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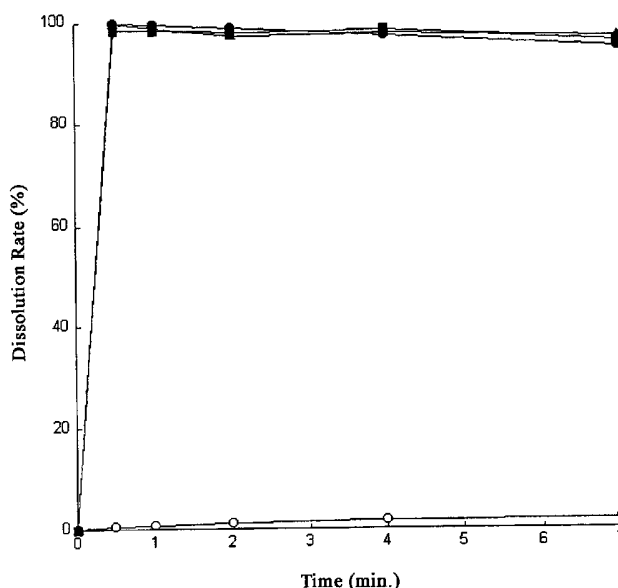
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(54) Title: CONTROLLED RELEASE COMPOSITION COMPRISING FELODIPINE AND METHOD OF PREPARATION THEREOF



(57) Abstract: The present invention relates to a controlled release composition comprising felodipine, a fatty acid ester of sucrose and a copolymer of methacrylic acid and a method for producing the same. The composition according to the present invention can effectively enhance the solubility of felodipine. The method according to the present invention comprising the steps of dissolving felodipine, a fatty acid ester of sucrose and a copolymer of methacrylic acid in an organic solvent and uniformly combining with an excipient, followed by drying, can effectively solve the problems involved in using the conventional solid dispersions, such as residual organic solvent, difficulty in stirring due to a high viscosity of the solid dispersion at the end phase of drying, and ununiformity of content.



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CONTROLLED RELEASE COMPOSITION COMPRISING FELODIPINE AND METHOD OF PREPARATION THEREOF

Technical Field

5 The present invention relates to a controlled release composition comprising felodipine, a fatty acid ester of sucrose and a copolymer of methacrylic acid and a method for producing the same.

Background Art

10 Felodipine, whose chemical name is 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridindicarboxylic acid ethylmethyl ester, is a drug with calcium antagonistic activity which is useful for treating circulatory system diseases and has a very low solubility in water of 0.5 mg/L.

 The solubility in poorly water-soluble drugs such as felodipine can be a
15 limiting factor in the development of preparations thereof since the dissolution of the active ingredients plays an important role in absorption process and bioavailability. Several methods for enhancing the absorption of felodipine with low water solubility have been described in the prior art. For example, US PAT NO. 5,071,642, WO NO. 9,702,017 and WO NO. 9,623,499 disclosed methods for producing controlled release
20 preparations comprising felodipine, in which the dissolution rate of felodipine has been improved by solubilization, by melting felodipine under a high temperature with polyethylene glycols, Poloxamer and the like, which have a high molecular weight, in order to increase the water solubility of felodipine, and the mixture is formulated into controlled release preparations using a water-soluble polymer or fat-soluble polymer as

a base for sustained release agents. However, these methods have disadvantages that their preparation procedures require particular care of safety in practical use.

Korean Patent Publication No. 95-2147, US PAT NO. 4,803,081 and US PAT NO. 4,942,040 remarkably improved the water solubility of felodipine by using non-ionic surfactants such as Cremophor®. However, the methods described in the above the patents have a disadvantage that felodipine precipitates as time passes. Also, Korean Patent Publication No. 10-315872 disclosed a method for producing a sustained release preparation, comprising the steps of dissolving felodipine in an organic solvent, adding polyvinylpyrrolidone to the solution to form a binder solution and then adding the binder solution to an excipient mixture including a cellulose polymer, followed by combining the mixture. However, the method has problems in that it is not easy to form granules because a large amount of an organic solvent is used in the practical production process. Also, since the release rate of the drug may be affected by an amount of the binder and of cellulose polymers, it makes the control of the release rate difficult. Also, Korean Laid-Open Publication No. 2001-0073461 disclosed a method for producing a solid dispersion, in which felodipine and an enteric coating polymer are dissolved in a mixture of a polar solvent and a non-polar solvent and the solid dispersion is formed using a spray-dryer or mixer. In the case of felodipine, however, there is no need for use of the enteric coating polymer to reduce its release in the stomach. Also, the method needs complex equipments and processes and is not environmentally friendly way since toxic organic solvents such as dichloromethane or chloroform has to be used in the process.

The methods for producing a solid dispersion to increase the dissolution rate for a poorly soluble material, as mentioned above, are largely divided into two types: the melting methods and the solvent methods. The melting methods are carried out by

melting a poorly soluble drug with a carrier by heating, uniformly mixing and cooling the melt. However, these methods are disadvantageous in that heating may deteriorate the stability of a drug and the properties of the drug such as solubility may be changed by the cooling rate. Also, as the solid dispersion is formed with cooling, the increased
5 viscosity of the reaction mixture makes stirring more difficult. Therefore, it is not easy to produce a uniformly mixed solid dispersion of the drug and carriers so that the mass production of the solid dispersion in industrial application may have difficulties. The solvent methods are carried out by dissolving a poorly soluble drug and carriers in a solvent that can solubilize the drug and carriers at the same time and then removing the
10 solvent by drying to produce a solid dispersion. However, this method has a defect that residual solvent may affect physical and chemical stability of the formed solid dispersion. Further, as the solvent is volatilized, the drug and carrier may precipitate due to the differences of solubility of the drug and carrier in the solvent. In addition, similar to the melting method, as the solid dispersion is formed with cooling, the
15 increased viscosity of the reaction mixture makes stirring more difficult. Therefore, it is not easy to produce a uniformly mixed solid dispersion of the drug and carriers and the mass production of the solid dispersion in industrial application may have difficulties. The solid dispersions produced from the two types of methods should be further subjected to an additional process for dosage formulation, such as preparation of
20 pellets or preparation of matrix tablets to form controlled release formulations, making the production process complicated.

In order to solve the problems involved in the prior art as described above, the present inventors have made every endeavor and found that fatty acid ester of sucrose can be a superior carrier for a solid dispersion of felodipine and the solid dispersion of
25 felodipine using the fatty acid ester of sucrose shows an increased solubility of

felodipine. The present invention has been completed based on such findings. Also, the present inventors have found that the method according to the present invention can effectively solve the problems of the prior art, such as residual organic solvent, difficulty in stirring due to the high viscosity of the solid dispersion at the end phase of drying, and ununiformity of content, and the controlled release of a drug in a desired form can be achieved without an additional process of dosage formulation, and have thereby completed the present invention.

Therefore, it is an object of the present invention to provide a controlled release composition comprising felodipine, a fatty acid ester of sucrose and a copolymer of methacrylic acid, and a method for producing the same.

Disclosure of the Invention

The present invention is directed to a controlled release composition comprising felodipine, a fatty acid ester of sucrose and a copolymer of methacrylic acid.

The fatty acid ester of sucrose used in the composition of the present invention is used to increase water solubility of felodipine and its content can be preferably 0.1 to 5 parts by weight, more preferably 0.5 to 2 parts by weight, based on 1 part by weight of felodipine. The fatty acid ester of sucrose used in the composition according to the present invention has advantages that the solubility of felodipine can be considerably increased and moreover, such effect can be achieved only in a small amount as compared to other carriers for solid dispersion.

Preferred fatty acid esters of sucrose that can be used in the present invention include ester compounds consisting of sucrose and fatty acids. Monoester is such a sucrose ester that is combined one mole of fatty acid with one mole of sucrose. Diester is obtained using two moles of fatty acid and triester is obtained using three

moles of fatty acid. Representative examples of such fatty acid esters of sucrose include sucrose monostearate, sucrose distearate (commercially available from Gattefosse under the trade name SUCRO ESTER 7), sucrose mono-distearate (commercially available from Gattefosse under the trade name SUCRO ESTER 11),
5 sucrose monopalmitate (commercially available from Gattefosse under the trade name SUCRO ESTER 15), sucrose dipalmitate, sucrose monolaurate, sucrose dilaurate, sucrose monooleate, sucrose dioleate, sucrose monocaprate, sucrose dicaprate, sucrose monocaprylate, sucrose dicaprylate, sucrose monomyristate, sucrose dimyristate, sucrose monolinolenate, sucrose dilinolenate and the like. In the present invention,
10 any one selected from the group of the above listed compounds or a mixture of two or more thereof can be used.

The copolymer of methacrylic acid used in the composition of the present invention is used to make felodipine release in a controlled way and its content can be preferably 0.1 to 10 parts by weight, more preferably 1 to 5 parts by weight, based on 1
15 part by weight of felodipine. The copolymer of methacrylic acid is advantageous in that altering the content of the copolymer can easily control the dissolution rate of felodipine.

Preferred copolymers of methacrylic acids which can be used in the present invention include copolymers of methacrylic acid with acrylic esters or methacrylic
20 esters. Representative examples of such copolymers include poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) (commercially available from Röhm under the trade name "Eudragit E"), poly(methacrylic acid, ethyl acrylate) (commercially available from Röhm under the trade name "Eudragit L"),
poly(methacrylic acid, methyl methacrylate) (commercially available from Röhm under the trade name "Eudragit S"), and poly(ethyl acrylate, methyl methacrylate,
25 the trade name "Eudragit S"), and poly(ethyl acrylate, methyl methacrylate,

trimethylammonioethyl methacrylate chloride) (commercially available from Röhm under the trade name "Eudragit RL" and "Eudragit RS"). In the present invention, any one selected from the above listed compounds or a mixture of any two or more thereof can be used.

5 In order to increase the powder property of a solid dispersion, the composition may further comprise an excipient including one selected from the group consisting of lactose, dextrin, starches, microcrystalline cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose, methyl cellulose, polyethylene glycols, polyoxyethylene glycolated natural or hydrogenated castor oil
10 derivatives, polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene-fatty acid esters, polyoxyethylene-polyoxypropylene block copolymer, sodium dioctyl sulfosuccinate or sodium lauryl sulfate, phospholipids, propylene glycol mono-fatty acid esters or propylene glycol di-fatty acid esters, trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols, mono-glycerides, di-
15 glycerides, mono/di-glycerides, sorbitan fatty acid esters, silicon dioxide, hydrotalcite, aluminum magnesium silicate, aluminum hydroxide, aluminum silicate, magnesium aluminum metasilicate and bentonite, or a mixture of two or more thereof.

 In another aspect, the present invention is directed to a method for preparing a controlled release composition of felodipine comprising the steps of dissolving
20 felodipine, a fatty acid ester of sucrose and a copolymer of methacrylic acid in an organic solvent, combining the solution with an excipient and drying the solvent. In the method according to the present invention, the components of felodipine, the fatty acid ester of sucrose and the copolymer of methacrylic acid may be heated, preferably at the range of 40 °C to 80 °C to be readily dissolved in the organic solvent. When the
25 reaction temperature is lower than the foregoing range, felodipine, the fatty acid ester of

sucrose and the copolymer of methacrylic acid may not be completely dissolved. Also when the temperature is higher than the foregoing range, the drug may be decomposed.

The organic solvent useful in the method according to the present invention is any one that can dissolve felodipine, the fatty acid ester of sucrose and the copolymer of methacrylic acid, including, for example, methanol, ethanol, isopropanol, acetone and
5 methylene chloride, or a mixture of two or more thereof. The content of the organic solvent is preferably 1 to 50 parts by weight, more preferably 4 to 20 parts by weight, based on 1 part by weight of felodipine.

The method according to the present invention, in which felodipine, a fatty acid
10 ester of sucrose and a copolymer of methacrylic acid are dissolved in an organic solvent and the solution is uniformly combined with an excipient, followed by drying solvent, can effectively solve the problems involved in using conventional solid dispersions, such as residual organic solvent, difficulty in stirring due to the high viscosity of the solid dispersions at the end phase of drying, and ununiformity of content. Also, it
15 makes possible to achieve controlled release of the drug in a desired form without an additional process for dosage formulation, resulting in simplifying the production process. Further, since only altering the content of a copolymer of methacrylic acid can control the drug release rate, it leads to provide controlled release compositions of felodipine having an advantage in terms of quality control of the products.

20 The composition of the present invention can be formulated into tablets, capsules, granules or pellets and the tablet dosage form is particularly preferred. For example, the composition may be directly filled in hard capsule as granules, may be mixed with a lubricant and other pharmaceutical additives and filled in hard capsule as powders or granules, or may be mixed with a pharmaceutical additive necessary for
25 tableting and compressed to form tablets.

Brief Description of the Drawings

The above objects, and other features and advantages of the present invention will become more apparent after a reading of the following detailed description when
5 taken in conjunction with the drawings, in which:

Fig. 1 is a graph showing the results of the dissolution test according to Experiment Example 2 (○ : raw material of felodipine, ● : Preparation Example 1, ■ : Preparation Example 2 and ▲ : Preparation Example 3); and

Fig. 2 is a graph showing the results of the dissolution test according to
10 Experiment Example 3 (○ : Example 1, ● : Example 2, □ : Example 3, ■ : Example 4 and ▲ : Example 5).

Best mode for carrying out the invention

Now, the present invention will be described in more detail by way of the
15 following examples. These examples are intended to be illustrative of the invention and are not in any way intended to limit its scope.

Example 1

Controlled release tablets containing the following composition were prepared
20 as follows.

Felodipine 5 g

Sucrose monopalmitate (SUCRO ESTER 15, manufactured by Gattefosse) 5 g

Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate
25 chloride) (Eudragit RS100, manufactured by Röhm) 11 g

Lactose 176 g

Magnesium stearate 3g

5 Felodipine and sucrose monopalmitate were added to about 40ml of ethanol and heated to about 60°C with stirring to obtain a clear solution. To the solution, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) was added and stirred at about 60°C to give a clear solution. Then, lactose was added, and the resulting mixture was combined and granulated, followed by drying. The dried granules were milled in a certain size and mixed with magnesium stearate as a
10 lubricant. Using a tabletting machine, controlled release tablets containing 5 mg of felodipine per a tablet were obtained.

Example 2

Controlled release tablets containing the following composition were prepared
15 according to the procedure of Example 1.

Felodipine 5 g

Sucrose monopalmitate (SUCRO ESTER 15, manufactured by Gattefosse) 5 g

20 Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) (Eudragit RS100, manufactured by Röhm) 15 g

Lactose 172 g

Magnesium stearate 3g

Example 3

25 Controlled release tablets containing the following composition were prepared

according to the procedure of Example 1.

Felodipine 5 g

Sucrose monopalmitate (SUCRO ESTER 15, manufactured by Gattefosse) 5 g

5 Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate
chloride) (Eudragit RS100, manufactured by Röhm) 17 g

Lactose 170 g

Magnesium stearate 3g

10 **Example 4**

Controlled release tablets containing the following composition were prepared
according to the procedure of Example 1.

Felodipine 5 g

15 Sucrose monopalmitate (SUCRO ESTER 15, manufactured by Gattefosse) 5 g

Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate
chloride) (Eudragit RS100, manufactured by Röhm) 19 g

Lactose 168 g

Magnesium stearate 3g

20

Example 5

Controlled release tablets containing the following composition were prepared
according to the procedure of Example 1.

25 Felodipine 5 g

- Sucrose monopalmitate (SUCRO ESTER 15, manufactured by Gattefosse) 5 g
- Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) (Eudragit RS100, manufactured by Röhm) 22 g
- Lactose 165 g
- 5 Magnesium stearate 3g

The following Preparation Examples and Comparative Examples are provided for comparison between solubility of the solid dispersion using a fatty acid ester of sucrose and that of various solid dispersions.

10

Preparation Example 1

Controlled release tablets containing the following composition were prepared as follows.

- 15 Felodipine 5 g
- Sucrose monopalmitate (SUCRO ESTER 15, manufactured by Gattefosse) 5 g
- Lactose 190 g

Felodipine and sucrose monopalmitate were added to about 40ml of ethanol and heated to about 60°C with stirring to obtain a clear solution. Then, lactose was added to the solution and the resulting mixture was combined and granulated, followed by drying. The dried granules were passed through a No. 20 sieve (Tyler sieve) to have a uniform size.

20

Preparation Example 2

25

The procedure of Preparation Example 1 was repeated, except that sucrose mono-distearate (SUCRO ESTER 11, manufactured by Gattefosse) was used as a fatty acid ester of sucrose instead of sucrose monopalmitate.

5 **Preparation Example 3**

The procedure of Preparation Example 1 was repeated, except that sucrose distearate (SUCRO ESTER 7, manufactured by Gattefosse) was used as a fatty acid ester of sucrose instead of sucrose monopalmitate.

10 **Preparation Example 4**

The procedure of Preparation Example 1 was repeated, except that 2.5 g of sucrose monopalmitate (SUCRO ESTER 15, manufactured by Gattefosse) was used.

Preparation Example 5

15 The procedure of Preparation Example 1 was repeated, except that 10 g of sucrose monopalmitate (SUCRO ESTER 15, manufactured by Gattefosse) was used.

Comparative Example 1. Preparation of solid dispersion of felodipine-PEG 20000

20 Felodipine 5 g
 PEG 20000 5 g
 Lactose 190 g

 Felodipine and PEG 20000 were added to about 40ml of ethanol and heated to
25 about 60°C with stirring to obtain a clear solution. Then, lactose was added to the

solution and the resulting mixture was combined and granulated, followed by drying. The dried granules were passed through a No. 20 sieve (Tyler sieve) to have a uniform size.

5. **Comparative Example 2. Preparation of solid dispersion of felodipine-poloxamer 407**

Solid dispersions were prepared according to the procedure of Comparative Example 1, except that 5 g of Poloxamer 407 was used instead of PEG 20000.

10 **Comparative Example 3. Preparation of solid dispersion of felodipine-Cremophor RH40**

Solid dispersions were prepared according to the procedure of Comparative Example 1, except that 5 g of Cremophor RH40 was used instead of PEG 20000.

15 **Comparative Example 4. Preparation of solid dispersion of felodipine-polyvinylpyrrolidone K30**

Solid dispersions were prepared according to the procedure of Comparative Example 1, except that 5 g of polyvinylpyrrolidone K30 was used instead of PEG 20000.

20 **Comparative Example 5. Preparation of solid dispersion of felodipine-polyvinylpyrrolidone K90**

Solid dispersions were prepared according to the procedure of Comparative Example 1, except that 5 g of polyvinylpyrrolidone K90 was used instead of PEG 20000.

25 **Experimental Example 1. Measurement of solubility**

The solid dispersions of felodipine-fatty acid ester of sucrose prepared in Preparations Examples 1, 2 and 3, and felodipine solid dispersions prepared in Comparative Examples 1, 2, 3, 4 and 5 were measured for the solubility. The solubility was determined as follows. Excess amount of sample was added to a Cetyl trimethyl ammonium bromide buffer, pH 6.5, followed by stirring at 37°C for 1 hour. The resulting mixture was centrifuged and the supernatant was analyzed by high performance liquid chromatography. The results are shown in Table 1 below.

【Table 1】

	Concentration ($\mu\text{g}/\text{ml}$)
Preparation Example 1: Solid dispersion of felodipine-sucrose monopalmitate	24.1
Preparation Example 2: Solid dispersion of felodipine-sucrose mono-distearate	20.5
Preparation Example 3: Solid dispersion of felodipine-sucrose distearate	19.8
Comparative Example 1: Solid dispersion of felodipine-PEG 20000	6.3
Comparative Example 2: Solid dispersion of felodipine-poloxamer 407	7.4
Comparative Example 3: Solid dispersion of felodipine-Cremophor RH40	5.8
Comparative Example 4: Solid dispersion of felodipine-polyvinylpyrrolidone K30	8.2
Comparative Example 5: Solid dispersion of felodipine-polyvinylpyrrolidone K90	5.3

As seen from the above Table 1, it was confirmed that the solid dispersions of felodipine-fatty acid ester of sucrose prepared according to the method of present invention show considerably enhanced solubility of felodipine, as compared to the solid dispersions prepared in Comparative Examples.

Experimental Example 2. Dissolution test

The granules prepared in Preparation Examples 1, 2 and 3 respectively containing 5 mg of felodipine and the same amount of raw felodipine were subjected to a dissolution test. The used dissolution solution was a buffer of pH 6.5 containing 1 M dihydrogen sodium phosphate, 0.5 M monohydrogen sodium phosphate and Cetyl trimethyl ammonium bromide. The content of felodipine was determined by high performance liquid chromatography.

The results of the analysis are shown in Fig. 1 and it is noted that the solid dispersions prepared in Preparation Examples 1, 2 and 3 show considerably higher dissolution rate, as compared to that of raw felodipine.

Experimental Example 3. Dissolution test

The tablets prepared in Examples 1, 2, 3, 4 and 5 were subjected to a dissolution test. The used dissolution solution was a buffer of pH 6.5 containing 1 M dihydrogen sodium phosphate, 0.5 M monohydrogen sodium phosphate and Cetyl trimethyl ammonium bromide. The content of felodipine was determined by high performance liquid chromatography.

The results of the analysis are shown in Fig. 2. As seen from the dissolution profile of felodipine shown in Fig. 2, it is noted that altering the content of the copolymer can easily control the dissolution rate of felodipine.

Industrial applicability

As described above, the composition according to the present invention can

effectively increase the solubility of felodipine, and the method according to the present invention, comprising the steps of dissolving felodipine, a fatty acid ester of sucrose and a copolymer of methacrylic acid in an organic solvent and uniformly combining with an excipient, followed by drying, can effectively solve the problems involved in using the conventional solid dispersions, such as residual organic solvent, difficulty in stirring due to a high viscosity of the solid dispersion at the end phase of drying, and ununiformity of content. Also, it makes possible to achieve controlled release of drug in a desired form without an additional process for dosage formulation, resulting in simplifying the production process. Further, since only altering the content of a copolymer of methacrylic acid can control the drug release rate, it leads to provide controlled release compositions of felodipine having an advantage in quality control of products.

CLAIMS

1. A controlled release composition of felodipine comprising felodipine, a fatty acid ester of sucrose and a copolymer of methacrylic acid.

5

2. The composition according to claim 1, wherein the content of the fatty acid ester of sucrose is 0.1 to 5 parts by weight based on 1 part by weight of felodipine.

3. The composition according to claim 1, wherein the fatty acid ester of sucrose is one selected from the group consisting of sucrose monostearate, sucrose distearate, sucrose mono-distearate, sucrose monopalmitate, sucrose dipalmitate, sucrose monolaurate, sucrose dilaurate, sucrose monooleate, sucrose dioleate, sucrose monocaprate, sucrose dicaprate, sucrose monocaprylate, sucrose dicaprylate, sucrose monomyristate, sucrose dimyristate, sucrose monolinolenate and sucrose dilinolenate, or a mixture of two or more thereof.

15

4. The composition according to claim 1, wherein the content of the copolymer of methacrylic acid is 0.1 to 10 parts by weight based on 1 part by weight of felodipine.

5. The composition according to claim 1, wherein the copolymer of methacrylic acid is one selected from the group consisting of poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate), poly(methacrylic acid, ethyl acrylate), poly(methacrylic acid, methyl methacrylate) and poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride), or a mixture of two or more thereof.

25

6. The composition according to any one of claims 1 to 5, wherein the composition further comprises one or more excipient selected from the group consisting of lactose, dextrin, starches, microcrystalline cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose, methyl cellulose, polyethylene glycols, polyoxyethylene glycolated natural or hydrogenated castor oil derivatives, polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene-fatty acid esters, polyoxyethylene-polyoxypropylene block copolymer, sodium dioctyl sulfosuccinate, sodium lauryl sulfate, phospholipids, propylene glycol mono-fatty acid esters or propylene glycol di-fatty acid esters, trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols, mono-glycerides, di-glycerides, mono/di-glycerides, sorbitan fatty acid esters, silicon dioxide, hydrotalcite, aluminum magnesium silicate, aluminum hydroxide, aluminum silicate, magnesium aluminum metasilicate and bentonite.

15

7. The composition according to any one of claims 1 to 5, wherein the composition is formulated into one selected from the group consisting of tablets, capsules, granules or pellets.

20

8. A method for preparing the controlled release composition of felodipine according to claim 1, comprising the steps of dissolving felodipine, a fatty acid ester of sucrose and a copolymer of methacrylic acid in an organic solvent, combining the solution with an excipient and drying the solvent.

25

9. The method according to claim 8, wherein the dissolution is carried out at a

temperature in the range of 40 °C to 80 °C.

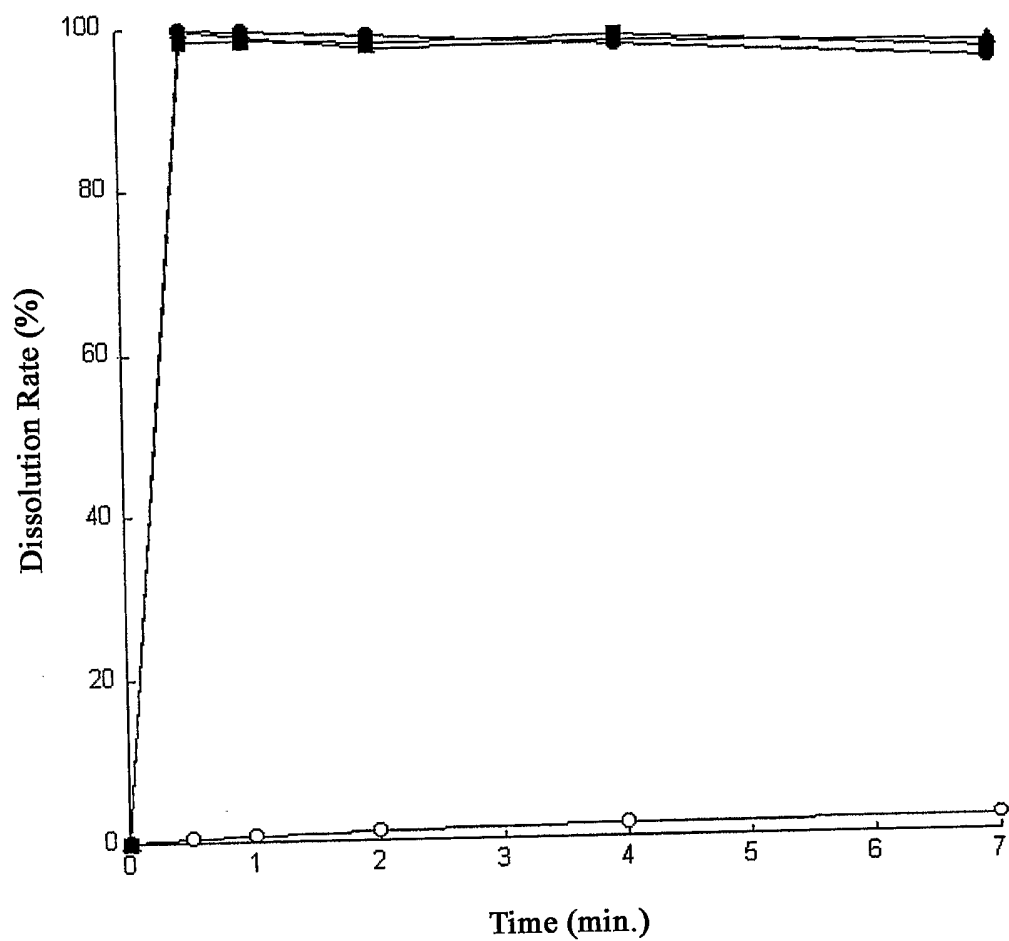
10. The method according to claim 8, wherein the content of the organic solvent is 1 to 50 parts by weight based on 1 part by weight of felodipine.

5

11. The method according to claim 8, wherein the organic solvent is one selected from the group consisting of methanol, ethanol, isopropanol, acetone and methylene chloride, or a mixture of two or more thereof.

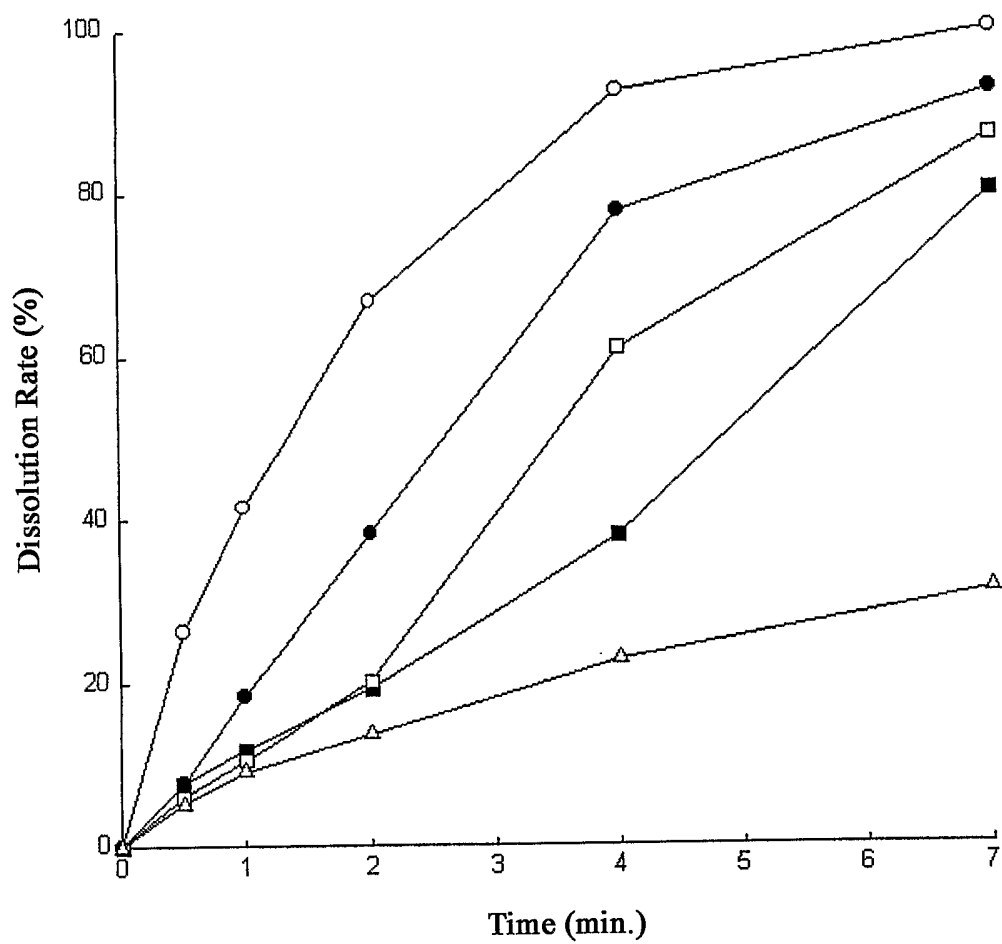
1/2

Fig.1



2/2

Fig.2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/00552

A. CLASSIFICATION OF SUBJECT MATTER		
IPC7 A61K 47/34		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) IPC7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Korean Patents and applications for inventions since 1975		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS(STN), SCISEARCH(STN), IPA(STN), PASCAL(STN), BIOTECHNO(STN), BABS(STN), MedLine, Delphion		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 230332 A1 (N.V.SANICO) 29 JULY 1987 See abstract, claims and page 2	1-11
P, A	B.K.KIM, et al., "Preparation and characterization of drug-loaded polymethacrylate microspheres by an emulsion solvent evaporation method," Journal of Microencapsulation, Taylor&Francis healthsciences, United Kingdom, 2002. 11. 1, Vol.19, No.6, pp811-822, See the whole document	1-11
A	EP 311582 A1 (Aktiebolaget Hassle) 12 APRIL 1989 See the whole document	1-11
A	US 6383471 B1 (Lipocine Inc.) 7 MAY 2002 See the whole document	1-11
A	US 6267985 B1 (Lipocine Inc.) 31 JULY 2001 See the whole document	1-11
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
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Date of the actual completion of the international search 18 JUNE 2003 (18.06.2003)		Date of mailing of the international search report 19 JUNE 2003 (19.06.2003)
Name and mailing address of the ISA/KR  Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140		Authorized officer CHANG, Jin Ah Telephone No. 82-42-481-5602 

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR03/00552

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 230332 A1	29.07.1987	DK16187	14.07.1987
		F1870092	14.07.1987
		N0870104	14.07.1987
		NL8600050	03.08.1987
		ZA8700216	26.08.1987
		JP62209025	14.09.1987
EP 311582 A1	12.04.1989	SE8703881	08.10.1987
		DK558688	09.04.1989
		F1884636	09.04.1989
		N0884269	10.04.1989
		AU2237488	13.04.1989
		CN1032490	26.04.1989
		JP1128917	22.05.1989
		US4942040	17.07.1990
		NZ226245	28.08.1990
		PH25568	08.08.1991
		AU615211	26.09.1991
		PT88711	31.12.1992
		CA1312286	05.01.1993
		DE3877492	13.05.1993
		MX169243	26.06.1993
		GR3006788	30.06.1993
		IL87922	08.07.1993
		ES2053815	01.08.1993
		IE63084	22.03.1995
		HU210461	28.04.1995
		HK6296	19.01.1996
		KR9609411	19.07.1996
		CY1896	27.09.1996
US 6383471 B1	07.05.2002	W0200059475	12.10.2000
		AU200037637	23.10.2000
US 6267985 B1	31.07.2001	W0200010196	11.01.2001
		AU200053131	22.01.2001
		EP1194120	10.04.2002