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(54) **NOUVELLE FORMULATION PHARMACEUTIQUE**
(54) **NEW PHARMACEUTICAL FORMULATION**

(57) An extended relase preparation of felodipine containing the active compound dissolved or dispersed in a solubilizer as well as a process for the preparation thereof.

Abstract

An extended relase preparation of felodipine containing the active compound dissolved or dispersed in a solubilizer as well as a process for the preparation thereof.

# NEW PHARMACEUTICAL FORMULATION

## Field of the invention

The present invention relates to a pharmaceutical extended release formulation of felodipine, and to methods of preparing such a formulation.

The object of this invention is to obtain a solid formulation with good bioavailability and extended release of the active substance.

## Background of the invention

Pharmaceuticals with very poor water solubility present formulation problems due to their slow rate of dissolution. Their efficacy can be severely limited and large interindividual variations of absorption can occur. Felodipine is a drug having very low solubility. Felodipine is commonly classified as a calcium antagonist, which are widely used for the treatment of cardiovascular disorders such as ischaemic heart disease and arterial hypertension. Felodipine has a solubility of only 0.5 mg/l in water at 25°C.

Several ways to increase drug absorption have been described in the prior literature. One way is described in DE-A-3024858, where a sparingly soluble substituted dihydropyridine, nicardipine, is used in its amorphous form in order to obtain increased absorption of the active compound from the intestine. Another way is described in EP-A-47899, where very small crystals of a practically insoluble dihydropyridine, nifedipine, have been used in order to increase the extent of the biovailability. These methods and others are also described in "Techniques of solubilization of drugs", Ed S.H. Yalkowsky in Drugs and the pharmaceutical sciences, Vol. 12. Of particular relevance to the present invention is that surfactant solubilizing agents may be employed in order to increase the bioavailability of the drugs with very low solubility. It is stated that the improvement of absorption properties can be ascribed to three processes: (1) increased wetting, (2) increased

permeability of membranes and (3) solubilization. The cited publication describes several examples and serves as a good review of the state of the art concerning the solubilizing of drugs, especially in order to increase the bioavailability of drugs with very low solubility.

From DE-A-3400106 controlled release preparations are known containing one or more natural, partially synthetic or synthetic polymers, one or more lipophilic and/or hydrophilic solvent(s) or thickener(s) together with one or more pharmaceutically active compound(s). In the examples it is described to use a solubilizer in an amount by weight to the active compound which is much less than 1:1.

In the medical treatment of various diseases, e.g. in the cardiovascular, gastrointestinal and chemotherapeutic field, it is an advantage to have a constant concentration of the administered drug in the blood. Thus an extended release of the drug from the pharmaceutical preparation is wanted.

It is important that the extended release preparation delivers the amount of drug needed to maintain an adequate and even effect during the entire therapeutic dosage interval. This usually means that the drug should be delivered at a constant rate to give an even concentration of administered drug in the blood. This is of specific importance for drugs having a small therapeutic index, that is a small difference between effective and toxic concentration. A delayed and constant release of the drug will also be of importance for locally irritating drugs having potential risk of causing gastrointestinal disturbances when present in large local concentrations or for drugs having a short elimination half-life. In the latter case a less frequent administration and thus better patient compliance (cf. Hayes R.B. et al. Clin.Pharm.Ther. (1977), 22, p. 125-130) may be obtained with extended release preparations compared with conventional dosage forms.

A drug in extended release form is generally given via the oral route. The preparations should preferably give an extended and reproducible release of drug and contribute to a reproducible absorption, have no toxic or irritating constituents and be suitable also for

high dosage drugs. Conventionally, extended release is achieved by controlling dissolution and/or diffusion of medicament from the dosage form. Several materials are employed for this purpose e.g. waxes, fatty materials, polymers, natural, synthetic and semisynthetic gums. Among the gums, hydroxypropyl methylcellulose (HPMC) constitutes an important class because of its pH-independent properties as well as its semisynthetic origin. A review of cellulose ethers in hydrophilic matrices for oral controlled release dosage forms is given by Alderman D.A. Int.J.Pharm.Tech.&Prod.Mfr (1984), 5(3) 1-9. The chemical treatment of HPMC to generate a desired constitution and the use of these qualities are disclosed in US 3 087 790, US 4 226 849, US 4 357 469 and US 4 369 172. SE-A-8008646-5 describes a combination of HPMC and hydroxypropyl cellulose which is used to control the release rate of a pharmaceutically active compound.

When a hydrophilic matrix is used the soluble polymer forms a gelatinous layer around the tablet after the exposure of the tablet to gastro-intestinal fluids or saliva. The relase of the drug is limited by the rate of water penetration into, and diffusion of drug through, the gel formed (Bamba et al. Int.J.Pharm. (1979), 2, 307). Erosion of the gel structure is also an important release mechanism of a drug from the system. The polymers used have to hydrate rapidly in order to protect the tablet from fast dissolution (Alderman 1984).

The rate of absorption of a drug with very low solubility into the circulation from the intestinal tract is closely related to the rate of dissolution. Since a low dissolution rate generally results in a low extent of bioavailability it is difficult to decrease the rate of absorption, i.e. increase the duration, without at the same time lowering the extent of bioavailability.

US 4 803 081 discloses an extended release preparation of an active compound with very low solubility containing the active compound dissolved or dispersed in a semi-solid or liquid non-ionic solubilizer and whereby the amount by weight of the solubilizer is at least equal to the amount by weight of the active compound.

Description of the invention

It is an object of the present invention to provide a formulation of felodipine that shows prolonged and nearly constant rate of drug absorption for a period of at least 24 hours and concurrently maintains a high extent of bioavailability. A further object is to provide a formulation that is easy to manufacture. A still further object of the invention is to provide a formulation that contains a low amount of solubilizer. The solubilizers suitable according to the invention are defined below. The active compound is preferably dissolved or dispersed in the solubilizer. In the solution the drug is included in a micell-structure formed by the solubilizer. The mixture of the drug and the solubilizer is incorporated into a pharmaceutical formulation, which gives prolonged release.

In a first embodiment the present invention relates to a solid formulation with extended release of felodipine comprising felodipine dissolved or dispersed in a solubilizer selected from the group consisting of a polysorbate, a poloxyethylated glycol monoether, a polyoxyethylated alkyl phenol, a poloxamer, a polyoxyethylene castor oil derivative, a polyoxyethylene stearate or another fatty acid ester with PEG, a glyceride, a sorbitan ester, and a sucroglyceride.

In a further embodiment the present invention relates to a process for the preparation of a solid formulation with extended release of felodipine whereby the active compound is dissolved or dispersed in a solubilizer selected from the group consisting of a solid formulation with extended release of felodipine characterized in that it comprises felodipine dissolved or dispersed in a solubilizer selected from the group consisting of a polysorbate, a poloxyethylated glycol monoether, a polyoxyethylated alkyl phenol, a poloxamer, a polyxyethylene castor oil derivative, a polyoxyethylene stearate or another fatty acid ester with PEG, a glyceride, a sorbitan ester, and a sucroglyceride, whereafter the mixture is incorporated into a suitable release controlling system in a known way and formed to a pharmaceutical dosage unit.

The solubilizers suitable for the formulations according to the invention are semi-solid or liquid non-ionic surface active agents at ambient temperature, such as non-ionic esters and/or ethers of polylethylene glycols:

*a) Polysorbates* - complex mixtures of partial esters of sorbitol and it mono- and di-anhydrides condensed with an approximate number of moles of ethylene oxide. Examples - Tweens; Crillets; Capmul derivatives; Liposorbs; etc. See page 375 ( the reference here and later is to Handbook of Pharmaceutical Excipients, 2nd ed; Eds: A Wade and PJ Woller, Pharmaceutical Press 1994).

*b) Polyoxyethylated glycol monoethers (polyoxyethylene alkyl ethers)*, i e alkyl chains with ethylene oxide chains. Examples are C16E7 (heptaoxyethylene glycol monohexadecylether), Cetomacrogol 1000 BPC, Brij or Atlas series. See page 367 + 556.

*c) Polyoxyethylated alkyl phenols*, e g Tritons;

*d) Poloxamers*, i e block copolymers of the type PEO-PPO-PEO where PEO = polyethylene oxide and PPO = polypropylene oxide with different chainlengths (also known as e g Pluronics). See page 352.

*e) Polyoxyethylene castor oil derivatives* - ethylene oxide reacted with (hydrogenated) castor oil (triglycerides of (hydrogenated) stearic acid). Example Chremophors. See page 371.

*f) Polyoxyethylene stearates and other fatty acid esters with PEG.* Examples Solutol and Labrasol. See page 379.

*g) Special substances*, e g TPGS (tocopheryl polyethylene glycol succinate); glycofurol (See page 213).

Further solubilizers, not belonging to the class of non-ionic esters and/or ethers of polyethylene glycols, suitable for the preparation according to the invention are

*h) Glycerides (mono-glycerides),* e g, Monoolein (Glyceryl monooleate), Capmul, Captex, Imwitor, Gelucire, Myverol etc. See page 207.

*i) Sorbitan esters* - partial esters of sorbitol and its mono- and di-anhydrides with oleic acid, eg Spans etc. See page 473.

*j) Sucroglycerides - sucrose esters of fatty acids.*

*k) Special substances* - cyclodextrins solid; See page 147.

Particularly preferred solubilizers are within categories a)-g):

- Different types of Chremophor: Chremophor EL, RH 40, RH 60
- Pluronics F127 or F68 (Poloxamer 407 and 188)
- Solutol HS 15
- Labrasol
- Cetomacrogol 1000 or Brij 97

and within categories h)-k):

- Gelucire 44/14 or Gelucire 50/13
- Imwitor 742
- Monoolein (glyceryl monooleate) in combination with a medium chain monoglyceride, i e Myverol 18-99 + Capmul
- Span 20 or Span 80.

The active compound mixed with the solubilizer is incorporated into different kinds of known controlled release systems, e.g. a hydrophilic gel system, beads coated with a rate controlling membrane, which can be a diffusion retarding coating or a disintegrating coating or tablets with an inert porous matrix. According to the invention the solubilized drug is preferably combined with a hydrophilic gel system, namely a hydrophilic swelling matrix e.g. HPMC. This form of controlled release mechanism is a suitable way to control the release of the micelles of drug and solubilizer. The technical properties are good and also the performance in vivo is good. Among different hydrophilic materials tested, HPMC, hydroxypropyl methylcellulose, is the best gel-forming material. Other examples of suitable compounds effecting the release of the active compound from the hydrophilic gel system are guar gum, xanthan gum, carboxypolymethylene, different cellulosic materials e.g. hydroxyethyl cellulose, sodium carboxymethylcellulose and hydroxypropyl cellulose, lactose, aluminium silicate and polyethylene oxide.

The preparation according to the invention contains 20-80% by weight, preferably 30-50% by weight of the hydrophilic gel system.

It is especially preferable to use HPMC having a hydroxypropyl content of 4-12% by weight, especially about 8.5% by weight and a viscosity lower than 100 cps, e.g. 6.15 and/or 50 cps. The viscosity is measured by a standardized method described e.g. in United States Pharmacopeia XXI, 1985, p. 672.

The final formulation is e.g. in the form of a gel tablet. By a careful choice of fillers and binders as well as gel forming material the preparation can be manufactured into a commercially acceptable form, e.g. a tablet or a hard gelatin capsule comprising the gel forming granulate, that shows unexpectedly good absorption of the active compound as well as a prolonged duration of action. In the formulation according to the invention the proportions between the active compound and the solubilizer varies in the range from 1:0.01 to 1:10, preferably in the range from 1:0.1 to 1:8, and most preferably in the range

from 1:0.5 to 1:6. When any of the solubilizers a) – g) is selected the proportions is preferably in the range from 1:0.01 to 1:1.

Also other types of controlled release formulations may be used according to the invention e.g. tablets with an inert porous matrix; capsules comprising granules with a diffusion retarding coating or a disintegrating coating.

The tablets with an inert porous matrix are obtained by mixing the drug and solubilizer with water-insoluble polymers or waxes and with fillers and binders. Polyvinylacetate, polyvinylchloride, ethylcellulose, paraffin and cellulose acetate phthalate could be used as suitable diffusion-retarding polymers. The filles and binders are solid, powdered carriers such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivative, gelatine or other suitable carrier. The mixture is moistened with a solvent, e.g. water or ethanol or a solution consisting of e.g. water and a polymer e.g. polyvinylpyrrolidone. Also a lubricating agent e.g. magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol wax may be added. The mixture is then formed to tablets.

The capsules comprising granules with extended release characteristics are obtained by making a core material containing the drug and the solubilizer together with fillers. The surface of the core is then coated with diffusion-retarding water insoluble polymers or waxes. The granules are then filled into hard gelatine capsules. The core material could e.g. be prepared by mixing the drug and the solubilizer with carefully selected fillers such as lactose, sorbitol, starch, cellulose derivatives or other suitable fillers. The mixture is moistened with a solvent, e.g. water or ethanol or a solution consisting of e.g. water and a polymer e.g. polyvinylpyrrolidone. The mass is formed to granules e.g. by extrusion and spheronization. The surfaces of the cores formed are coated with a solution consisting of a solvent e.g. methylene chloride and/or isopropyl alcohol and water insoluble polymers e.g. ethylcellulose. The granules are filled in hard gelatine capsules.

Working Examples

The following examples illustrate the invention. In all experiments the formulations were made with different types of polymers and solubilizers. The polymers used were: PEO (polyethylene oxide) with molecular weights of 4,000,000 g/mol (PEO 4´), 2,000,000 g/mol (PEO 2´), and 900,000 (PEO 0.9´); HPMC (hydroxypropyl methyl cellulose) with two different viscosities (60SH50 and 10,000); and HEC (hydroxy ethyl cellulose) of high (HEC HHX), medium (HEC HX), and low (HEC M) molecular weights. The surfactants used were: SDS (sodium dodecylsulfate), CTAB (cetyl trimethylammonium bromide), Gelucire®, and sulfobetaine. Filler and lubricants were AMS (aluminium magnesium silicate) and SSF (sodium stearyl fumarate). The tablets were typically made by dissolving felodipine in ethanol. A mixture of AMS and surfactant were then granulated with the felodipine solution. The granulate was dried at 50 $^{0}$C for about 16 hrs, and then mixed with the polymer and SSF. The tablets (diameter = 9 mm) were then made with a Kilian hydraulic press with a round punch.

In-vitro Dissolution (drug release)

Tablets were tested in 500 ml of phosphate buffer pH 6.5 containing 0.4 % cetyl trimethylammonium- bromide (CTAB) using USP dissolution apparatus II. A specially made quadrangular basket of gauze wire was used in order to keep the tablets in well defined position in the dissolution vessel. The stirring rate was 100 rpm and the temperature 37°C. The surfactant CTAB was added to the dissolution media to obtain sink conditions. Samples were withdrawn for analysis (absorbance of felodipine at 362 nm in a 1 cm cell). Amounts released of felodipine were determined from a calibration curve obtained from measurements of the absorbance of standard felodipine solutions based on the same medium as used in the release experiments.

**Example 1. Formulations of felodipine in PEO 4′ with felodipine/surfactant = 1/1 w/w.**

| | | | | | |
|---|---|---|---|---|---|
| Felodipine | 5 | 5 | 5 | 5 | mg |
| EtOH 99.9 | 30 | 30 | 30 | 30 | mg |
| PEO 4' | 160 | 160 | 160 | 160 | mg |
| AMS | 30 | 30 | 30 | 30 | mg |
| SDS | 5 | | | | mg |
| CTAB | | 5 | | | mg |
| Gelucire | | | 5 | | mg |
| Sulfobetaine | | | | 5 | mg |
| SSF | 2 | 2 | 2 | 2 | mg |

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**Result: % released felodipine from the different formulations of example 1.**

| TIME/hrs | SDS | CTAB | Gelucire | Sulfobetaine |
|---|---|---|---|---|
| 1 | 4 | 4 | 4 | 5 |
| 2 | 13 | 13 | 12 | 11 |
| 4 | 29 | 28 | 28 | 27 |
| 6 | 48 | 45 | 45 | 42 |
| 8 | 66 | 62 | 64 | 61 |
| 10.3 | 84 | 79 | 82 | 77 |

**Example 2. Formulations of felodipine in PEO 4′ with felodipine/surfactant = 1/0.1 w/w.**

| | | | | | |
|---|---|---|---|---|---|
| Felodipine | 5 | 5 | 5 | 5 | mg |
| EtOH 99.9 | 30 | 30 | 30 | 30 | mg |
| PEO 4' | 160 | 160 | 160 | 160 | mg |
| AMS | 30 | 30 | 30 | 30 | mg |
| SDS | 0.5 | | | | mg |
| CTAB | | 0.5 | | | mg |
| Gelucire | | | 0.5 | | mg |
| Sulfobetaine | | | | 0.5 | mg |
| SSF | 2 | 2 | 2 | 2 | mg |

**Result: % released felodipine from the different formulations of example 2.**

| TIME/hrs | SDS | CTAB | Gelucire | Sulfobet |
|---|---|---|---|---|
| 1 | 4 | 4 | 5 | 6 |
| 2 | 8 | 9 | 9 | 11 |
| 4 | 23 | 21 | 24 | 26 |
| 6 | 40 | 40 | 42 | 44 |
| 8 | 57 | 55 | 56 | 62 |
| 11 | 80 | 78 | 79 | 86 |

**Example 3. Formulations of felodipine in PEO 2′ with felodipine/surfactant = 1/1 w/w.**

| | | |
|---|---|---|
| Felodipine | 5 | Mg |
| EtOH 99.9 | 30 | Mg |
| PEO 2' | 160 | Mg |
| AMS | 30 | Mg |
| SDS | 5 | Mg |
| SSF | 2 | Mg |

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**Result: % released felodipine from the formulation of example 3. Results from duplicate experiments reported.**

| TIME/hrs | SDS | SDS |
|---|---|---|
| 1 | 9 | 9 |
| 2 | 20 | 24 |
| 4 | 34 | 36 |
| 6 | 58 | 61 |
| 8 | 77 | 79 |

**Example 4. Formulations of felodipine in PEO 0.9´ with felodipine/surfactant = 1/1 w/w.**

| | | |
|---|---|---|
| Felodipine | 5 | Mg |
| EtOH 99.9 | 30 | Mg |
| PEO 0.9' | 160 | Mg |
| AMS | 30 | Mg |
| SDS | 5 | Mg |
| SSF | 2 | Mg |

**Result: % released felodipine from the formulation of example 4. Results from duplicate experiments reported. The tablets were completely dissolved before 6 hrs.**

| TIME/hrs | SDS | SDS |
|---|---|---|
| 1 | 15 | 15 |
| 2 | 38 | 35 |
| 4 | 85 | 87 |

**Example 5. Formulations of felodipine in PEO 4´ with felodipine/surfactant = 1/7 w/w.**

| | | |
|---|---|---|
| Felodipine | 5 | Mg |
| EtOH 99.9 | 30 | Mg |
| PEO 4' | 160 | Mg |
| AMS | 15 | Mg |
| SDS | 35 | Mg |
| SSF | 2 | Mg |

**Result: % released felodipine from the formulation of example 5.**

| TIME/hrs | SDS |
|---|---|
| 1 | 8 |
| 2 | 16 |
| 4 | 31 |
| 6 | 53 |
| 8 | 63 |

**Example 6. Formulations of felodipine in HPMC 60SH50/10 000 with felodipine/surfactant = 1/1 w/w.**

| | | | | | |
|---|---|---|---|---|---|
| Felodipin e | 5 | 5 | 5 | 5 | mg |
| EtOH 99.9 | 30 | 30 | 30 | 30 | mg |
| HPMC 60SH50 | 56 | 56 | 56 | 56 | mg |
| HPMC 10 000 | 104 | 104 | 104 | 104 | mg |
| AMS | 30 | 30 | 30 | 30 | mg |
| SDS | 5 | | | | mg |
| CTAB | | 5 | | | mg |
| Gelucire | | | 5 | | mg |
| Sulfobetaine | | | | 5 | mg |
| SSF | 2 | 2 | 2 | 2 | mg |

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**Result: % released felodipine from the different formulations of example 6.**

| TIME/hrs | SDS | CTAB | Gelucire | Sulfobetaine |
|---|---|---|---|---|
| 1 | 5 | 5 | 4 | 5 |
| 2 | 11 | 10 | 11 | 10 |
| 4 | 25 | 21 | 24 | 24 |
| 6 | 41 | 36 | 39 | 39 |
| 7.5 | 53 | 46 | 51 | 51 |
| 10.5 | 77 | 68 | 73 | 77 |

**Example 7. Formulations of felodipine in HPMC 60SH50/10 000 with felodipine/surfactant = 1/0.1 w/w.**

| | | | | | |
|---|---|---|---|---|---|
| Felodipine | 5 | 5 | 5 | 5 | mg |
| EtOH 99.9 | 30 | 30 | 30 | 30 | mg |
| HPMC 60SH50 | 56 | 56 | 56 | 56 | mg |
| HPMC 10 000 | 104 | 104 | 104 | 104 | mg |
| AMS | 30 | 30 | 30 | 30 | mg |
| SDS | 0.5 | | | | mg |
| CTAB | | 0.5 | | | mg |
| Gelucire | | | 0.5 | | mg |
| Sulfobetaine | | | | 0.5 | mg |
| SSF | 2 | 2 | 2 | 2 | mg |

**Result: % released felodipine from the different formulations of example 7.**

| TIME/hrs | SDS | CTAB | Gelucire | Sulfobetaine |
|---|---|---|---|---|
| 1 | 5 | 5 | 4 | 5 |
| 2 | 12 | 14 | 12 | 14 |
| 4 | 25 | 28 | 23 | 25 |
| 6 | 39 | 45 | 38 | 42 |
| 8 | 55 | 60 | 53 | 56 |

**Example 8. Formulations of felodipine in HEC HHX with felodipine/surfactant = 1/1 w/w.**

| | | | | | |
|---|---|---|---|---|---|
| Felodipine | 5 | 5 | 5 | 5 | mg |
| EtOH 99.9 | 30 | 30 | 30 | 30 | mg |
| HEC HHX | 160 | 160 | 160 | 160 | mg |
| AMS | 30 | 30 | 30 | 30 | mg |
| SDS | 5 | | | | mg |
| CTAB | | 5 | | | mg |
| Gelucire | | | 5 | | mg |
| Sulfobetaine | | | | 5 | mg |
| SSF | 2 | 2 | 2 | 2 | mg |

**Result: % released felodipine from the different formulations of example 8.**

| TIME/hrs | SDS | CTAB | Gelucire | Sulfobetaine |
|---|---|---|---|---|
| 1 | 3 | 4 | 4 | 4 |
| 2 | 6 | 7 | 6 | 7 |
| 4 | 9 | 10 | 9 | 9 |
| 10 | 27 | 30 | 27 | 26 |
| 16.3 | 46 | 54 | 57 | 56 |
| 18 | 51 | 61 | 62 | 61 |
| 20 | 58 | 69 | 68 | 67 |
| 22 | 67 | 75 | 72 | 74 |
| 24.5 | 76 | 82 | 78 | 79 |

**Example 9. Formulations of felodipine in HEC HHX with felodipine/surfactant = 1/0.1 w/w.**

| | | | | | |
|---|---|---|---|---|---|
| Felodipine | 5 | 5 | 5 | 5 | mg |
| EtOH 99.9 | 30 | 30 | 30 | 30 | mg |
| HEC HHX | 160 | 160 | 160 | 160 | mg |
| AMS | 30 | 30 | 30 | 30 | mg |
| SDS | 0.5 | | | | mg |
| CTAB | | 0.5 | | | mg |
| Gelucire | | | 0.5 | | mg |
| Sulfobetaine | | | | 0.5 | mg |
| SSF | 2 | 2 | 2 | 2 | mg |

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**Result: % released felodipine from the different formulations of example 9.**

| TIME/hrs | SDS | CTAB | Gelucire | Sulfobetaine |
|---|---|---|---|---|
| 1 | 5 | 6 | 5 | 6 |
| 4.5 | 12 | 10 | 9 | 10 |
| 6 | 14 | 14 | 14 | 15 |
| 8 | 21 | 20 | 20 | 22 |
| 16 | 42 | 43 | 43 | 45 |
| 18 | 47 | 49 | 49 | 60 |
| 22 | 61 | 56 | 56 | 65 |
| 24 | 67 | 62 | 62 | 72 |

**Example 10. Formulations of felodipine in HEC M with felodipine/surfactant = 1/1 w/w.**

| | | |
|---|---|---|
| Felodipine | 5 | Mg |
| EtOH 99.9 | 30 | Mg |
| HEC M | 160 | Mg |
| AMS | 30 | Mg |
| SDS | 5 | Mg |
| SSF | 2 | Mg |

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**Result: % released felodipine from the formulation of example 10. The results from duplicate experiments are reported.**

| TIME/hrs | SDS | SDS |
|---|---|---|
| 1 | 9 | 9 |
| 2 | 18 | 21 |
| 4 | 28 | 30 |
| 6 | 46 | 49 |
| 8 | 67 | 65 |

**Example 11. Formulations of felodipine in HEC HX with felodipine/surfactant = 1/1 w/w.**

| | | |
|---|---|---|
| Felodipin | 5 | Mg |
| EtOH 99.9 | 30 | Mg |
| HEC HX | 160 | Mg |
| AMS | 30 | Mg |
| SDS | 5 | Mg |
| SSF | 2 | Mg |

**Result: % released felodipine from the formulation of example 11. Results from duplicate experiments are reported.**

| TIME/hrts | SDS | SDS |
|---|---|---|
| 1 | 3 | 3 |
| 2 | 8 | 10 |
| 4 | 24 | 25 |
| 10 | 66 | 76 |

Claims

1. A solid formulation with extended release of felodipine comprising felodipine dissolved or dispersed in a solubilizer selected from the group consisting of a polysorbate, a poloxyethylated glycol monoether, a polyoxyethylated alkyl phenol, a poloxamer, a polyoxyethylene castor oil derivative, a polyoxyethylene stearate or another fatty acid ester with PEG, a glyceride, a sorbitan ester, and a sucroglyceride.

2. A formulation according to claim 1, wherein the solubilizer is a poloxyethylated glycol monoether.

3. A formulation according to claim 2, wherein the solubilizer is Cetomacrogol 1000 or Brij 97.

4. A formulation according to claim 1, wherein the solubilizer is a poloxamer.

5. A formulation according to claim 4, wherein the solubilizer is Pluronics F 127 or F 68.

6. A formulation according to claim 1, wherein the solubilizer is a polyoxyethylene castor oil derivative and the proportion of the amount of weight of felodipine : amount of weight of the solubilizer is in the range from 1:0.01 to 1:1.

7. A formulation according to claim 6, wherein the solubilizer is a Chremophor.

8. A formulation according to claim 1, wherein the solubilizer is a polyoxyethylene stearate or another fatty acid ester with PEG.

9. A formulation according to claim 8, wherein the solubilizer is Solutol HS 15 or Labrasol.

10. A formulation according to claim 1, wherein the solubilizer is a glyceride.

11. A formulation according to claim 10, wherein the solubilizer is Gelucire 44/14, Gelucire 50/13, Imwitor 742, monoolein in combination with a medium chain monoglyceride.

12. A formulation according to claim 1, wherein the solubilizer is a sorbitan ester.

13. A formulation according to claim 12, wherein the solubilizer is Span 20 or Span 80.

14. A formulation according to any of the preceding claims, wherein proportion of the amount of weight of felodipine : amount of weight of the solubilizer is in the range from 1:0.01 to 1:10, preferably from 1:0.1 to 1:8, and most preferably 1:0.5 to 1:6.

15. A formulation according to any of the preceding claims wherein the release is controlled by an inert porous matrix, a diffusion retarding coating or a disintegrating coating.

16. A formulation according to any of the preceding claims wherein the release is controlled by a hydrophilic gel system.

17. A formulation according to claim 16 wherein the hydrophilic gelforming component constitutes between 20-80% by weight of the formulation.

18. A formulation according to claims 16 and 17 wherein the hydrophilic gel system comprises hydroxypropyl methylcellulose.

19. A formulation according to claim 18 wherein the hydroxypropyl methylcellulose has a hydroxypropyl content of 4-12% by weight.

20. A formulation according to one or more of the claims 16-19 wherein the hydrophilic gel system contains carboxypolymethylene.

21. A formulation according to one or more of the claims 16-19, wherein the hydrophilic gel system contains guar gum or xanthan gum.

22. A formulation according to one or more of the claims 16-19, wherein the hydrophilic gel system contains a cellulosic material, such as hydroxyethyl cellulose, sodium carboxymethyl cellulose or hydroxypropyl cellulose.

23. A formulation according to one or more of the claims 16-19, wherein the hydrophilic gel system contains lactose, aluminium silicate or polyethylene oxide.

24. A process for the preparation of a solid formulation with extended release of felodipine characterized in that the active compound is dissolved or dispersed in a solubilizer selected from the group consisting of a solid formulation with extended release of felodipine characterized in that it comprises felodipine dissolved or dispersed in a solubilizer selected from the group consisting of a polysorbate, a poloxyethylated glycol monoether, a polyoxyethylated alkyl phenol, a poloxamer, a polyxyethylene castor oil derivative, a polyoxyethylene stearate or another fatty acid ester with PEG, a glyceride, a sorbitan ester, and a sucroglyceride, whereafter the mixture is incorporated into a suitable release controlling system in a known way and formed to a pharmaceutical dosage unit.