Abstract: The present invention relates to an anhydrate of crystalline S(-)-amlodipine camsylate and a preparation method thereof. The anhydrate of crystalline S(-)-amlodipine camsylate exhibits excellent physical and chemical properties including non-hygroscopicity, solubility, stability, and photostability, and is superior in formulation processability and long-term storage safety.
Description

CRYSTALLINE S-(-)-AMLODIPINE CAMSYLATE ANHYDRIDE AND PREPARATION METHOD THEREOF

Technical Field
[1] The present invention relates to an anhydrate of crystalline S(-)-amlodipine camsylate and a method of preparing the same.

[2] Background Art
[3] Amlodipine, the IUPAC Name of 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, is a long-acting calcium channel blocker useful in the treatment of cardiovascular diseases, such as angina pectoris, hypertension and congestive heart failure, etc.

[4] Amlodipine is a chiral compound with a chiral center. In general, pure stereoisomers are known to have better therapeutic effects than stereoisomer mixtures. Furthermore, chiral compounds tend to have different pharmacokinetic profiles, depending on the steric arrangement of the isomer compounds or their salts. There are two possible stereoisomers of amlodipine, because of its one chiral center, that is, R- (+)-amlodipine and S(-)-amlodipine, that are different from each other in pharmacokinetic profile. The R(+)- isomer of amlodipine is a potent inhibitor of smooth muscle cell migration despite its lack of calcium channel-blocking activity (U. S. Pat. No. 6,080,761). It is useful for preventing and treating atherosclerosis. On the other hand, the S(-)-isomer of amlodipine is a potent calcium channel blocker. For ideal use as a calcium channel blocker, amlodipine is administered in the form of S(-)-amlodipine, substantially free of its R(+)-amlodipine (U.S. Pat. No. 6,057,344). U. S. Pat. No. 6,291,490 also discloses S(-)-amlodipine, teaching that S(-)-amlodipine avoids the adverse effect of amlodipine in racemic mixtures.

[5] European Patent Publication No. 89,1167 discloses an acid adduct as an example of a pharmaceutically acceptable amlodipine salt. The pharmaceutically acceptable acid adduct is formed from an acid that forms a nontoxic acid adduct including a pharmaceutically acceptable anion, such as hydrochloride, hydrobromide, sulfate, phosphate, acetate, malate, fumarate, lactate, tartrate, citrate or gluconate.

[6] The pharmaceutically acceptable salts of S(-)-amlodipine have unique physical properties comparing with salts of racemic amlodipine. As distinct from salts of racemic amlodipine, almost none of which form hydrates, pharmaceutically acceptable salts of S(-)-amlodipine are in the most part in the form of hydrates.


For use in pharmaceutical formulations, S-(-)-amlodipine salts must meet physical and chemical standards: 1) non-hygroscopicity, 2) high solubility, 3) high thermal stability, 4) high photostability and 5) low viscosity. In addition, requirements of acids suitable for use in pharmaceutically acceptable salts include non-pharmaceutical properties, harmlessness, and processing feasibility.

Currently commercially available is S-(-)-amlodipine besylate, which is in the form of 2.5 hydrate (water content: 7.5%). But S-(-)-amlodipine besylate requires precious water control during preparation procedure due to its high water content, and scrupulous care for preparation of amlodipine formulation or long-term storage of raw materials depending upon weather.

Disclosure of Invention

Technical Problem

As such, salts in a hydrous form suffer from disadvantages in that they are difficult or inconvenient to manage because their hydration varies depending on processing conditions, are hygroscopic, and are inferior in stability to those in anhydrous forms. When processed into pharmaceutical formulations, hydrous salts show high viscosity.

Existing in the form of hydrates, most currently used S-(-)-amlodipine salts are difficult to formulate into pharmaceutical preparations.

Therefore, there is a need for pharmaceutical salts of S-(-)-amlodipine that are imparted with physical properties good enough to overcome the problems encountered in the prior art.

Leading to the present invention, intensive and thorough research into S-(-)-amlodipine salts, conducted by the present inventors, aiming to solve the problems encountered with hydrous forms of optically pure isomers, resulted in the finding that an anhydrate of crystalline S-(-)-amlodipine camsylate, produced by the reaction of S-(-)-amlodipine with camphorsulfonic acid which is non-hygroscopic, non-corrosive and easy to manage. An anhydrate of crystalline S-(-)-amlodipine camsylate exhibits excellent physical and chemical properties including non-hygroscopicity, solubility,
stability, and photostability, and is superior in formulation processability and long-term storage safety.

[16] Technical Solution

[17] It is an object of the present invention to provide an anhydrate of crystalline S-(-)-amlodipine camsylate, and a method for preparing the same.

[18] [19] [20]

Brief Description of the Drawings

[21] FIG. 1 is an XRD(X-ray Diffraction) diagram of the anhydrate of crystalline S-(-)-amlodipine (IR)-(−)-10-camsylate according to Example 1 of the present invention.

[22] FIG. 2 is an XRD(X-ray Diffraction) diagram of the anhydrate of crystalline S-(-)-amlodipine (IS)-(+)10-camsylate according to Example 3 of the present invention.

[23]

Best Mode for Carrying Out the Invention

[24] In accordance with an aspect thereof, the present invention provides an anhydrate of crystalline S-(-)-amlodipine camsylate, represented by the following Chemical Formula 1:

<Chemical Formula 1>

[25]

[26]

[27] [28]

The anhydrate of crystalline S-(-)-amlodipine camsylate in accordance with the present invention includes an anhydrate of crystalline S-(-)-amlodipine (IR)-(−)-10-camsylate and an anhydrate of crystalline S-(-)-amlodipine (IS)-(+)10-camsylate, has X-ray diffraction peaks at diffraction angles of 7.80°, 9.18°, 9.56°, 11.38°, 12.78°, 13.10°, 13.84°, 15.48°, 15.68°, 17.38°, 18.94°, 19.92°, 21.78°, 23.16°, 24.64°, 25.86° and 26.44°, and has a melting point of 94-99 °C.
Compared to commercially available S-(-)-amlodipine besylate 2.5 hydrate (brand name: Levotension), the anhydrate of crystalline S-(-)-amlodipine camsylate in accordance with the present invention has an equivalent or higher level of non-hygroscopicity and stability, and exhibits an equivalent or high level of solubility at pH 1.2-6.8. Particularly, being far superior in photostability and formulation processability, the anhydrate of crystalline S-(-)-amlodipine camsylate can be used as an anti-hypertensive that is required to be stored for a long period of time due to a prolonged term of use thereof. By the term "photostability" as used herein for the compound of the present invention, it is meant that after exposure to a light source at 25°C for 4 weeks, the content of the active ingredient remains 90% or more, preferably 95% or more, and more preferably 98% or more of its activity.

Anhydrous and non-hygroscopic as it is, the compound of the present invention has an equivalent to or higher solubility than that of S-(-)-amlodipine besylate 2.5 hydrate.

In accordance with another aspect thereof, the present invention provides a method for preparing an anhydrate of crystalline S-(-)-amlodipine camsylate.

As illustrated by the following Reaction Scheme 1, the preparation method according to the present invention features a reaction between S-(-)-amlodipine and camphorsulfonic acid in an inert organic solvent or distilled water (H_2O) to afford an anhydrate of crystalline S-(-)-amlodipine camsylate.

Camphorsulfonic acid, the material for the compound of the present invention, is currently widely used for drugs and medicines and is a stable colorless solid that is neither hygroscopic nor caustic. In addition, camphorsulfonic acid is sufficiently harmless to the body to be safe for use in pharmaceutical preparations and sufficiently convenient to handle to be applicable in the mass production of pharmaceutical preparations. Since the camphorsulfonic acid includes optical isomers, such as (IR)-(-)-10-camphorsulfonic acid and (IS)-(+)10-camphorsulfonic acid, they are used as the camphorsulfonic acid.

Therefore, the S-(-)-amlodipine camsylate according to the present invention refers
to a compound obtained through a reaction of S(-)-amlodipine and any one of the 
(IR)-(−)-10-camphorsulfonic acid and (RS)-(−)-10-camphorsulfonic acid.

Examples of the inert organic solvent suitable for the preparation method of the
present invention include acetone, ethyl acetate, methanol, ethanol, isopropanol, ace-
tonitrile, hexane, isopropyl ether, t-butyl methyl ether, and mixtures thereof. Further,
S(-)-amlodipine camsylate, prepared using distilled water as a reaction solvent, is
anhydrous and non-hygroscopic, unlike the fact known through the prior art.

A detailed description is given of the preparation method of the present invention,
below.

First, S(-)-amlodipine is dissolved in an organic inert solvent or distilled water.
The inert organic solvent or distilled water is used in a volumetric amount (ml) 5-50
times the weight (g) of the S(-)-amlodipine used, and preferably in a volumetric
amount (ml) 8-16 times the weight (g) of the S(-)-amlodipine used. To this solvent is
added (IR)-(−)-10-camphorsulfonic acid or (RS)-(−)-10-camphorsulfonic acid in an
amount of 1-2 equivalents, and preferably 1.02-1.2 equivalents per equivalent of S-
(-)-amlodipine. Reaction at -10 - 50°C, preferably at 15 - 30°C for 0.5 - 5 hours, and
preferably 1 - 3 hours, affords an anhydrous, crystalline S(-)-amlodipine camsylate.

Through the above mentioned preparation method of the present invention, the
anhydrate of crystalline S(-)-amlodipine camsylate can be produced at a yield of 80% or
higher.

The anhydrate of crystalline S(-)-amlodipine camsylate produced by the method of
the present invention exhibits excellent physical and chemical properties including
non-hygroscopicity, solubility, stability, photostability, formulation processability and
long-term storage safety.

In accordance with a further aspect thereof, the present invention provides a phar-
macutical composition for the prevention or treatment of cardiovascular diseases,
comprising as an active ingredient the anhydrate of crystalline S(-)-amlodipine
camsylate prepared by the method of the present invention.

In addition to the anhydrate of crystalline S(-)-amlodipine camsylate, the phar-
maceutical composition of the present invention may comprise at least one known
active ingredient useful in the prevention or treatment of cardiovascular diseases.

For dosage forms, the pharmaceutical composition of the present invention may be
formulated in combination with at least one pharmaceutically acceptable vehicle.
Examples of the pharmaceutically acceptable vehicle include saline, sterile water,
Ringer's solution, buffered saline, a dextrose solution, a maltodextrin solution,
glycerol, ethanol and combinations thereof. If necessary, a conventional additive, such
as an antioxidant, a buffer, an anti-bacterial agent, etc., may be added to the
composition. Also, the pharmaceutical composition of the present invention may optionally be formulated with a diluent, a dispersing agent, a surfactant, a binder and/or a lubricant, into an injection, such as an aqueous solution, a suspension, an emulsion, etc., a tablet, a capsule, a granule or a pill. Furthermore, the formulation of the pharmaceutical composition of the present invention may be conducted according to methods known in the art, such as that described in Remington's Pharmaceutical Science (most recent edition), Mack Publishing Company, Easton PA, depending on the disease and/or ingredients.

The pharmaceutical composition of the present invention may be administered orally or non-orally (e.g., intravenously, subcutaneously, intraperitoneally, or topically) at a dose depending on various factors including the patient's weight, age, gender, state of health, diet, administration time, administration route and method, excretion rate, severity of illness, and the like. The anhydride of crystalline S-(−)-amlodipine camsylate may be administered in a single dose or in several doses per day with a daily dose ranging from 0.1 to 100 mg/kg, and preferably from 2.5 to 10 mg/kg.

For the prevention or treatment of cardiovascular diseases, the pharmaceutical composition of the present invention may be used alone or in combination with other therapies, including surgical therapy, hormonal therapy, chemical therapy and/or a biological response regulator.

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

Mode for the Invention

EXAMPLE 1: Preparation of Anhydrate of Crystalline S-(−)-Amlodipine (IR)-(−)-10-Camsylate

13g (0.0316mol) of S-(−)-amlodipine was dissolved in 120 ml of isopropanol. 6.96g (1.05 eq.) of (IR)-(−)-10-camphorsulfonic acid was added to this solution and dissolved therein. Subsequently, to this solution was added 200 ml of t-butyl methyl ether, followed by stirring at 25 °C for 2 hours to afford a precipitate. After filtration, the precipitate was washed and purified with 50 ml of t-butyl methyl ether and dried in a vacuum to produce 16.7 g of an anhydrate of S-(−)-amlodipine (IR)-(−)-10-camsylate as a white crystalline solid (yield: 84%, water content: 0.15%).

The anhydrate of crystalline S-(−)-amlodipine (IR)-(−)-10-camsylate was analyzed to determine diffraction angles using an X-ray powder diffraction method, and
measured for melting point with an increase in temperature at a rate of 1°C/min from 50 to 200°C through a melting point measurement method (Melting Point Method I of General Test Methods in Korean Pharmacopoeia IV or Melting Point-Capillary Method of European Pharmacopoeia IV).

The X-ray diffraction spectrum of anhydrate of the above produced crystalline S-(-)-amlodipine (IR)-(−)-10-camsylate is shown in FIG. 1, and its elemental analysis data and melting point are given as follows.


- Elemental Analysis for C_{36}H_{42}ClN_{2}O_{9} [found(%) (C: 56.11, H: 6.59, N: 4.36, O: 22.42), calculated(%) (C: 56.30, H: 6.62, N: 4.30, O: 22.50)],

- m.p.(Melting point): 94-99°C.

EXAMPLE 2: Preparation of Anhydrate of Crystalline S(-)-Amlodipine (IR)-(−)-10-Camsylate

13g (0.0316mol) of S(-)-amlodipine was slurried with 200 ml of distilled water, followed by the addition of 6.96 g (1.05 eq.) of (IR)-(−)-10-camphorsulfonic acid thereto. Stirring for 2 hours at normal temperature formed a crystalline precipitate in the complete solution at a temperature of 25°C. After filtration, the crystalline precipitate was washed with 20 ml of distilled water and dried at 40°C in a vacuum to afford 16.62 g of S(-)-amlodipine (IR)-(−)-10-camsylate anhydride (yield: 83%, water content: 0.34%).

The elemental analysis data and melting point of the anhydrate of crystalline S-(-)-amlodipine (IR)-(−)-10-camsylate are given as follows.

- Elemental analysis for C_{36}H_{42}ClN_{2}O_{9} [found(%) (C: 56.11, H: 6.59, N: 4.36, O: 22.42), calculated(%) (C: 56.22, H: 6.65, N: 4.32, O: 22.55)],

- m.p.: 94-99°C.

EXAMPLE 3: Preparation of Anhydrate of Crystalline S(-)-Amlodipine (IS)-(−)-10-Camsylate

16.8 g of an anhydrate of S(-)-amlodipine (IS)-(−)-10-camsylate, which is a white crystalline solid, was produced using the same method as in Example 1, except that (IS)-(−)-10-camphorsulfonic acid was used instead of (IR)-(−)-10-camphorsulfonic acid (yield: 84%, water content: 0.20%).

The X-ray diffraction spectrum of the anhydrate of crystalline S(-)-amlodipine (IS)-(−)-10-camsylate is shown in FIG. 2, and its elemental analysis data and melting
point are given as follows.

- Elemental Analysis for C$_{36}$H$_{42}$ClN$_2$O$_9$S [found(%) (C: 56.11, H: 6.59, N: 4.36, O: 22.42), calculated(%) (C: 56.21, H: 6.58, N: 4.40, O: 22.45)],

- m.p.: 94-99 °C.

**EXAMPLE 4: Preparation of Anhydrate of Crystalline S-(-)-Amlodipine (IS)-(+)10-Camsylate**

- Elemental Analysis for C$_{30}$H$_{42}$ClN$_2$O$_9$S [found(%) (C: 56.11, H: 6.59, N: 4.36, O: 22.42), calculated(%) (C: 56.21, H: 6.58, N: 4.40, O: 22.45)],

- m.p.: 94-99 °C.

**EXAMPLE 4**: Preparation of Anhydrate of Crystalline S-(-)-Amlodipine (IS)-(+)10-Camsylate

16.63 g of an anhydrate of S-(-)-amlodipine (IS)-(+)10-camsylate, which is a white crystalline solid, was produced using the same method as in Example 2, except that (IS)-(+)10-camphorsulfonic acid was used instead of (IR)-(+)10-camphorsulfonic acid (yield: 83%, water content: 0.25%).

The elemental analysis data and melting point of the anhydrate of crystalline S-(-)-amlodipine (IS)-(+)10-camsylate are given as follows.

- Elemental Analysis for C$_{30}$H$_{42}$ClN$_2$O$_9$S [found(%) (C: 56.11, H: 6.59, N: 4.36, O: 22.42), calculated(%) (C: 56.21, H: 6.58, N: 4.40, O: 22.45)],

- m.p.: 94-99 °C.

Comparative Example 1: Preparation of S-(-)-Amlodipine Besylate 2.5 Hydrate

S-(-)-amlodipine was prepared according to the method described in U. S. Pat. No. 6,046,338. S-(-)-amlodipine besylate 2.5 hydrate was prepared from S-(-)-amlodipine using the method disclosed in Korean Patent Laid-Open Publication No. 10-2005-37498.

**EXPERIMENTAL EXAMPLE 1**: Hygroscopicity Test

The anhydrates of crystalline S-(-)-amlodipine camsylate prepared in Examples 1 and 3, and the S-(-)-amlodipine besylate 2.5 hydrate prepared in Comparative Example 1 were measured for water content (K.F. moisture%) at 25°C under various humidity conditions (25%, 60%, 75%, and 95%).

The results are summarized in Table 1, below.

<table>
<thead>
<tr>
<th>Storage Conditions (Relative)</th>
<th>25%</th>
<th>60%</th>
<th>75%</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
As shown in Table 1, the anhydrate of crystalline S-(-)-amlodipine (lR)-(-)-10-camsylate (Example 1) and the anhydrate of crystalline S-(-)-amlodipine (lS)-(+)-10-camsylate (Example 3) were found to show no hygroscopicity under various humidity conditions. In contrast, S-(-)-amlodipine besylate 2.5 hydrate of Comparative Example 1, which is currently commercially available, was high in water content from the beginning. The desired form in manufacturing pharmacy is maintaining the anhydrate form at the beginning and non-hygroscopic form under high humidity.

**EXPERIMENTAL 2: Solubility Test**

The anhydrate of crystalline S-(-)-amlodipine (IR)(-)-10-camsylate prepared in Example 1, the anhydrate of crystalline S-(-)-amlodipine (IS)(+)-10-camsylate prepared in Example 3 and the S-(-)-amlodipine besylate 2.5 hydrate prepared in Comparative Example 1 were measured for solubility at 25°C under various pH conditions.

The results are summarized in Table 2, below.

**Table 2**

<table>
<thead>
<tr>
<th>Solvents</th>
<th>Ex. 1</th>
<th>Ex. 3</th>
<th>C. Ex. 1</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>4.34</td>
<td>4.30</td>
<td>2.51</td>
<td>pH buffered solution according to Korean Pharmacopeia</td>
</tr>
<tr>
<td>pH 1.2</td>
<td>26.01</td>
<td>25.43</td>
<td>3.12</td>
<td></td>
</tr>
<tr>
<td>pH 4.0</td>
<td>24.89</td>
<td>22.87</td>
<td>2.94</td>
<td></td>
</tr>
<tr>
<td>pH 6.8</td>
<td>1.24</td>
<td>1.25</td>
<td>1.39</td>
<td></td>
</tr>
</tbody>
</table>

(Units: mg/ml)

As is understood from the data of Table 2, the solubility of the anhydrate of
crystalline S-(-)-amlodipine (lR)-(−)-10-camsylate of the present invention (Example 1) and the solubility of the anhydrate of crystalline S(-)-amlodipine (IS)-(+)10-camsylate of the present invention (Example 3) were equivalent to or higher than that of S(-)-amlodipine besylate 2.5 hydrate (Comparative Example 1) in distilled water and buffers over a wide range of pH values.

**EXPERIMENTAL EXAMPLE 3: Stability Test**

1. Stability in Solid State

The anhydrate of crystalline S(-)-amlodipine (IR)-(−)-10-camsylate prepared in Example 1, the anhydrate of S(-)-amlodipine (IS)-(+)10-camsylate prepared in Example 3 and the S(-)-amlodipine besylate 2.5 hydrate prepared in Comparative Example 1 were subjected to an acceleration test at 60°C.

**<HPLC Analysis Condition>**
- Detector: UV absorbance (at 237 nm),
- Column: Octadecyl silica gel C18 (4.6mm x 150mm, 5D),
- mobile phase: Potassium dihydrogen phosphate monobasic (0.03 M): Methanol = 4: 6 (by volume)
- Flow rate: 1.5 ml/min.

The results are summarized in Table 3, below.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Initial stage</th>
<th>1 week</th>
<th>2 week</th>
<th>4 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex. 1</td>
<td>99.7%</td>
<td>99.7%</td>
<td>99.7%</td>
<td>99.6%</td>
</tr>
<tr>
<td>Ex. 3</td>
<td>99.7%</td>
<td>99.7%</td>
<td>99.7%</td>
<td>99.7%</td>
</tr>
<tr>
<td>C. Ex. 1</td>
<td>99.6%</td>
<td>99.6%</td>
<td>99.7%</td>
<td>99.6%</td>
</tr>
</tbody>
</table>

(Unit: HPLC content %)

All of the anhydrate of crystalline S(-)-amlodipine (IR)-(−)-10-camsylate of the present invention (Example 1), the anhydrate of crystalline S(-)-amlodipine (IS)-(+)10-camsylate of the present invention (Example 3) and the S(-)-amlodipine besylate 2.5 hydrate (Comparative Example 1), as seen in Table 3, were found to undergo little change in content as measured by the 60°C acceleration test, suggesting that the anhydrate of crystalline S(-)-amlodipine camsylate of the present invention was as good in thermal stability as S(-)-amlodipine besylate 2.5 hydrate.
2. Stability in Aqueous Solution State

To evaluate the stability of samples in aqueous solution state, the anhydrate of crystalline S-(-)-amlodipine (IR)-(-)-10-camsylate prepared in Example 1, the anhydrate of crystalline S-(-)-amlodipine (IS)-(+)10-camsylate prepared in Example 3 and the S-(-)-amlodipine besylate 2.5 hydrate prepared in Comparative Example 1 were dissolved in distilled water before storage for 4 weeks at 25\(^\circ\)C in the dark with the content thereof monitored. The observation was made under the same conditions as in the HPLC analysis for evaluating the stability of samples in a solid state.

This stability test revealed that none of the anhydrate of crystalline S-(-)-amlodipine (IR)-(-)-10-camsylate of the present invention (Example 1), the anhydrate of crystalline S-(-)-amlodipine (IS)-(+)10-camsylate of the present invention (Example 3) and the S-(-)-amlodipine besylate 2.5 hydrate (Comparative Example 1) were degraded. Also, no significant content changes were observed in any of them.

**EXPERIMENTAL EXAMPLE 4: Photostability Test**

The anhydrate of crystalline S-(-)-amlodipine (IR)-(-)-10-camsylate prepared in Example 1, the anhydrate of crystalline S-(-)-amlodipine (IS)-(+)10-camsylate prepared in Example 3 and the S-(-)-amlodipine besylate 2.5 hydrate prepared in Comparative Example 1 were stored for 4 weeks at 25\(^\circ\)C in a photostability chamber in accordance with ICH guidelines and were exposed to a light source. An observation was made of content (HPLC) change under the same conditions as in the HPLC analysis for evaluating the stability of samples.

The results are given in Table 4, below.

<table>
<thead>
<tr>
<th></th>
<th>Initial Stage</th>
<th>After 4 weeks at 25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Content(HPLC)</td>
<td>Content(HPLC)</td>
</tr>
<tr>
<td>Ex. 1</td>
<td>99,7%</td>
<td>91,9%</td>
</tr>
<tr>
<td>Ex. 3</td>
<td>99,7%</td>
<td>91,4%</td>
</tr>
<tr>
<td>C. Ex. 1</td>
<td>99,2%</td>
<td>79,6%</td>
</tr>
</tbody>
</table>

As shown in Table 4, little change of content and initial color, white was observed in the anhydrate of crystalline S-(-)-amlodipine (IR)-(-)-10-camsylate of the present invention (Example 1) and the anhydrate of crystalline S-(-)-amlodipine (IS)-(+)10-camsylate of the present invention (Example 3). In contrast, S-(-)-amlodipine besylate 2.5 hydrate (Comparative Example 1) turned yellow from
white with a decrease in content from 99.2% to 79.6% during exposure to the light source.

[132] Thus, the anhydrate of crystalline S-(-)-amlodipine camsylate according to the present invention was confirmed to be highly photostable. Photostability is a very important factor for anti-hypertensives because they are generally administered over a long period of time.

[134] **Industrial Applicability**

[135] The anhydrate of crystalline S-(-)-amlodipine camsylate produced by the method of the present invention exhibits excellent physical and chemical properties including non-hygroscopicity, solubility, stability and photostability, and is superior in formulation processability and long-term storage safety.
Claims

[1] A anhydrate o f crystalline S-(-)-amlodipine camsylate, represented by the following Chemical Formula 1:

<Chemical Formula 1>

[2] The anhydrate of crystalline S-(-)-amlodipine camsylate according to claim 1, wherein the anhydrate is an anhydrate of crystalline S-(-)-amlodipine (LR)-(-)-10-camsylate or an anhydrate of crystalline S-(-)-amlodipine (IS)-(+)10-camsylate.

[3] The anhydrate of crystalline S-(-)-amlodipine camsylate according to claim 1, wherein the anhydrate has X-ray diffraction peaks at diffraction angles of 7.80°, 9.18°, 9.56°, 11.38°, 12.78°, 13.10°, 13.84°, 15.48°, 15.68°, 17.38°, 18.94°, 19.92°, 21.78°, 23.16°, 24.64°, 25.86° and 26.44°, with a melting point ranging from 94 to 99°C.

[4] A method for preparing an anhydrate of crystalline S-(-)-amlodipine camsylate represented by the following reaction scheme 1, comprising a reaction between S-(-)-amlodipine and camphorsulfonic acid in an inert organic solvent or distilled water (H₂O):

<Reaction Scheme 1>

[5] The method according to claim 4, wherein the camphorsulfonic acid is (LR)-(-)-10-camphorsulfonic acid or (IS)-(+)10-camphorsulfonic acid.

[6] The method according to claim 4, wherein the inert solvent is selected from a group consisting of acetone, ethyl acetate, methanol, ethanol, isopropanol, acetoneitrile, hexane, isopropyl ether, t-butyl methyl ether, and a combination thereof.
[7] The method according to claim 4, wherein the camphorsulfonic acid is used in an amount of 1-2 equivalents per equivalent of S-(-)-amlodipine.

[8] A pharmaceutical composition for prevention or treatment of cardiovascular disease, comprising the anhydrate of crystalline S-(-)-amlodipine camsylate of claim 1 as an active ingredient.

[9] The pharmaceutical composition for prevention or treatment of cardiovascular disease according to claim 8, wherein the cardiovascular disease is selected from a group consisting of angina pectoris, hypertension and congestive heart failure.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

C07D 211/90(2006.01)

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)
IPC 8 as above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKIPASS, STN (REGISTRY, CA)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
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<th>Category*</th>
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Date of the actual completion of the international search
04 FEBRUARY 2008 (04 02 2008)

Date of mailing of the international search report
05 FEBRUARY 2008 (05.02.2008)

Name and mailing address of the ISA/KR
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