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(54) Title: ORGANIC ACID SALT OF AMLODIPINE

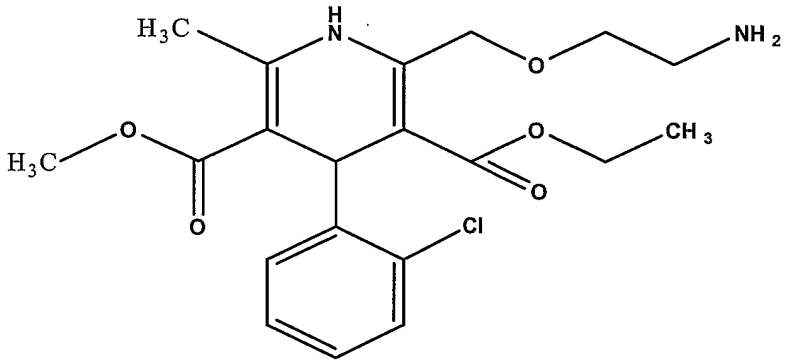
(57) Abstract: Disclosed are a novel organic acid salt of amlodipine, its preparation method, and a pharmaceutical composition containing the same as a therapeutically active ingredient.

ORGANIC ACID SALT OF AMLODIPINE

Technical Field

The present invention relates to a novel organic acid salt of amlodipine (2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl 5-methyl ester), represented by the following chemical formula 1, its preparation method, and a pharmaceutical composition containing the same as an effective ingredient.

[Chemical Formula 1]



Background Art

With activity to block calcium channels in the body, amlodipine is used for the treatment of hypertension. This calcium channel blocker is found in many prior arts.

European Pat. Laid-Open Publication No. 89,167 discloses acid salts of amlodipine which can be formed from acids which may form nontoxic acid addition salts with pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, sulfate, phosphate,

acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, etc.

U. S. Pat. No. 6,291,490 introduces a pharmaceutical composition containing as an active ingredient S-(-)-amlodipine which possesses potent activity in treating hypertension while avoiding adverse effects associated with the administration of the racemic mixture of amlodipine.

Both U. S. Pat. No. 4,879,303 and Korean Pat. Laid-Open Publication No. 1989-3375 disclose amlodipine besylate, saying that amlodipine besylate is superior over other salts of amlodipine, such as hydrochloride, acetate and mesylate in physicochemical properties including (1) solubility, (2) stability, (3) non-hygroscopicity, and (4) processability for tablet formulation.

However, since amlodipine besylate in current use is relatively low in solubility at pH 1-7.4, saturation pH is regarded as an important factor. Salts which provide solutions having a pH close to that of blood (7.4) in distilled water are preferred because they are readily biocompatible and can easily be buffered to the required pH range without altering their solubility. Since the saturation pH of amlodipine besylate is as low as a pH of 6.6, there is a need for salts whose saturation pH in distilled water is close to 7.4 (pH of blood). Additionally, amlodipine besylate is found to be sensitive to light, so that decomposition products are observed when the salt is exposed to light.

Further, amlodipine besylate is disadvantageous due to benzene sulfonic acid used in its production process. That is, benzene sulfonic acid is difficult to industrially treat as it is corrosive and toxic. In addition, its high hygroscopicity requires special procedures for its transport, delivery and use. Another disadvantage is that the water content of benzene sulfonic acid is high content of water, amounting to about 10%. In order to avoid these problems, ammonium benzene sulfonate is employed as an alternative, but with the

concomitant generation of ammonia gas. This method needs additional processes for absorbing and inactivating ammonia gas (PCT Publication No. WO1999/52873).

Disclosure of the Invention

Leading to the present invention, the intensive and thorough research into therapeutically effective organic acid salts of amlodipine, conducted by the present inventors aiming to overcome the problems encountered in prior arts, resulted in the finding that amlodipine camphorsulfonate has excellent physicochemical properties including solubility, non-hygroscopicity, chemical and light stability, and processability for dosage formation, as well as the fact that camphorsulfonic acid is less toxic and corrosive than benzene sulfonic acid, so that the amlodipine camphorsulfonate is industrially and medically useful.

Therefore, it is an object of the present invention to provide a camphorsulfonic acid salt of amlodipine.

It is another object of the present invention to provide a method for preparing a camphorsulfonic acid salt of amlodipine.

It is a further object of the present invention to provide a pharmaceutical composition containing the camphorsulfonic acid salt of amlodipine as a therapeutically active ingredient.

In accordance with an aspect of the present invention, there is provided a camphorsulfonic acid salt of amlodipine, preferably a light-stable camphorsulfonic acid salt of amlodipine, more preferably amlodipine (1S)-(+)-10-camphorsulfonate or amlodipine (1R)-(-)-10-camphorsulfonate, and most preferably a crystalline camphorsulfonic acid salt of amlodipine.

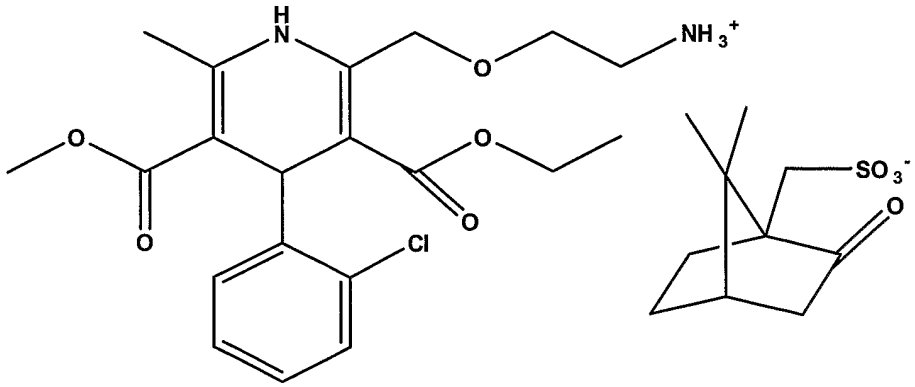
In accordance with another aspect of the present invention, there is provided a method for preparing a camphorsulfonic acid salt of amlodipine, in which amlodipine is reacted with camphorsulfonic acid and preferably with (1S)-(+)-10-camphorsulfonic acid or (1R)-(-)-10-camphorsulfonic acid in an inert solvent.

In accordance with a further aspect of the present invention, there is provided a pharmaceutical composition effective for the treatment of ischemic cardiac disorders or hypertension, comprising a therapeutically effective amount of amlodipine camphorsulfonate and a pharmaceutically acceptable diluent or carrier preferably in the dosage form of tablets, capsules, solutions or injectables.

Best Mode for Carrying Out the Invention

The present invention encompasses amlodipine camphorsulfonate, represented by the following chemical formula 2.

[Chemical Formula 2]



Compared to amlodipine besylate in a commercially acceptable form, amlodipine

camphorsulfonate exhibits equal or better non-hygroscopicity, formulation processability and chemical stability. Especially, providing solutions having a pH close to that of blood (7.4) as well as being far more stable to light compared to conventional organic acid salts, the amlodipine camphorsulfonate of the present invention can be stably stored for a long period of time without losing its medicinal effect as an anti-hypertensive agent.

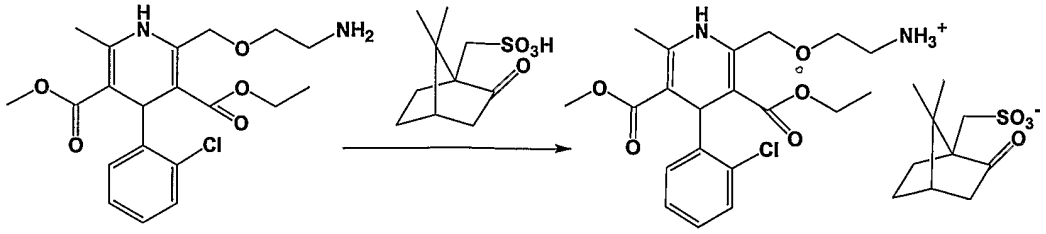
The present invention also encompasses light-stable amlodipine camphorsulfonate. The term "light-stable" as used herein means that after the salt is stored for 4 weeks at 25 °C with exposure to sunlight, its mass is maintained at 90 % or more of the original mass, preferably at 95 % or more, and more preferably at 98 % or more.

Camphorsulfonic acid suitable for the preparation of the amlodipine camphorsulfonate of the present invention may be a racemic mixture or preferably an optically pure material, that is, (1S)-(+)-10-camphorsulfonic acid or (1R)-(-)-10-camphorsulfonic acid.

Camphorsulfonic acid salts of amlodipine according to the present invention may be in a crystal form or an amorphous form with preference to a crystal form.

The present invention also encompasses a method for preparing camphorsulfonic acid salts of amlodipine. The salts can be prepared by reacting amlodipine with camphorsulfonic acid in an inert solvent, as seen in the following reaction formula 1.

[Reaction Formula 1]



Camphorsulfonic acid used as reactant is preferably be an optically pure material, that is, (1S)-(+)-10-camphorsulfonic acid or (1R)-(-)-10-camphorsulfonic acid.

Camphorsulfonic acid, a stable and white solid with FDA permission for use in pharmaceuticals, is commercially available as a white solid (purity 98% or higher) and does not show hygroscopicity, corrosiveness and toxicity. With these properties, camphorsulfonic acid is easily handled and safely produced on a mass scale.

Examples of the inert solvent suitable for the preparation of the salts of the present invention include ethyl acetate, methanol, ethanol, isopropanol, acetonitrile, hexane, isopropyl ether and etc., with preference to methanol.

In the inert solvent, camphorsulfonic acid is used in the amount of 1-2 equivalents, and preferably in the amount of 1.02-1.2 equivalents, per equivalent of amlodipine. The reaction is performed at –5 to 30 °C and preferably at 0 to 15 °C for 0.5 to 5 hours and preferably for 1 to 3 hours.

According to the method of the present invention, amlodipine camphorsulfonate can be prepared at a yield of 90 % or higher.

Also, the present invention encompasses a pharmaceutical composition effective in treating ischemic cardiac disorders or hypertension, which comprises a therapeutically effective amount of amlodipine camphorsulfonate and a pharmaceutically acceptable diluent or carrier.

The composition of the present invention may be formulated into oral dosage forms including, but not limited to, granules, powders, solutions, tablets, capsules, dry syrup and the like, or parenteral dosage forms including injectables. The composition of the present invention is preferably formulated in the dosage form of tablets, capsules, solutions or injectables.

To be therapeutically effective, amlodipine camphorsulfonate is administered in the amount of 2-10 mg per day on the basis of the weight of amlodipine. In a unit dosage form, amlodipine camphorsulfonate is contained in the amount of 3-16 mg.

In practical use, amlodipine camphorsulfonate can be combined as the active ingredient in admixture with a pharmaceutically acceptable diluent or carrier selected from among excipients, disintegrants, binders and lubricants, and mixtures thereof. The carrier may take a wide variety of forms depending on the form of the preparation desired for administration. In preparing the composition in a solid dosage form such as a tablet or a hard capsule, there may be employed microcrystalline cellulose, lactose, low-substituted hydroxycellulose and the like as an excipient; sodium starch glycollate, anhydrous monohydrogenphosphate and the like as a disintegrant; polyvinylpyrrolidone, low-substituted hydroxypropylcellulose, hydroxypropylcellulose and the like as a binder; and magnesium stearate, silica, talc and the like as a lubricant.

A formulation may comprise an additive to provide sheen to the tablet such as anhydrous dibasic calcium phosphate. To prevent atmospheric moisture from penetrating into the tablet, it may have a water-insoluble coating. The coating base must have a dense molecular structure and is preferably poorly soluble in water. Suitable for the base is a polymeric material selected from among methacrylic acid copolymer, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, hydroypropylmethylcellulose acetate

succinate, polyvinyl alcohol and combinations thereof. Also, the coating may comprise conventional additives such as plasticizers, preservatives, coloring agents, light shielders, etc.

The composition of the present invention may be solutions such as sterile aqueous solution or injectables. Preferably such solution contains from 10 to 40% of propylene glycol and sodium chloride, sufficient to avoid hemolysis (e.g. about 1%).

A better understanding of the present invention may be obtained in light of the following examples which are set forth to illustrate, but are not to be construed to limit the present invention.

EXAMPLES

Amlodipine camphorsulfonate prepared according to the present invention was tested for various physical properties. First, the salt was formulated into tablets, capsules and aqueous solutions to test the processability for dosage formation. Also, amlodipine camphorsulfonate was compared with amlodipine besylate with regard to hydroscopicity, solubility, saturation pH, stability and light stability.

In the following reference examples, conventional salts of amlodipine were prepared according to methods disclosed in the art.

REFERENCE EXAMPLE 1: Preparation of Amlodipine Besylate

Amlodipine was prepared as disclosed in Korean Pat. Publication No. 87-809. The method described in Korean Pat. Publication No. 95-7228 was adopted to produce amlodipine besylate.

REFERENCE EXAMPLE 2: Preparation of Amlodipine para-toluenesulfonate

In 100 ml of methanol was dissolved 20 g of para-toluenesulfonic acid. To the solution, 40 g of the amlodipine prepared in Reference Example 1 in 500 ml of methanol was added dropwise, followed by stirring at 23 °C for 3 hours.

After being filtered off, the solid thus produced was washed with 100 ml of methanol and 100 ml of n-hexane and dried in vacuo.

REFERENCE EXAMPLE 3: Preparation of Amlodipine Hydrochloride

To 100 ml of methanol was added 12 ml of conc-hydrochloric acid. 54 g of amlodipine prepared in Reference Example 1 in 500 ml of methanol was added dropwise, followed by stirring at 23 °C for 3 hours.

After being filtered off, the solid thus produced was washed with 100 ml of methanol and 100 ml of n-hexane and dried in vacuo.

EXAMPLE 1: Preparation of Amlodipine (1S)-(+)-10-Camphorsulfonate

In a 1L three-neck flask, (1S)-(+)-10-camphorsulfonic acid (24.36g, 1.05 equivalents) was dissolved in methanol (200 ml). To the flask was added dropwise a solution of amlodipine (40.8g, 0.1 mole) in methanol (300 ml). The resulting solution was stirred at 23 °C for 2 hours, cooled to 7 °C and stirred again for 1 hour to produce precipitates. The precipitates were washed at 5 °C with methanol (100 ml) and n-hexane (100 ml), filtered,

and dried at 35 °C in vacuo to afford 57.6 g of amlodipine (1S)-(+)-camphorsulfonate as a white crystalline solid (Yield 90%).

The element analysis and melting point of the amlodipine (1S)-(+)-10-camphorsulfonate prepared above were determined.

TABLE 1

	Element analysis for C30H41ClN2O9S (%)				
Found	C: 55.9	H: 6.4	N: 4.3	S: 5.2	O: 21.6
Calculated	C: 56.2	H: 6.5	N: 4.4	S: 5.0	O: 22.5

Melting point: 210 °C

(measured by capillary melting point method with heating rate of about 1 ℃/minute)

EXAMPLE 2: Preparation of Amlodipine (1R)-(-)-10-Camphorsulfonate

In a 1L three-neck flask, (1R)-(-)-10-camphorsulfonic acid (24.36g, 1.05 equivalents) was dissolved in methanol (200 ml). To the flask was added dropwise a solution of amlodipine (40.8g, 0.1 mole) in methanol (300 ml). The resulting solution was stirred at 22 °C for 2 hours, cooled to 7 °C and stirred again for 1 hour and then filtered to produce precipitates. The precipitates were washed at 5 °C with methanol (100 ml) and n-hexane (100 ml), and dried at 35 °C in vacuo to afford 57.6 g of amlodipine (1R)-(-)-camphorsulfonate as a white crystalline solid (Yield 90%).

The element analysis and melting point of the amlodipine (1R)-(-)-10-camphorsulfonate prepared above were determined.

TABLE 2

	Element analysis for C30H41ClN2O9S (%)				
Found	C: 55.9	H: 6.4	N: 4.3	S: 5.1	O: 21.7
Calculated	C: 56.2	H: 6.5	N: 4.4	S: 5.0	O: 22.5

Melting point: 210 °C

(measured by capillary melting point method with heating rate of about 1 ℃/minute)

EXAMPLE 3: Formulation of Tablet Containing Amlodipine Camphorsulfonate

The ingredients given in Table 3 were formulated to prepare a tablet containing amlodipine camphorsulfonate.

TABLE 3

Ingredients	Contents (mg per tablet)
Amlodipine camphorsulfonate	5.0 based on Amlodipine
Low-substituted Hydroxypropylcellulose	65
Microcrystalline Cellulose	120
Sodium Starch Glycollate	4
Magnesium Stearate	2

The ingredients were blended and the blend was compressed using a roller press from Jowoon Machinery, and then formulated into the tablets using a tableting machine from Erweka.

EXAMPLE 4: Formulation of Tablet Containing Amlodipine Camphorsulfonate

The ingredients given in Table 4 were formulated to prepare a tablet containing amlodipine camphorsulfonate.

TABLE 4

Ingredients	Contents (mg per tablet)
Amlodipine camphorsulfonate	5.0 based on Amlodipine
Lactose	180
Cross Povidone	6
Polyvinylpyrrolidone K90	6
Sodium Starch Glycollate	4
Magnesium Stearate	2

Lactose, cross povidone and polyvinylpyrrolidone K90 were preblended. The pre-blend was granulated according to a fluidized bed assembly method (SPIRA FLOW) and the granules were blended with the remaining ingredients and formulated into tablets using a tableting machine from Erweka.

EXAMPLE 5: Formulation of Capsule Containing Amlodipine Camphorsulfonate

The ingredients given in Table 5 were formulated to prepare a capsule containing amlodipine camphorsulfonate.

TABLE 5

Ingredients	Contents (mg per capsule)
Amlodipine camphorsulfonate	5.0 based on Amlodipine
Low-substituted Hydroxypropylcellulose	65
Microcrystalline Cellulose	120
Sodium Starch Glycollate	4
Magnesium Stearate	2

The ingredients were blended and the blend was compressed using a roller press from Jowoon Machinery, and then the resulting materials were filled into hard gelatin capsules using a capsule filling machine from Bosche.

EXAMPLE 6: Formulation of Capsule Containing Amlodipine Camphorsulfonate

The ingredients given in Table 6 were formulated to prepare a capsule containing amlodipine camphorsulfonate.

TABLE 6

Ingredients	Contents (mg per tablet)
Amlodipine camphorsulfonate	5.0 based on Amlodipine
Lactose	180
Cross Povidone	6
Polyvinylpyrrolidone	6
Sodium Starch Glycollate	4
Magnesium Stearate	2

Lactose, cross povidone and polyvinylpyrrolidone K90 were preblended. The pre-blend was granulated according to a fluidized bed assembly method (SPIRA flow) and the granules were blended with the remaining ingredients and filled in hard gelatin capsules using a typical capsule filling device (Bosche).

EXAMPLE 7: Test for Hygroscopicity of Amlodipine Camphorsulfonate

Amlodipine camphorsulfonate prepared in Example 1 and amlodipine besylate prepared in Reference Example 1 were tested for hygroscopicity by measuring their water contents (K.F. water%) at 25 °C with humidity varying. The results are given in Table 7, below.

TABLE 7

Humidity (RH)		25%	60%	75%	95%
Storage Period (week)	Initial	1	1	1	1
Camphorsulfonate (%)	0.1	0.05	0.1	0.15	0.17
Besylate (%)	0.14	0.10	0.09	0.15	0.17

As shown in Table 7, the non-hydrogscopicity of amlodipine camphorsulfonate is equal to or better than that of amlodipine besylate. With a hygroscopicity of 0.5% or less at a relative humidity of 95%, the salt is suitable for the formulation of tablets, capsules, injectables, and the like

EXAMPLE 8: Test for Solubility of Amlodipine Camphorsulfonate

Solubilities of amlodipine camphorsulfonate prepared in Example 1 and amlodipine besylate prepared in Reference Example 1 in various solvents were measured at 25 °C. The results are given in Table 8, below. The solubilities (mg/ml) of Table 6 are values based on the weight of amlodipine converted from the salts.

TABLE 8

Solvents	Salts (mg/ml)		Note
	Camphorsulfonate	Besylate	
Dist. Water	1.28	1.29	Ionic Strength 0.2 buffer Dissolved at 37°C
pH 2	1.25	1.29	
pH 4	1.35	1.32	
pH 6	1.32	1.28	
pH 7	0.65	0.64	
pH 7.4	1.3	1.35	
pH 8	1.22	1.25	
Saturated Sol'n pH	7.2	6.6	

As shown in Table 8, amlodipine camphorsulfonate in buffers of various pH values and distilled water exhibits a solubility behavior similar to that of amlodipine besylate. However, while the saturation pH of amlodipine besylate is as low as pH 6.6, amlodipine camphorsulfonate shows a saturation pH of 7.2 which is close to the pH value of blood, indicating that amlodipine camphorsulfonate is of good pharmaceutical properties.

EXAMPLE 9: Test for Stability of Amlodipine Camphorsulfonate

1. Chemical stability of amoldipine camphorsulfonate in solid state

Amlodipine camphorsulfonate prepared in Example 1 and amlodipine besylate prepared in Reference Example 1 were subjected to accelerated test at 60 °C and the results are summarized in Table 7, below.

TABLE 9

Salts	Storage Period			
	initial	1 week	2 weeks	4 weeks

Camphorsulfonate	99.8%	99.8%	99.7%	99.7%
Besylate	99.6%	99.6%	99.4%	99.2%

(Unit HPLC content%)

HPLC Analysis Conditions:

Detector: UV Absorbance (at 237 nm)

Column: Octadesyl silica gel C18 (4.6mmx150mm, 5 μm)

Mobile Phase: Potassium dihydrogenphosphate monobasic (0.03M): methanol=4:6 (v/v)

Flow Rate: 1.5 ml/min

As shown in Table 9, almost no changes occurred in the content of amlodipine camphorsulfonate, like amlodipine besylate, as measured by the accelerated test at 60 °C. The data of Table 9 demonstrate that, comparable to that of amlodipine besylate, the chemical stability of amlodipine camphorsulfonate is excellent with regard to temperature.

2. Chemical stability of amlodipine camphorsulfonate in aqueous state

To investigate the stability in an aqueous state, amlodipine camphorsulfonate prepared in Example 1 and amlodipine besylate prepared in Reference Example 1 were separately dissolved in distilled water. The resulting aqueous solutions were stored at 25 °C for 4 weeks in complete darkness, after which a measurement was made of the contents of the salts with resort to HPLC under the same conditions as in the solid state.

The results of the light-shielded stability test indicate that neither decomposition products nor content change was found in both amlodipine camphorsulfonate and amodipine besylate.

EXAMPLE 10: Test for light Stability of Amlodipine Camphorsulfonate

Amlodipine camphorsulfonate prepared in Example 1, amlodipine besylate, and other salts of amlodipine prepared in Reference Examples 1 to 3 were employed. These samples were stored at 25 °C for 4 weeks while being exposed to sunlight. A measurement was made of the contents of the salts with resort to HPLC under the same conditions as in the chemical stability test. The results are given in Table 10, below.

TABLE 10

Salts	Initial	Stored 4 weeks, 25°C sunlight
	Content (HPLC)	Content (HPLC)
Camphorsulfonate	99.5%	98.0%
Besylate	99.2%	82.5%
Tosylate	99.2%	72.0%
Hydrochloride	99.0	60.5%

As shown in Table 10, a smaller reduction in the content was found in amlodipine camphorsulfonate than in the other salts of amlodipine. It was also found that amlodipine besylate turned yellow from white while amlodipine camphorsulfonate showed no color change. These data accordingly show that amlodipine camphorsulfonate is superior in light stability to amlodipine besylate and thus is very advantageous in the application for anti-hypertensives which are usually used for a long period of time.

Industrial Applicability

Taken together, the data presented in the above examples indicate that the amlodipine camphorsulfonate of the present invention has excellent physicochemical properties including non-hygroscopicity, chemical and light stability, solubility and

processability for dosage formulation. Especially, with the saturation pH value (pH 7.2) close to that of blood, amlodipine camphorsulfonate is easy to deliver with in the body of a patient. In addition, this salt can be stored for a long period of time due to its superior light stability. Further, free of corrosiveness and toxicity, camphorsulfonic acid is industrially useful.

What is Claimed Is:

1. A camphorsulfonic acid salt of amlodipine.

2. The camphorsulfonic acid salt of amlodipine as defined in claim 1, wherein the camphorsulfonic acid salt is stable to light.

3. The camphorsulfonic acid salt of amlodipine as defined in claim 1, wherein the camphorsulfonic acid is (1S)-(+)-10-camphorsulfonic acid or (1R)-(-)-10-camphorsulfonic acid.

4. The camphorsulfonic acid salt of amlodipine as defined in claim 1, wherein the salt is in crystalline form.

5. A method for preparing amlodipine camphorsulfonic acid salt, in which amlodipine is reacted with camphorsulfonic acid in an inert solvent.

6. The method as defined in claim 5, wherein the camphorsulfonic acid is (1S)-(+)-10-camphorsulfonic acid or (1R)-(-)-10-camphorsulfonic acid.

7. A pharmaceutical composition for the treatment of ischemic cardiac disorders or hypertension, comprising a therapeutically effective amount of the camphorsulfonic acid salt of amlodipine of any one of claims 1 to 4, and a pharmaceutically acceptable diluent or carrier.

8. The pharmaceutical composition as defined in claim 7, wherein the composition is in the dosage form of a tablet or a capsule.

9. The pharmaceutical composition as defined in claim 7, wherein the composition is in the dosage form of solutions or injectables.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/01522

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 211/86

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 C07D 211/86

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
Japanese Patents and applications for inventions since 1975

Electronic data base consulted during the internatational search (name of data base and, where practicable, search terms used)

CAPLUS(STN), MEDILINE(STN), USPATFULL, NPS, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 244944 A2 (PFIZER LIMITED) 31 MAR. 1987 SEE THE WHOLE DOCUMENT	1 - 9
A	US 4572909 A (PFIZER INC.) 25 FEB. 1986 SEE THE WHOLE DOCUMENT	1 - 9
X	US 6057344 A (SEPRACOR INC.) 02 MAY 2000 SEE COL. 11(LINE 1 - LINE 9)	1
A	US 4806557 A (PFIZER INC.) 21 FEB. 1989 SEE COL. 3 (LINE 50 - LINE 57)	1 - 9
X, P	KR 1020020076561 A (HANMI PHARMACEUTICAL CO.) 11 OCT. 2002 SEE THE WHOLE DOCUMENT	1 - 9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 OCTOBER 2003 (21.10.2003)	21 OCTOBER 2003 (21.10.2003)

Name and mailing address of the ISA/KR
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Republic of Korea
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
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