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(54) Title: BENIDIPINE HYDROCHLORIDE

(57) Abstract: Disclosed is a method for preparing benidipine hydrochloride, which comprising: 1) during the pre-treatment stage including acylchloridizing the main ring of dihydropyridine and then linking the side chain to synthesize directly benidipine hydrochloride, ultrasound technology is introduced, and the reactant material is dispersed and dissolved by ultrasound to increase reaction rate; and/or 2) during the post-treatment stage, ultrasound technology is introduced and crude crystals or product obtained by heating to dryness of benidipine hydrochloride obtained via the method described above or any other synthetic routes is dissolved once more and then highly purified benidipine hydrochloride is obtained by ultrasound.
**BENIDIPINE HYDROCHLORIDE**

**Field of the invention**

The present invention belongs to medicine field and relates to a method of preparing highly purified benidipine hydrochloride by ultrasonic technology. Specifically, the method of the present invention comprises: 1) during the pre-treatment stage, including acylchloridizing the main ring of dihydropyridine and then linking the side chain to synthesize directly benidipine hydrochloride, ultrasound technology is introduced, and the reactant material is dispersed and dissolved by ultrasound, and/or 2) during the post-treatment stage, ultrasonic technology is introduced and crude crystal (or product obtained by heating to dryness) of benidipine hydrochloride obtained via the method described above or other possible synthetic routes is dissolved once more and then highly purified benidipine hydrochloride is obtained by ultrasound.

**Background of the invention**

Benidipine hydrochloride, whose chemical name is (±)-(R*)-1,4-dihydro-2,6-dimethyl-4-(meta-nitrophenyl)-3,5-pyridinedicarbolate methyl ester [(R*)-l-benzyl-3-piperidine alcohol ester], belongs to dihydropyridine receptor antagonist. It can bind to dihydropyridine receptors at the binding site with high affinity and high specificity, and shows a strong inhibitory effect on Ca\(^{2+}\) channel. Benidipine not only has an inhibitory effect on muscular (L-type) Ca\(^{2+}\) channel, but also has an inhibitory effect on voltage-dependent N- and T-type Ca\(^{2+}\) channels. It is, up to now, the only calcium antagonist that can inhibit all the three Ca\(^{2+}\) channels mentioned above. Furthermore, benidipine has highly affinity with cell membrane, has vascular selectivity and renal protection effect. Therefore, it is an ideal, safe and effective agent for the treatment of hypertension and renal parenchymal hypertension and angina.

There are two chiral atoms in the molecule of benidipine hydrochloride, which locate on site 4 of the dihydropyridine ring and site 3' of the side chain piperidine ring. Accordingly, benidipine hydrochloride has 4 optical
isomers: (S)-(S)-(+)-a, (R)-(R)-(-)-a, (R)-(S)-(+)^ and (S)-(R)-(-)^, and
the active ingredients for drug are the mixture of (S)-(S)-(+)-a and (R)-(R)-(-)OL Therefore, it is necessary to separate a and β isomers during the post-treatment stage of benidipine hydrochloride preparation.

Based on the order of synthesis of dihydropyridine main ring, there mainly are two groups of total 5 synthesis routes of benidipine hydrochloride. Among them, there are two routes which involve synthesis of the main ring first: 1) acylchloridizing the main ring of dihydropyridine and then linking the side chain to synthesize directly benidipine hydrochloride; 2) After acylchloridizing the main ring of dihydropyridine, 3-piperidinol and then benzyl is added. The routes involve the synthesis of the main ring later includes the following; 1) synthesizing the main ring via β-aminocrotonate; 2) synthesizing the main ring via acetylacetate ester; 3) the One-pot method involving 3-nitrobenzaldehyde, β-aminocrotonate and acetylaceate ester.

Several synthetic routes of benidipine hydrochloride and its analogues have been disclosed in EP0063365A1, EP0161877A2, JP57-171968A, EP0106275A2, etc. Among them, EP0106275A2 gave a summary of the synthetic pathways of benidipine hydrochloride. In all of the above references, it was mentioned to separate the benidipine hydrochloride prepared through column chromatography and spit it into its a and β isomers, thus obtain the therapeutically active (±)-a- benidipine hydrochloride.

In order to obtain a highly purified benidipine hydrochloride meeting pharmaceutical use, it is necessary to perform multiple recrystallization with acetone and/or ethanol. Moreover, the crystallization condition is relatively strict since it should be performed below freezing point or even below -20°C. Furthermore, the crystallization process usually need a relatively long time (more than 24 hours).

JP2007-8819A thus disclosed a method for preparing highly purified benidipine hydrochloride meeting pharmaceutical use by first preparing the monohydrate of benidipine hydrochloride.

All of the methods mentioned above involve multiple steps, and even require column chromatography to effectively separate the isomers. These
methods are not only time and labor consuming, but also need great amount of organic solvents, which will bring about negative impacts on both the society wealth and environmental protection.

**Summary of the invention**

The present invention mainly uses the direct synthesis method of benidipine hydrochloride including acylchloridizing main ring of dihydropyridine and then linking the side chain. 1) During the pre-treatment stage for preparing benidipine hydrochloride, ultrasound technology is introduced, and the reactant material is dispersed and dissolved by ultrasound, and thus the reactant disperses evenly into the reaction medium to render the reaction perform stably and rapidly. Therefore, the reaction rate is enhanced. 2) During the post-treatment stage, the benidipine hydrochloride, which is obtained by the method described above or by other possible synthesis routes, is formed into crude crystal of benidipine hydrochloride by heating reaction solvent to dryness or other feasible methods. Then after the crude crystal of benidipine hydrochloride or the products obtained from heating to dryness are dissolved a suitable solvent, ultrasound technology is introduced. By ultrasound crystallization, unexpected effective separation of benidipine hydrochloride isomers may be achieved. The purity of benidipine hydrochloride a isomers obtained is above 98.6% (HPLC area normalization method), the crystallization duration is shortened from 24 hours to 30 minutes, and the yield is also increased greatly. Figure 1 is a liquid chromatography of benidipine hydrochloride crude crystal or product obtained by heating to dryness using HPLC area normalization method; Figure 2 is a liquid chromatography of ultrasound crystal obtained using HPLC area normalization method; and Figure 3 is a liquid chromatography of mother liquor after crystallization by ultrasound using HPLC area normalization method.

The present invention not only avoids the separation process by column chromatography, and simplifies the process to make operation easier, and reduces use and discharge of organic solvents, but also allows saving of human and material resources, and time and cost, and is in favor of environmental protection.
During the pre- and post-treatment stages of benidipine hydrochloride synthesis, suitable temperature for ultrasound crystallization is -78 °C~100 °C, preferably -5°C to 30°C. Suitable ultrasound frequency is 20 kHz—500 kHz, preferably 20 kHz—100 kHz. Suitable ultrasound power is 1 mW—5000 W, preferably 1 W—500 W. The duration of the ultrasound is 1 minute to 24 hours, preferably 3 minutes to 120 minutes. Suitable solvent for preparing benidipine hydrochloride under ultrasound is lower-carbon-number ketone, lower-carbon-number alcohol, lower-carbon-number ether, lower-carbon-number acid, lower-carbon-number ester, dichloromethane, chloroform, acetic anhydride or commonly used small molecule solvents. Preferred solvents are selected from the group consisting of acetone, ethanol, methanol, N,N-dimethylformamide (DMF), acetonitrile, diethyl ether, dichloromethane and water.

The preparation procedure of benidipine hydrochloride in the present invention are as follows:

(1) Under ultrasound condition, dihydropyridine main ring [chemical name: 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid monomethyl ester] is dispersed evenly in appropriate amount of mixed solution of N,N-dimethylformamide (DMF) and dichloromethane. The resultant suspension is cooled in ice-bath condition, and thionyl chloride is added. The mixture is stirred until the solution becomes clear and the main ring, i.e., monochloro acylate [monochloro acylated 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid monomethyl ester] is obtained.

(2) Under or not under ultrasound conditions, add reactive amount of pyridine (alcohol) side chain [l-benzyl-3-hydroxypiperidine], and allow reaction for a certain period of time.

(3) The reaction solution is washed with water and saturated saline for several times. Solvent is recycled to obtain crude crystal of benidipine hydrochloride (containing a and β isomers, and other related substances).

(4) The crude crystal of benidipine hydrochloride (obtained via the reactions described above or via other suitable synthesis routes) is dissolved in suitable single or mixed solvent, and ultrasound is applied
for a certain time at a suitable power. After one or more times of crystallization, a-benidipine hydrochloride is obtained directly as light yellow powdery crystal, with a purity of over 98.6% (HPLC area normalization method).

**Brief description of the drawings**

Fig. 1 is a liquid chromatography of benidipine hydrochloride crude crystal or product obtained by heating to dryness using HPLC area normalization method;

Fig. 2 is a liquid chromatography of ultrasound crystal obtained using HPLC area normalization method;

Fig. 3 is a liquid chromatography of mother liquor after crystallization by ultrasound using HPLC area normalization method.

**Detailed description of the invention**

The present invention will be described in detail in combination with the following Examples.

**Example 1**

Under ultrasound, 10 g of dihydropyridine main ring, i.e., [2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid monomethyl ester] was placed into 200 mL reaction flask, and 14 mL N,N-dimethylformamide (DMF) and 56 mL dichloromethane was added. To the resultant homogeneous suspension was added 2.4 mL of thionyl chloride under ice-bath, then the mixture was stirred for 1 hour to obtain a clear solution.

Then, 6.3 g of pyridine (alcohol) side chain, i.e., [l-benzyl-3-hydroxypiperidine] was added and stirred for 2.5 hours under ice-bath.

The reaction solution was washed with 40 mL water ($\times$ 4) and 40 mL saturated saline solution ($\times$ 1). The dichloromethane solution was dried for two hours by adding 4 g of anhydrous sodium sulfate. Then, sodium sulfate solid was removed by filtering, and dichloromethane was recycled under reduced pressure to obtain a yellow to red crude crystal (herein after referred to as crude crystal of benidipine hydrochloride).
The crude crystal mentioned above was dissolved in 100 mL acetone, and ultrasounded at 150 W and 40 MHz for 7 minutes, filtered under reduced pressure and dried to obtain 5.9 g of crystal as yellow powder (yield 36.2%).

Example 2

3.0 g of 3-nitrobenzaldehyde, 2.6 g of β-aminocrotonate and 2.6 g of ethyl acetoacetate were dissolved in a mixed solvent of 10 mL DMF and 50 mL dichloromethane. The reaction mixture was stirred for 3 h at 50°C, washed with water, dried. The solvent was recycled to obtain a yellow to red crude crystal of benidipine hydrochloride.

Example 3

10 g of benidipine hydrochloride crude crystal was dissolved in 60 mL acetone. Ultrasonification was performed for 8 minutes at 200 W and 80 MHz. The reaction mixture was filtered under reduced pressure. Then the crystal above was dissolved in 5 mL ethanol by heating under refluxing. 40 mL acetone was added under untrasonification at 150 W and 40 MHz and ultrasonification was continued for 8 minutes. The mixture was filtered under reduced pressure and dried to obtain 3.2 g of crystal as light yellow powder.

Example 4

10 g of benidipine hydrochloride crude crystal was dissolved in 100 mL acetone + 1 mL absolute ethanol. Ultrasonification was performed for 10 minutes at 150 W and 40 MHz. The mixture was filtered under reduced pressure and dried to obtain light yellow powdery crystal.

Example 5

10 g of benidipine hydrochloride crude crystal was dissolved in 100 mL acetone + 5 mL water. Ultrasonification was performed for 17 minutes at 150 W and 40 MHz. The mixture was filtered under reduced pressure and dried to obtain light yellow powdery crystal.

Example 6

10 g of benidipine hydrochloride crude crystal was dissolved in 100 mL isopropanol. 7 mL acetonitrile was added under untrasonification at 150
W and 40 MHz and untrasonification was continued for 10 minutes. The mixture was filtered under reduced pressure and dried to obtain light yellow powdery crystal.

Example 7

10 g of benidipine hydrochloride crude crystal was dissolved in 10 mL DMF. 10 mL water was added under untrasonification at 250 W and 40 MHz and untrasonification was continued for 10 minutes. The mixture was filtered under reduced pressure and dried to obtain light yellow powdery crystal.

Example 8

10 g of benidipine hydrochloride crude crystal was dissolved by heating in 1000 mL ethanol. Ultrasonification was performed for 10 minutes at 150 W and 40 MHz. The mixture was filtered under reduced pressure and dried to obtain 2.8 g crystal as light yellow powder. The mother liquor was allowed stand for 24 hours, filtered under reduced pressure and dried to obtain 4.1 g crystal as light yellow powder.

Example 9

10 g of benidipine hydrochloride crude crystal was dissolved in 100 mL ethanol + 5 mL water by heating. Ultrasonification was performed for 10 minutes at 150 W and 80 MHz. The mixture was filtered under reduced pressure and dried to obtain light yellow powdery crystal.

Example 10

10 g of benidipine hydrochloride crude crystal was dissolved in 40 mL methanol by heating. Ultrasonification was performed for 10 minutes at 200 W and 40 MHz. The mixture was filtered under reduced pressure to obtain light yellow powdery crystal.

Example 11

10 g of benidipine hydrochloride crude crystal was dissolved in 40 mL methanol + 5 mL water by heating. Ultrasonification was performed for 10 minutes at 200 W and 40 MHz. The mixture was filtered under reduced pressure to obtain light yellow powdery crystal.
Example 12
10 g of benidipine hydrochloride crude crystal was dissolved in 30 mL dichloromethane. Ultrasonification was performed for 18 minutes at 200 W and 80 MHz. The mixture was filtered under reduced pressure to obtain light yellow powdery crystal.

Example 13
10 g of benidipine hydrochloride crude crystal was dissolved in 40 mL acetonitrile by heating. Ultrasonification was performed for 10 minutes at 150 W and 80 MHz. The mixture was filtered under reduced pressure to obtain light yellow powdery crystal.

Example 14
10 g of benidipine hydrochloride crude crystal was dissolved in 40 mL acetonitrile + 5 mL water by heating. Ultrasonification was performed for 10 minutes at 150 W and 80 MHz. The mixture was filtered under reduced pressure to obtain light yellow powdery crystal.

Example 15
10 g of benidipine hydrochloride crude crystal was dissolved in 10000 mL water by heating. Ultrasonification was performed for 20 minutes at 150 W and 80 MHz. The mixture was filtered under reduced pressure to obtain light yellow powdery crystal.

Technical effect Example

Purity test of benidipine hydrochloride (area normalization method):

Chromatography conditions

Detector: ultraviolet absorption detector (detection wavelength: 237nm)

Chromatography column: stainless steel column: 4.6 mm x 10 cm, with octadecylsilyl (ODS) silica as filler.

Column temperature: constant, about 25°C

Mobile phase: mixed solution of 0.05 mol/L potassium dihydrophosphate solution (pH 3.0): methanol : tetrahydrofuran (65:27:8)
Flow rate: adjusted to render the retention time of benidipine hydrochloride to be about 20 min.

Chromatogram record time: about 2 times of the peak time of benidipine hydrochloride

The purity of benidipine hydrochloride obtained in Example 1 was detached to be ^98.6%.
CLAIMS

1. A method for preparing highly purified benidipine hydrochloride by ultrasound technology, comprises: 1) during the pre-treatment stage including acylchloridizing the main ring of dihydropyridine and then linking the side chain to synthesize directly benidipine hydrochloride, ultrasound technology is introduced, and the reactant material is dispersed and dissolved by untrasound, and/or 2) during the post-treatment stage, ultrasound technology is introduced and crude crystal (or product obtained by heating to dryness) of benidipine hydrochloride obtained via the method described above or other possible synthetic routes is dissolved once more and then highly purified benidipine hydrochloride is obtained by untrasound.

2. The method according to Claim 1, wherein ultrasound technology is introduced into the pre-treatment stage of benidipine hydrochloride synthesis, in order to improve dispersion, dissolution and homogenization of reactants, and help to enhance the reaction speed.

3. The method according to Claim 1, wherein the crude crystal of benidipine hydrochloride may be prepared according to the method of Claim 1, but it may also be synthesized through other possible synthetic routes, for example, acylchloridizing the main ring of dihydropyridine and then joining 3-piperidinol and then benzyl; or benidipine hydrochloride may be prepared by One-pot' method involving 3-nitrobenzaldehyde, β-aminocrotonate and acetylacetate; or benidipine hydrochloride may also be prepared by synthesis of main ring via β-aminocrotonate, or acetylacetate.

4. The method according to Claim 1, wherein the crude crystal of benidipine hydrochloride of Claim 1 is re-dissolved in suitable solvent,
and then crystallization is performed for one or more times under ultrasound, and highly purified benidipine hydrochloride is obtained.

5. The method according to any one of Claims 1 and 4, wherein the crystallization under ultrasound is performed at a temperature of -78 °C to 100 °C, preferably -5 °C to 30 °C.

6. The method according to any one of Claims 1 and 4, wherein the solvent used to prepare highly purified benidipine hydrochloride is selected from the group consisting of a lower-carbon-number ketone, a lower-carbon-number alcohol, a lower-carbon-number ether, a lower-carbon-number acid, a lower-carbon-number ester, dichloromethane, chloroform, acetic anhydride or other commonly used small molecule solvents alone, or any combination of two or more solvents; preferably acetone, ethanol, methanol, N,N-dimethylformamide (DMF), acetonitrile, diethyl ether, dichloromethane and water alone, or any combination of two or more solvents.

7. The method according to any one of Claims 1 and 4, wherein the frequency of the ultrasound ranges from 10 kHz to 500 kHz, preferably 15 kHz to 100 kHz.

8. The method according to any one of Claims 1 and 4, wherein the power for the ultrasound ranges from 1 mW to 5000 W, preferably 1 W to 3000 W.

9. The method according to any one of Claims 1 and 4, wherein the duration of the ultrasound ranges from 1 minute to 24 hours, preferably 3 minutes to 120 minutes.
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<th>Plate Tailor Factor</th>
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Fig. 1
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**Fig. 2**
The table below summarizes the chromatographic analysis results:

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**Fig. 3**
### INTERNATIONAL SEARCH REPORT

**International application No.:** PCT/CN201 1/080293

**C07D 211/90 (2006.01)**

According to International Patent Classification (IPC) or to both national classification and IPC

### A. CLASSIFICATION OF SUBJECT MATTER

<table>
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<td>Hydrochloride; ultrasonic; untrasound; sonication; ultrasound; ultrasonography;</td>
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### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**IPC:** C07D

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)

- WPI; EPODOC; CPRS; CNKI; CAPLUS: benidipine; hydrochloride; ultrasonic; untrasound; sonication; ultrasound; ultrasonography; 91599-74-5

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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* 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
  - “L” document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason as specified
  - “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

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Date of mailing of the international search report: 02 Feb. 2012 (02.02.2012)

Name and mailing address of the ISA/CN:
The State Intellectual Property Office, the P.R.China
6 Xitucheng Rd., Jiemin Bridge, Haidian District, Beijing, China 100088
facsimile No. 86-10-62019451

Authorized officer: SHA, Lei
Telephone No. (86-10)62084375

Form PCT/ISA /210 (second sheet) (July 2009)
## INTERNATIONAL SEARCH REPORT
### Information on patent family members

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