Abstract:

World Intellectual Property Organization

Inventors:

Disclosed herein an improved process for the preparation of polymorphic Form I of clopidogrel hydrogen sulfate.
AN IMPROVED PROCESS FOR THE PREPARATION OF CLOPIDOGREL HYDROGEN SULFATE FORM I

FIELD OF INVENTION

The present invention relates to an improved process for the preparation of polymorphic Form I of clopidogrel hydrogen sulfate.

BACKGROUND OF INVENTION

Clopidogrel hydrogen sulfate is a platelet aggregation inhibitor, which was described first time in EP281459. The synthetic process claimed in this patent leads to the preparation of clopidogrel hydrogen sulfate, subsequently given the name Form I. It has now been discovered that clopidogrel hydrogen sulfate can exists in different crystalline forms, which differ from each other by their stability, their physical properties, their spectral characteristics and the process for their preparation.

WO99/65915 discloses two polymorphs of clopidogrel hydrogen sulfate referred as Form I and Form II, although Form I is already disclosed in EP281459 patent. Both forms are crystallized from acetone under different conditions but according to the disclosure of WO99/65915, Form II of clopidogrel hydrogen sulfate is thermodynamically more stable than Form I. This encourages the inventor to explore reliable solvent/solvent mixture for the preparation of clopidogrel hydrogen sulfate Form I, where the spontaneous transformation into Form II can be avoided.

US 6,767,913 discloses various polymorphs of clopidogrel hydrogen sulfate i.e. Form III, IV, V and amorphous forms and processes of preparation thereof.

US 2003/1 14479 discloses novel processes for the preparation of clopidogrel hydrogensulfate i.e. Form I, Form III, Form IV, Form V and the amorphous forms. US'479 further discloses a novel process for preparation of Form I, wherein the amorphous clopidogrel hydrogensulfate is converted to Form I using t-butyl methyl ether.

US 2006/0041 136 discloses process for the preparation of Form I from clopidogrel base or clopidogrel hydrogen sulfate in alcohols or their esters.

US 2006/0047121 discloses process for the preparation of Form I by dissolving clopidogrel hydrogen sulfate Form II in C1-C5 carboxylic acid, followed by precipitation from aliphatic or cyclic ether.
WO2005/104663 discloses process for the preparation of clopidogrel hydrogen sulfate Form I, by dissolving clopidogrel base in methyl propyl ketone, methyl isopropyl ketone, diethyl ketone or ethyl acetate and ketones mixture, cooling the resulting solution of about -10 to 20°C, adding concentrated sulphuric acid and maintaining the resultant solution at about 10 to 30°C to precipitate clopidogrel hydrogen sulfate Form I crystals.

WO2006/087729 discloses process for the preparation of clopidogrel hydrogen sulfate Form I by dissolving clopidogrel base in acetic acid followed by adding ether solution containing sulfuric acid to precipitate Form I.

US 2006/0183907 discloses process for the preparation of clopidogrel hydrogen sulfate Form I by reacting clopidogrel base with concentrated sulfuric acid in ethyl acetate followed by seeding with crystals of Form I.

US 2006/0205766, discloses another process for preparation of clopidogrel hydrogen sulfate Form I by reacting clopidogrel base with sulfuric acid in 2-propanol or 2-butanol, followed by seeding with crystals of Form I.

Besides this WO2004/048385, WO2005/100364 and WO 2005/016931 also discloses process for the preparation of clopidogrel hydrogen sulfate Form I.

The processes disclosed in the above mentioned prior arts have one or more disadvantages such as isolation of pure Form I of clopidogrel hydrogen sulfate, which is difficult to achieve since the same solvent system is used for the preparation of Form I and more stable Form II. Besides this, during the formation of clopidogrel hydrogen sulfate Form I, amorphous material is also formed. The said amorphous material remains as contaminant, in the eventual Form I. Furthermore, the presence of amorphous material in the Form I reduces the stability of Form I and forms/increases other impurities. Moreover, the processes disclosed in the prior arts are not industrially feasible and environmental friendly.

In view of the above disadvantage of the prior art processes, there is a need to develop an industrially feasible and cost effective process for the preparation of clopidogrel hydrogen sulfate Form I, in high yield and high polymorphic purity, which is free from the contamination of other forms preferably Form II.
OBJECT AND SUMMARY OF THE INVENTION

It is a principal object of the present invention to improve upon limitations in the prior arts by providing an improved process for the preparation of Form I of clopidogrel hydrogen sulfate.

It is another object of the present invention to provide a commercially viable, economical and environment friendly process for the preparation of Form I of clopidogrel hydrogen sulfate.

It is yet another object of the present invention to provide an improved process for the preparation of polymorphic Form I of clopidogrel hydrogen sulfate, which is free from the contamination of Form II or other existing polymorphic forms.

It is still another object of the present invention to provide an improved process for the preparation of polymorphic Form I of clopidogrel hydrogen sulfate, which is free flowing, non-sticky and easily filterable solid on commercial scale, to improve the isolation.

In accordance with one preferred embodiment of the present invention, there is provided a process for the preparation of polymorphic Form I of clopidogrel hydrogen sulfate comprising the steps of dissolving clopidogrel base in an organic solvent selected from ether, ester or mixture thereof; mixing the resulting solution with sulfuric acid and alcoholic solvent and isolating clopidogrel hydrogen sulfate Form I.

In accordance with another preferred embodiment of the present invention, there is provided a process for the preparation of polymorphic Form I of clopidogrel hydrogen sulfate comprising the steps of dissolving clopidogrel hydrogen sulphate in an alcoholic solvent, adding antisolvent selected from ether, ester or mixture thereof and isolating clopidogrel hydrogen sulfate Form I.

DETAILED DESCRIPTION OF THE INVENTION

While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

The present invention provides a commercially viable and cost effective process for preparing clopidogrel hydrogen sulfate Form I in high yield and high polymorphic purity.
An improved process for the preparation of polymorphic Form I of clopidogrel hydrogen sulfate comprising the steps of:

a) dissolving clopidogrel base in an organic solvent selected from ether, ester or mixture thereof;

b) mixing the resulting solution with sulfuric acid and alcoholic solvent and

c) isolating clopidogrel hydrogen sulfate Form I.

Clopidogrel base, as used in step (a) can be prepared from any of the processes described in prior art.

Ether solvent used in step (a) is selected from C3-C8 ethers like di-ethyl ether, di-isopropyl ether, methyl t-butyl ether, di-n-butyl ether and the like. Ester solvent used in step (a) is selected from esters of C1-C4 carboxylic acid like methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like. The more preferred organic solvent is methyl t-butyl ether or n-butyl acetate.

Reaction of step (a) is carried out at temperature range of -5 to 10°C, preferably at 0 to 5°C.

Alcoholic solvent used in step (b) is selected from the group comprising of methanol, ethanol, propanol, isopropanol, n-butanol, 2-butanol, t-butanol and the like. The preferred alcoholic solvent is n-butanol.

Reaction of step (b) is carried out at temperature range of -10 to 10°C, preferably at -5 to 5°C.

Isolation of clopidogrel hydrogen sulfate Form I in step (c) is performed by any conventional method like filtration.

An improved process for the preparation of polymorphic Form I of clopidogrel hydrogen sulfate comprising the steps of:

a) dissolving clopidogrel hydrogen sulphate in an alcoholic solvent;

b) adding anti-solvent selected from ether, ester or mixture thereof and

c) isolating clopidogrel hydrogen sulfate Form I.

Clopidogrel hydrogen sulphate, as used in step (a) can be prepared from any of the processes described in prior art.

Alcoholic solvent used in step (a) is selected from the group comprising of methanol, ethanol, propanol, isopropanol, n-butanol, 2-butanol, t-butanol and the like. The preferred alcoholic solvent is n-butanol.
Ether solvent used in step (b) is selected from C₃-Cs ethers like di-ethyl ether, di-isopropyl ether, methyl t-butyl ether, di n-butyl ether and the like. Ester solvent used in step (b) is selected from esters of C1-C4 carboxylic acid like methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like. The more preferred anti-solvent is methyl t-butyl ether or n-butyl acetate.

Reaction of step (b) is carried out at temperature range of -10 to 10°C, preferably at -5 to 5°C.

Isolation of clopidogrel hydrogen sulfate Form I in step (c) is performed by any conventional method like filtration.

The process for the preparation of Form I of clopidogrel hydrogen sulfate described in the present invention is demonstrated in the examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

**Example-1**

**Preparation of Clopidogrel Hydrogen sulfate Form I**

Clopidogrel camphor sulfonate salt (50g) was taken in toluene at 20-30°C. The aqueous solution of sodium bicarbonate was added and stirred. The pH of the reaction mass was adjusted to 7.0-8.5. The layers were separated and aqueous layer was extracted with toluene (100 ml). The organic solvent was evaporated under vacuum to obtain oily mass. The oily mass was dissolved in methyl t-butyl ether (1100 ml) at 20-30°C. In another flask concentrated sulfuric acid (8.0 g) and «-butanol (100ml) was mixed by stirring at temperature between -5 to 5°C. To the resulting solution, methyl t-butyl ether solution containing clopidogrel base was added within 2-3 h. The resulting mass was stirred for 4-5 h at temperature between -5 to 5°C. The temperature was then raised to 20-30°C and stirred for 32 h. The precipitated solid was filtered, washed with methyl t-butyl ether and dried under vacuum at 50-60°C to obtain polymorphic Form I of clopidogrel hydrogen sulfate.

Yield: 30g; HPLC Purity: 99.86%

**Example-2**

**Preparation of Clopidogrel Hydrogen sulfate Form I**

Clopidogrel hydrogen sulfate salt (20g) was taken in dichloromethane (100 ml) at 20-30°C. The aqueous solution of sodium bicarbonate (120 ml) was added and stirred. The pH of the reaction mass was adjusted to 7.0 - 8.5. The layers were
separated and organic solvent was evaporated under vacuum to obtain clopidogrel base as oily mass. The oily mass was dissolved in methyl t-butyl ether (200 ml). The reaction mass was cooled to 0-5°C and methanol (2 ml) and concentrated sulfuric acid (2.5ml) and methyl t-butyl ether (100 ml) was mixed. To the resulting solution, methyl t-butyl ether solution containing clopidogrel base was added at temperature between 0°C - 5°C within 1-2 h. The temperature of the mass was then raised to 20-30°C and stirred for 10-12 h at same temperature. The precipitated solid was filtered, washed with methyl t-butyl ether and dried under vacuum to obtain polymorphic Form I of clopidogrel hydrogen sulfate.

Yield: 16.4g; HPLC Purity: 99.28%

Example-3
Preparation of Clopidogrel Hydrogen sulfate Form I

Clopidogrel base (23 g) was dissolved in di-isopropyl ether (540 ml). The reaction mass was cooled to -5 to 5°C. To it n-butanol (60 ml) and concentrated sulfuric acid (5.14 g) and di-isopropyl ether (100 ml) were mixed. The temperature of the mass was then raised to 20-30°C and stirred for 32 h at same temperature. The precipitated solid was filtered, washed with di-isopropyl ether and dried under vacuum to obtain polymorphic Form I of clopidogrel hydrogen sulfate.

Yield: 18g; HPLC Purity: 99.68%

Example-4
Preparation of Clopidogrel Hydrogen sulfate Form I

Clopidogrel base (38 g) was dissolved in n-butyl acetate (800 ml). Methanol (4 ml) and sulfuric acid (2.5ml) was added to reaction mass and cooled to 10-15°C. The temperature of the mass was then raised to 20-30°C and stirred for 18 h. The precipitated solid was filtered, washed with n-butyl acetate and dried under vacuum to obtain polymorphic Form I of clopidogrel hydrogen sulfate.

Yield: 40g; HPLC Purity: 99.28%

Example-5
Preparation of Clopidogrel Hydrogen sulfate Form I

Clopidogrel hydrogen sulfate (50 g) was stirred with methanol (100 ml) to get clear solution. Then methanol was evaporated at 40-45°C till 5-10% methanol content remained and allowed it to come at 20-30°C. Then n-butyl acetate (900 ml) was added, seeded with crystals of Form-I of clopidogrel hydrogen sulfate and stirred for
18 h. The precipitated solid was filtered, washed with n-butyl acetate and dried under vacuum to obtain polymorphic Form I of clopidogrel hydrogen sulfate.

Yield: 46 g; HPLC Purity: 99.56%

While this invention has been described in detail with reference to certain preferred embodiments, it should be appreciated that the present invention is not limited to those precise embodiments. Rather, in view of the present disclosure, which describes the current best mode for practicing the invention, many modifications and variations would present themselves to those skilled in the art without departing from the scope and spirit of this invention.
We claim:

1. A process for the preparation of polymorphic Form I of clopidogrel hydrogen sulfate comprising the steps of:
   a) dissolving clopidogrel base in an organic solvent selected from ether, ester or mixture thereof;
   b) mixing the resulting solution with sulfuric acid and alcoholic solvent and;
   c) isolating clopidogrel hydrogen sulfate Form I.

2. The process according to claim 1, wherein the ether solvent used in step (a) is selected from C3-C8 ethers such as di-ethyl ether, di-isopropyl ether, methyl t-butyl ether and di n-butyl ether.

3. The process according to claim 2, wherein the preferred ether is methyl t-butyl ether.

4. The process according to claim 1, wherein the ester solvent used in step (a) is selected from esters of C1-C4 carboxylic acid such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate.

5. The process according to claim 4, wherein the preferred ester is n-butyl acetate.

6. The process according to claim 1, wherein the alcoholic solvent used in step (b) is selected from C1-C4 alcohol.

7. The process according to claim 6, wherein the alcoholic solvent used is selected from the group comprising of methanol, ethanol, propanol, isopropanol, n-butanol, 2-butanol, t-butanol or mixture thereof.

8. The process according to claim 7, wherein the preferred alcoholic solvent is n-butanol.

9. The process according to claim 1, wherein reaction temperature in step (a) is -5 to 10°C.

10. The process according to claim 1, wherein reaction temperature in step (b) is -10 to 10°C.

11. A process for the preparation of polymorphic Form I of clopidogrel hydrogen sulfate comprising the steps of:
   a) dissolving clopidogrel hydrogen sulphate in an alcoholic solvent;
b) adding anti-solvent selected from ether, ester or mixture thereof and

c) isolating clopidogrel hydrogen sulfate Form I.

12. The process according to claim 11, wherein the alcoholic solvent used in step (a) is selected from C1-C4 alcohol.

13. The process according to claim 12, wherein the alcoholic solvent used is selected from the group comprising of methanol, ethanol, propanol, isopropanol, n-butanol, 2-butanol, t-butanol or mixture thereof.

14. The process according to claim 13, wherein the preferred alcoholic solvent is n-butanol.

15. The process according to claim 14, wherein the ether solvent used in step (b) is selected from C3-C8 ethers such as di-ethyl ether, di-isopropyl ether, methyl t-butyl ether and di n-butyl ether.

16. The process according to claim 15, wherein the preferred ether is methyl t-butyl ether.

17. The process according to claim 16, wherein the ester solvent used in step (b) is selected from esters of C1-C4 carboxylic acid such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate.

18. The process according to claim 17, wherein the preferred ester is n-butyl acetate.

19. The process according to claim 18, wherein reaction temperature in step (b) is -10 to 10°C.