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(54) Title: HYDROPHILIC (S)-AMLODIPINE SALTS OR THEIR HYDRATES AND PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The compounds of the invention, hydrophilic (S)-amlodipine salts or their hydrates and pharmaceutical compositions, are useful for the treatment of hypertension and angina. The molecular formula of the salt hydrates is C_{20}H_{29}N_{2}O_{5}Cl • n_{1}X • n_{2}H_{2}O, in which, X=organic acids, such as benzene sulfonic acid, aspartic acid, acetic acid, tartaric acid; inorganic acids, such as sulfuric acid and hydrobromic acid; monatomic acid n_{1}=1, biatomic acid, n_{1}=0.5; n_{2}=0, 1, 2. Hydrophilic (S)-amlodipine salts or their hydrates, with a very high bioavailability, can be made into pharmaceutical compositions.
HYDROPHILIC (S)-AMLODIPINE SALTS OR THEIR HYDRATES AND
PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

The invention is about hydrophilic (S)-amlodipine salts or their hydrates and pharmaceutical compositions. The molecular formula of the salt hydrates is C_{20}H_{25}N_{2}O_{5}Cl \cdot n_1 X \cdot n_2 H_2O, in which, X=organic acids, such as benzene sulfonic acid, aspartic acid, acetic acid, tartaric acid; inorganic acids, such as sulfuric acid and hydrobromic acid; monatomic acid n_1=1, biatomic acid, n_1=0.5; n_2=0, 1, 2.

Hydrophilic (S)-amlodipine salts or their hydrates have higher hydrophilicity, therefore their bioavailability is higher than other (S)-amlodipine salts. Hydrophilic (S)-amlodipine salts or their hydrates can be made into pharmaceutical compositions, such as tablet, capsule, transdermal drug delivery system, spray, injection, suppository, oral liquid and others. They can be made into compound preparations together with other antihypertensive or antihyperlipidemic drugs.

BACKGROUND OF THE INVENTION

(S)-amlodipine and its salts are long-acting calcium channel blockers, and are thus useful for the treatment of hypertension and angina.

Pfizer invented a feasible method for the separation of the enantiomers of amlodipine (WO95 / 25722), in very good optical purity and yield. The use of both dimethyl sulfoxide (DMSO) and chiral reagent tartaric acid are essential to this method.

ZHANG Xitian’s invention indicates that hexadeuterium dimethyl sulfoxide (DMSO–d_6), in optical purity of up to 100%e.e. and very good yield, is a chiral auxiliary reagent better than DMSO.

Sepracor, a company in the United States, applied for the patent about optically pure of (-) amlodipine (WO 93/10779). But the patent does not give a description of both the preparation and composition about hydrophilic (S)-amlodipine salts or their hydrates.

On March 17, 1999, (S)-amlodipine besylate tablets came into the market in China, but the product that only gave the molecular formula of
(S)-amlodipine besylate, C_{20}H_{25}N_{2}O_{5}C \cdot C_{6}H_{6}O_{3}S, has not disclosed the information about (S)-amlodipine salt capable of generating hydrate yet.

The hydrophilic (S)-amlodipine salts and their hydrates are more easily soluble in water, so it has a higher bioavailability and a better effect of medicine, so they are better than other (S)-amlodipine salt.

SUMMARY OF THE INVENTION

Amlodipine comprises S-enantiomer and R-enantiomer equivalently, in which (S)-amlodipine is an active ingredient for the treatment of hypertension and angina. Whether amlodipine can be absorbed by the body or not is the key to achieving the effect of medicine, similarly, whether (S)-amlodipine can be absorbed by the body or not is also the key to achieving the effect of medicine. (S)-amlodipine salt is more easily soluble in water than (S)-amlodipine, so it is more easily absorbed by the body. (S)-amlodipine salt has a different hydrophilicity. Hydrophilic (S)-amlodipine salt or its hydrate is more easily soluble in water than other (S)-amlodipine salts, so it is more easily absorbed by the body.

In general, the bioavailability of calcium channel blockers is 8 – 10% because they have a lower solubility in water, which leads to a lower bioavailability. Amlodipine besylate belongs to salts, so it is more easily soluble in water, which leads to a higher bioavailability. The bioavailability of amlodipine besylate is about 68 – 80%, not 100% yet. (S)-amlodipine besylate is much more easily soluble in water, so it is much more easily be absorbed by the body, achieving better potency.

Hydrophilic (S)-amlodipine salts and their hydrates are showed in Table 1.

The crystal water content and the dissociation temperature were measured by the PERKIN-ELMER 7 Series Thermal Analysis System and ¹H-NMR spectrometer. The dissociation temperature of the crystal water of (S)-amlodipine salt hydrates were within 110°C.

Table 1 The crystal water number and dissociation temperature of (S)-amlodipine salts
<table>
<thead>
<tr>
<th>Acid</th>
<th>Amlodipine</th>
<th>n₂(H₂O)</th>
<th>Dissociation temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>First dissociation temperature</td>
</tr>
<tr>
<td>benzene sulfonic acid</td>
<td>(S)</td>
<td>2</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>(S,R)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>methane sulfonic acid</td>
<td>(S)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(S,R)</td>
<td>1</td>
<td>45</td>
</tr>
<tr>
<td>acetic acid</td>
<td>(S)</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>(S,R)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>aspartic acid</td>
<td>(S)</td>
<td>2</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>(S,R)</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>tartaric acid (S, S)</td>
<td>(S)</td>
<td>1</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>(S,R)</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>tartaric acid (R, R)</td>
<td>(S)</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>(S,R)</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>maleic acid</td>
<td>(S)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(S,R)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>sulfuric acid</td>
<td>(S)</td>
<td>2</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>(S,R)</td>
<td>2</td>
<td>59</td>
</tr>
<tr>
<td>hydrochloric acid</td>
<td>(S)</td>
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<td>-</td>
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<td></td>
<td>(S,R)</td>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>hydrobromic acid</td>
<td>(S)</td>
<td>1</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>(S,R)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(S)-amlodipine salt hydrate can be generated in the synthetic process in the presence of aqueous medium, or by placing (S)-amlodipine salt in the air, or in the process of administration.

The solvent for the preparation of (S)-amlodipine salt hydrate was water. Under protection of nitrogen, (S)-amlodipine was added to the acid water solution at 60 °C equivalent to (S)-amlodipine and stirred until dissolution. With stirring stopped, it was then cooled to crystallize. The solid was collected by filtration and then dried at room temperature to give the hydrate. Every (S)-amlodipine salt hydrate has a different solubility, so an appropriate regulation of the water solution concentration of inorganic or organic acid is needed. The water solution of (S)-amlodipine salt can also be concentrated appropriately before crystallized. (S)-amlodipine salt dried in vacuo at an appropriate
temperature can produce the hydrate or solution of hydrate when encountering moist air or water.

(S)-amlodipine salts and their hydrates can be made into tablet, capsule, transdermal drug delivery system, spray, injection, suppository, oral liquid and others, in which the tablet and capsule are the most common.

Hydrophilic (S)-amlodipine salts and their hydrate, together with other antihypertensive drugs (such as diuretic, ACE inhibitor and AT1 receptor antagonist, epinephrine inhibitor and calcium channel blocker), can be made into compound preparations.

Hydrophilic (S)-amlodipine salts and their hydrate, together with other antihyperlipidemic drugs (Hmg-CoA reductase inhibitors, such as Simvastatin, Pravastatin, Lovastatin, Fluvastatin, atorvastatin) can be made into compound preparations.

**DESCRIPTION OF THE PREFERRED EMBODIMENTS**

**Example 1  Preparation of (S)-amlodipine besylate hydrate.**

5g (S)-amlodipine was put in 120 ml water. Then 1.4 g benzene sulfonic acid was added to it and stirred, which was heated to 60°C under protection of nitrogen. With stirring stopped after dissolution, the solution was cooled to room temperature and then crystallized overnight. The solid was collected by filtration, washing with 20 ml water, to give (S)-amlodipine besylate, which was dried at room temperature to constant weight, to give 6.6 g (90% of theoretical yield). Found: C 51.68%, H 5.72%, N 4.71%; Calc. for C_{20}H_{25}N_{2}O_{5}Cl • C_{6}H_{6}O_{3}S • 2H_{2}O: C 51.74%, H 5.80%, N 4.64%.

**Example 2  Preparation of (S)-amlodipine besylate tablets**

The ingredients are as follows:

1. (S)-amlodipine besylate dihydrate 3.678g
2. Microcrystalline cellulose (M80) 15g
3. Microcrystalline cellulose (A300) 20g
4. Lactose 53.822g
5. Starch 7g
6. Magnesium stearate 0.5g

1000 tablets
The above materials mixed uniformly were pressed to give a 100 mg tablet containing 2.5 mg (S)-amlodipine.

**Example 3 Preparation of (S)-amlodipine besylate capsule**

The ingredients are as follows:

<table>
<thead>
<tr>
<th>1. (S)-amlodipine dihydrate</th>
<th>besylate</th>
<th>3.678g</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Starch</td>
<td></td>
<td>30g</td>
</tr>
</tbody>
</table>

1000 capsules

The above materials mixed uniformly were put into 1000 capsules containing 2.5mg (S)-amlodipine each.

**INDUSTRIAL APPLICABILITY**

The invention is industrially feasible without any technical barrier. Because (S)-amlodipine salt capable of generating hydrate and its hydrate have a higher bioavailability than that of incapable of generating hydrate, it has a better effect of medicine.
What is claimed is:

1. The invention is (S)-amlodipine (C_{20}H_{25}N_{2}O_{5}Cl) salt capable of generating hydrate and its hydrate and pharmaceutical compositions.

2. Hydrophilic (S)-amlodipine, salt or its hydrate, such as (S)-amlodipine besylate, aspartic acid (S)-amlodipine, acetic acid (S)-amlodipine, (R, R) tartaric acid (S)-amlodipine (bihydrate), sulfuric acid (S)-amlodipine and hydrobromic acid (S)-amlodipine.

3. (S)-amlodipine salt hydrate can be generated in the synthetic process in the presence of aqueous medium, or by placing anhydro(S)-amlodipine in the air, or in the process of administration.

4. (S)-amlodipine salt hydrate comprises C_{20}H_{25}N_{2}O_{5}Cl \cdot n_1 X \cdot n_2 H_2O, in which, X=organic acids, such as benzene sulfonic acid, aspartic acid, acetic acid, tartaric acid; inorganic acids, such as sulfuric acid and hydrobromic acid; monatomic acid n_1=1, biatomic acid, n_1=0.5; n_2=0, 1, 2.

5. Hydrophilic (S)-amlodipine, salt or its hydrate can be prepared in the forms of tablet, capsule, transdermal drug delivery system, spray, injection, suppository, oral liquid and others, which are useful for the treatment of hypertension and angina.

6. Hydrophilic (S)-amlodipine salts and their hydrate, together with other antihypertensive drugs (such as diuretic, ACE inhibitor and AT1 receptor antagonist, epinephrine inhibitor and calcium channel blocker), can be made into compound preparations.

7. Hydrophilic (S)-amlodipine salts and their hydrate, together with antihyperlipidemic drugs can be made into compound preparations.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

C07D21/1190   A61K31/44

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 7  C07D   A61K

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)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
<td>X</td>
<td>US,B1, 6291490 (James W. Young, Palo Alto, CA) 18.09.01, col. 7, lines 14-22, col. 9, lines 53-62</td>
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<td>US,B1,6262092 (George Chang, ivoryton; Ernest S. Hatanaka, Gales Ferry, both of CT (US))</td>
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- **"&"** document member of the same patent family

Date of the actual completion of the international search: 2003.1.17

Date of mailing of the international search report: 2003.01.17

Authorized officer: lihongqi

Authorized officer: lihongqi

Telephone No.: 86-10-62093075
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