatty acids or hydrogenated aliphatic acids such as, for example, glyceryl mono-stearate, glyceryl distearate, glyceryl esters of hydrogenated castor oil and the like; oils such as mineral oil and the like. Fatty materials are preferably such with melting points between 30 and 90°C.

Most preferably fatty materials have a melting point from 45°C to 65°C and include glycerides such as glyceryl palmitates and stearates and fatty acids such as hydrogenated castor oil and fatty acid esters such as cetyl palmitate.

Preferably the weight ratio of Darodipine to the fatty material is from 10:0.2 to 10:5, especially 10:0,5 to 10:1; and of Isradipine to the fatty material from 1:0.3 to 1:2, especially 1:0.5 to 1:1.5, in particular 1:0.5 to 1:1.

The formulations contain preferably both hydroxypropyl-methyl-cellulose as the swellable agent and cetyl palmitate as the fatty material.

It is also convenient to incorporate in the formulation at least one of other soluble or insoluble pharmaceutical excipients such as calcium sulfate, calcium phosphate, lactose, mannitol, sucrose, sorbitol, colloidal silica, and magnesium stearate. Preferably a soluble excipient, especially lactose is present.
If these other excipients are present, then the weight ratio of Darodipine to the other excipients is conveniently from 10:1 to

1:2, especially 5:1 to 1:1; and of Isradipine to the other excipients from 1:4 to 1:15, especially 1:5 to 1:10.

The formulation may be produced in conventional manner by mixing the ingredients together, preferably melting the fatty material. The resultant mixture is in powder form. The powder can be pressed to form a tablet, but is preferably filled into a capsule.

If the fatty material is melted, the drug and additional excipients such as lactose, silica, calcium sulphate or calcium phosphate may be taken up in the molten fatty material. The mixture is then allowed to solidify and is then divided into small particles (granules).

The resultant granulate may be mixed with a, preferably porous, hydrophilic swellable substance and further excipients, e.g. magnesium stearate, and the mixture may be pressed to form a tablet or may be preferably filled into a capsule.

In a preferred aspect the present invention accordingly provides a formulation containing the active substance in a fatty material matrix granulate, the granulate particles being in contact with a hydrophilic swelling substance.

Preferably the swellable substance is present in a porous form.

We have surprisingly found that the formulations possess an excellent stability, despite the fact that the active substances are sensitive to many chemical reagents. Moreover, the formulations have a satisfactory pharmacodynamic and pharmacokinetic profile.

The resultant formulations in general have comparable bio-availability in standard clinical trials to conventional non-retarded formulations containing the same amounts of active substances. The formulations of the invention, even if administered once a day, may produce a therapeutic effect for at least 24 hours and even as much as 35 hours. The formulation for Darodipine and Isradipine may be administered only once a day in the known indications of the active substances at approximately the same daily doses as employed in the conventional non-retarded forms. Steady state studies show a narrow range between maximum and minimum active substance levels in the blood.

The formulations of the present invention are well tolerated.

Moreover, the present formulations provide similar profiles of activity in food interaction studies, e.g. before and after administration of breakfast, with fasted subjects.

The once-a-day formulations may be formulated in conventional manner, e.g. to be a capsule or tablet and may contain from 10 to 200 mg of active substance. Preferably they have the release profile as determined by in vivo or in vitro dissolution test, e.g. a release of about 34 percent of Darodipine and 50 to 65 percent of Isradipine over 6 hours in 0.1 NHCl, e.g. as in the experimental conditions in the Examples.

In the following examples all temperatures are in degrees Centigrade and are uncorrected.

Further information on the properties etc. of the pharmaceutical excipients named hereinafter may be obtained from the manufacturer, listed hereinafter, manufacturer's brochures or other sources,

especially H.P. Fiedler Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, 2nd Edition 1981, Edito Cantor, Aulendorf, W-Germany.

Silicon dioxide (silica) is e.g. brand Aerosil 200 available from Deutsche-Gold und Silberscheideanstalt, Frankfurt, W-Germany.

Glycerol ditripalmitostearat is e.g. brand Precirol Ato 5 available from ETS Gattefosse 929100 Boulogne-Brillancourt, France.

Hydroxypropylmethylcellulose 15000 cps and 4000 cps are e.g. brands Methocel K15M and Methocel 4EM available from Dow Chemical Company, Michigan 48640 USA.

Cetyl palmitate is e.g. brand Cutina CPA available from Henkel 4000, Düsseldorf, W-Germany, or is available from Gattefosse or from A/S Johan C. Martens and Company, Bergen, Norway.

Example 1:

| | Ingredient | mg |
|---|---|---|
| a) | Darodipine | 100 |
| b) | Lactose (200 mesh) | 30 |
| c) | Cetyl palmitate | 8 |
| d) | Hydroxypropylmethylcellulose (100,000 cps) | 60 |
| e) | Mg stearate | 2 |
| | | 200 |

Preparation

Ingredients a) and b) are sieved and mixed.
Ingredient c) is melted by heating to 60° and is added to the mixture which is heated to 55°C. The mass is stirred for 2 minutes or until it is a homogenous mixture and cooled overnight. The rushed mass is broken up and sieved (through 250 micron openings). Ingredients d) and e) are sieved (through 360 micron openings) and mixed in over 10 minutes. The mixture is then encapsulated.

In vitro release

| Time (hours) | Release of Darodipine |
|---|---|
| 1 | 7 |
| 2 | 14 |
| 4 | 25 |
| 6 | 34 |
| 24 | 97 |

EXAMPLE 2 : Capsule

| Ingredient | mg |
|---|---|
| a) Isradipine | 10 |
| b) Lactose | 97 |
| c) Glycerol ditripalmitostearate | 10 |
| d) Hydroxypropylmethylcellulose 4000 cps | 60 |
| e) Silica | 1 |
| f) Magnesium Stearate | 2 |
| | 180 |

Preparation (Charge of 6000 capsules)

Ingredients a) and b) are sieved and mixed. Ingredient c) is melted by heating to 56°C (m.p. 54°C) and is added to the mixture which is heated to 55°C. The mass is stirred for 2 minutes or until it is a homogenous mixture and cooled overnight. The rushed mass is broken up and sieved (through 250 micron openings). Ingredients d), e) and f) are sieved (through 360 micron openings) and mixed in over 10 minutes. The mixture is then encapsulated.

In vitro release

| Time (hours) | Release % |
|---|---|
| 1 | 11 |
| 2 | 19 |
| 4 | 43 |
| 6 | 64 |
| 24 | 102 |

EXAMPLE 3: Capsule

| Ingredients | | mg |
|---|---|---|
| a) Isradipine | | 10 |
| b) Microcristalline cellulose | | 97 |
| c) Cetyl palmitate | | 5 |
| d) Hydroxypropylmethylcellulose | 4000 cps | 45 |
| e) Silica | | 1 |
| f) Magnesium stearate | | 2 |
| | | 160 |

Preparation

In analogous manner to that disclosed in Example 2

In vitro release

| Time (hours) | Release % |
|---|---|
| 1 | 11 |
| 2 | 20 |
| 4 | 36 |
| 6 | 52 |
| 24 | 96 |

EXAMPLE 3: Capsule

| Ingredients | | mg |
|---|---|---|
| a) Isradipine | | 10 |
| b) Microcrystalline cellulose | | 47 |
| c) Cetyl palmitate | | 10 |
| d) Hydroxypropylmethyl cellulose | 15000 cps | 90 |
| e) Silica | | 1 |
| f) Magnesium stearate | | 2 |
| | | 160 |

In a clinical test a very good retard profile and relative bioavailability of the composition of Example 3 in fasted and in non-fasted subjects could be established, compared with non-retarded capsules containing the same amount of Isradipine.

Preparation

In analogous manner to that disclosed in Example 2.

In vivo release

In a study to evaluate the bioavailability of the capsule of Example 3, this capsule and a reference capsule containing Isradipine in a non-prolonged release form were administered to fasting subjects. The prolonged release capsule was additionally administered to non-fasted subjects.

The composition of the conventional reference capsule containing Isradipine in a non-prolonged release form was as follows:

| Ingredients | mg |
|---|---|
| a) Isradipine | 10 |
| b) Lactose | 167 |
| c) Corn starch | 128 |
| d) Sodium laurylsulphate | 5.5 |
| e) Silica | 1.5 |
| f) Polyethylenglycol 6000 | 8.0 |

The study employed an open-label three-way randomized crossover design in 9 healthy male volunteers, Subjects were given a single oral dose of either a non-prolonged release reference capsule (10 mg) in the fasted state or a prolonged release capsule according to Example 3 (10 mg) in the fasted and in the non-fasted state. The intervals between the three different administration periods were at least 7 days.

Blood samples of each volunteer were collected from 0 to 48 hours after each dose and plasma was analysed for Isradipine by using a RIA technique (detection limit 0.1 nanogram/ml).

The mean temporal plasma concentration data are plotted graphically in figure 1, in which

● = 10 mg prolonged release capsule in the fasted state

○ = 10 mg prolonged release capsule in the non-fasted state and

△ = 10 mg conventional non-prolonged release capsule.

Plasmaconcentration in nanogram/ml vs. time in hours

From the curves the following data are calculated:

| | Prolonged release capsule (10 mg) non-fasted state | Prolonged release capsule (10 mg) fasted state | Reference tablet (10 mg) fasted state |
|---|---|---|---|
| $AUC_0^{48}$ in ng h/ml | 34.73 | 34.67 | 49.65 |
| $C_{max}$ in ng/ml | 3.70 | 1.77 | 14,22 |
| $T_{max}$ (in hours) | 8,55 | 9 | 1.89 |

Geometric mean for n = 9 subjects,

$AUC_0^{48}$ = Aerea under the curve from 0 to 48 hours.

Compared with the reference form the relative bioavailability is more than 65%.

CLAIMS

1. A controlled release formulation for oral administration comprising

   - an active substance which is a 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate ester,

   - a pharmaceutically acceptable hydrophilic swellable substance and a pharmaceutically acceptable inert fatty material.

2. A formulation according to claim 1 containing Darodipine as the active substance.

3. A formulation according to claim 2, wherein the active substance is Isradipine.

4. A formulation according to any one of the preceding claims wherein the swellable substance is a cellulose hydrocolloid.

5. A formulation according to any one of the preceding claims wherein the swellable substance is hydroxypropylmethylcellulose.

6. A formulation according to any one of the preceding claims 2-5 wherein the fatty material is a hydrophobic material with a melting point between 30 and 90°C.

7. A formulation according to any one of the preceding claims 2-6 wherein the fatty material is a fatty acid ester.

8. A formulation according to any one of the preceding claims 1-7 wherein the fatty material is cetyl palmitate.

9. A formulation according to any one of the preceding claims containing from 5 to 40 mg of Isradipine.

10. A formulation according to any one of claims 3 to 9, wherein the weight ratio of Isradipine to the swellable substance is from 1:2 to 1:20.

11. A formulation according to any one of the preceding claims 2 to 10, wherein the weight ratio of Isradipine to the fatty material is from 1:0.3 to 1:2.

12. A formulation according to any one of the preceding claims 2-11 containing Hydroxypropylmethylcellulose as the swellable agent and cetyl palmitate as the fatty material.

13. A formulation according to claim 1 substantially as herein-before described with reference to any one of the Examples

14. A formulation according to any one of the preceding claims 2-13, containing the active substance in a fatty material matrix granulate, the granulate particles being in contact with a hydrophilic swelling substance.

15. A method for the preparation of a controlled release formulation for oral administration according to claims 1 to 14, which comprises mixing the active substance with a hydrophilic swellable substance and the fatty material.

16. A method according to claim 15, which comprises mixing the active substance with the molten fatty material, solidifying and granulating the mixture and mixing the granulate particles with the swellable substance.

17. A controlled release formulation for oral administration according to claim 1 and containing Isradipine, and having a relative bioavailability of more than 65% compared with a non controlled release oral Isradipine formulation on administration to a subject in the fasted state.

18. A controlled release formulation for oral administration according to claim 1 comprising an active substance which is a 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate ester), having bioavailability differences on administration to a subject in the fasted state and to a subject in the unfasted state of at most 20%,