Abstract: The invention relates to processes for the preparation of pure clopidogrel hydrochloride. More particularly, it relates to the preparation of clopidogrel hydrochloride having reduced methyl chloride content. The invention also relates to pharmaceutical compositions that include the pure clopidogrel hydrochloride.
PROCESSES FOR THE PREPARATION OF CLOPIDOGREL HYDROCHLORIDE

Field of the Invention

The invention relates to processes for the preparation of pure clopidogrel hydrochloride. More particularly, it relates to the preparation of clopidogrel hydrochloride having reduced methyl chloride content. The invention also relates to pharmaceutical compositions that include the pure clopidogrel hydrochloride.

Background of the Invention

Clopidogrel hydrochloride of Formula I is chemically, methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate hydrochloride.

Clopidogrel and its salts are used in the treatment of platelet aggregation inhibitory and anti-thrombotic effect.


French Patent FR 2,769,313 discloses an intermediate, (R)-2-benzenesulfonyloxy-2-(2-chlorophenyl) acetic acid methyl ester, and processes for its preparation. The ester is then converted to clopidogrel by substitution with tetrahydrothienopyridine.

U.S. Patent Nos. 4,847,265, 5,132,435, 6,215,005 and 6,258,961 disclose the processes of separating the (S)-enantiomer of clopidogrel.
Several processes have been reported for the preparation of clopidogrel or its salt and various polymorphic forms of clopidogrel for example, in U.S. Patent Nos. 6,080,875; 6,180,793 and 5,204,469; and European Patents EP 971,915; 981,529; 291,459; 465,358; 466,569 and 1,129,087; and International (PCT) Publication Nos. WO 2003051362; 2005016931; 2004072085; 2004026879; 2004020443; 2005026174; 2003051362; 2004013147; 2004074215; 2004081016; 2005003139 and 2005063708.

Summary of the Invention

In one general aspect there is provided pure clopidogrel hydrochloride having purity 99.9 % and more when measured by HPLC.

In another aspect there is provided a process for the preparation of pure clopidogrel hydrochloride having purity 99.5% or more. The process includes converting a salt of clopidogrel chiral auxiliary to clopidogrel base in one or more organic solvents; adding alcoholic hydrochloride; and isolating the pure clopidogrel hydrochloride.

The process may include further drying of the product obtained.

The process may produce the pure clopidogrel hydrochloride having a purity of 99.5% w/w or more when measured by HPLC. In particular, it may produce the pure clopidogrel hydrochloride having purity 99.9% w/w or more.

In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of pure clopidogrel hydrochloride having purity 99.9% or more; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In yet another aspect there is provided clopidogrel hydrochloride having methyl chloride content not more than 100 microgram/gm.
In yet another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of clopidogrel hydrochloride having less than 100 microgram/gm methyl chloride; and one or more pharmaceutically acceptable carriers, excipients or diluents.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

**Detailed Description of the Invention**

The inventors have developed a process for the preparation of pure clopidogrel hydrochloride, wherein the process includes the steps of:

a) converting clopidogrel chiral auxiliary salt to clopidogrel base in one or more organic solvents;

b) adding alcoholic hydrochloride; and

c) isolating the pure clopidogrel hydrochloride.

The clopidogrel chiral auxiliary salt may be treated in one or more water immiscible organic solvents with aqueous sodium bicarbonate solution. The solvent layer may be separated and concentrated. The residue so obtained may be dissolved in one or more of a suitable organic solvent and alcoholic hydrochloride may be added. The pure clopidogrel hydrochloride may be isolated from the reaction mass thereof.

The clopidogrel chiral auxiliary salt may be prepared by the processes known in the art. In particular, it may be prepared using the methods described in U.S. Patent No. 4,847,265.

The clopidogrel hydrochloride may be isolated from the solution by a technique which includes, for example, filtration, filtration under vacuum, evaporation, decantation, and centrifugation.

The term "chiral auxiliary" includes the non-limiting examples of salts of clopidogrel with chiral acids such as L-tartaric acid, D-tartaric acid, di-p-anisoyl-D-tartaric acid, D-tartaric acid momoparachloro anilide, dibenzoyl-D-tartaric acid Di-p-toluyl-D-
tartaric acid, Di-p-toluyl-L-tartaric acid, D-lactic acid, D-malic acid, lS-10-camphor sulfonic acid, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, D-mandelic acid, S(+)-l,l'-binaphthalene-2,2'-dihydrogen phosphate and mixtures thereof.

The term "water immiscible solvent" includes one or more of dichloromethane, trichloromethane, carbon tetrachloride, dichloroethane, toluene, ethyl acetate, and the like.

The term "alcoholic hydrochloride" includes methanolic hydrochloric acid, ethanolic hydrochloric acid, isopropanolic hydrochloric acid, and the like.

The clopidogrel base may be dissolved in a suitable organic solvent.

The term "suitable organic solvents" includes any solvent or solvent mixture in which clopidogrel base is soluble, including, for example, alcohols, ketones, esters, ethers and mixtures thereof.

A suitable alcohol includes one or more of methanol, ethanol and isopropanol.

Examples of ketones include acetone and methyl isobutyl ketone. Examples of esters include ethyl acetate and methyl acetate. Examples of ethers include 2-methoxyethanol, tetrahydrofuran and isopropyl ether.

The product obtained may be further or additionally dried. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or Fluid Bed Drier.

The resulting pure clopidogrel hydrochloride may be further converted into a finished dosage form.

The pure clopidogrel hydrochloride has a purity of 99.5% w/w or more. More particularly, the purity of clopidogrel hydrochloride is 99.9% w/w or more.
The inventors also have developed pharmaceutical compositions that contain the pure clopidogrel hydrochloride having purity 99.9% w/w or more, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

The inventors have also developed clopidogrel hydrochloride, wherein methyl chloride content is not more than 100 microgram/gm and are below the limits of methyl chloride recommended by the National Institute for Occupational Safety and Health (NIOSH). More particularly, the clopidogrel hydrochloride has methyl chloride content not more than 75 microgram/gm.

The exposure limit of methyl chloride recommended by the National Institute for Occupational Safety and Health (NIOSH) is 100 microgram/gm for each 8-hour work shift in a 40-hour workweek.

The inventors also have developed pharmaceutical compositions that include a therapeutically effective amount of clopidogrel hydrochloride having less than 100 microgram/gm methyl chloride; and one or more pharmaceutically acceptable earners, excipients or diluents.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Preparation of α-bromo-2-(2-chlorophenyl) acetic acid methyl ester

α-Bromo-2-chlorophenyl acetic acid (350.0 gm) was dissolved in methanol (1.18 Liter) and concentrated sulphuric acid (53.20 gm) was added. The reaction mixture was refluxed for 4 hours. After completion of the reaction, the reaction mixture was distilled out to get a syrupy mass. To the residual mass, water (560 ml) was added and the product was extracted into chloroform (560 ml). The chloroform layer was separated and was treated with 10% aqueous sodium bicarbonate solution (1.12 Litre). The chloroform extract was finally washed with water and chloroform was distilled out to get a syrupy mass of the titled compound. Yield: 352.0 gm, Purity: 95.85%.
Example 2: Preparation of clopidogrei camphor sulfonate salt

The methyl ester obtained in example 1 (352.0 gm) was dissolved in methanol (1.75 Litre) and sodium bicarbonate (264.65 gm) was added. To this reaction mixture, 4,5,6,7-tetrahydro thieno [3,2-c] pyridine hydrochloride (217.66 gm) was added and refluxed for 4 hours. After completion of the reaction, the methanol was distilled out to get a thick mass. To the thick mass so obtained, water (1.4 Litre) was added under stirring and it was extracted by chloroform (675 ml x 2). The chloroform was distilled out to get a thick residual mass. The thick residual mass was dissolved in acetone (1.125 Litre) at 35-40°C to get a clear solution and a solution of L(-)-camphor-10-sulphonic acid in acetone (170.69 gm dissolved in 635 ml of acetone) was added to it at 18-20°C temperature. The mixture was further stirred at 10-12°C for one hour followed by reflux for 4 hours. The mixture was cooled and the title compound was isolated.

Yield: 211.80 gm,
Specific rotation: +25.44°.

Example 3: Preparation of pure clopidogrei hydrochloride

The clopidogrei camphor sulphonate salt (21.0 gm) was dissolved in chloroform (650 ml) and treated with 10% aqueous sodium bicarbonate solution (1.16 Litre). The reaction mixture was stirred for two hours. The chloroform layer was distilled out to get a syrupy mass. The syrupy mass was dissolved in ethyl acetate (2.5 Litre) and the ethyl acetate was partially distilled out at atmospheric pressure (1050 ml). The reaction mixture was cooled to room temperature. To the residue so obtained, isopropanolic hydrochloric acid solution (26.0 % w/v, 58.65 ml) was added. The reaction mixture was stirred at room temperature for two hours and the pure clopidogrei hydrochloride was isolated.

Yield: 90.0 gm,
Purity by HPLC: 99.9%,
Methyl chloride: 74 microgram/gm.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.
Claims:

1. A process for the preparation of pure clopidogrel hydrochloride having a purity of 99.5% or more by HPLC, the process comprising:
   a) converting a salt of clopidogrel chiral auxiliary to clopidogrel base in one or more organic solvents;
   b) adding alcoholic hydrochloride; and
   c) isolating the pure clopidogrel hydrochloride.

2. The process of claim 1, wherein the clopidogrel chiral auxiliary salt comprises one or more salts of clopidogrel with chiral acids.

3. The process of claim 2, wherein the chiral acid comprises one or more of L-tartaric acid, D-tartaric acid, di-p-anisoyl-D-tartaric acid, D-tartaric acid momoparachloro anilide, dibenzoyl-D-tartaric acid monomethyl amide, Di-p-toluyl-D-tartaric acid, Di-p-toluyl-L-tartaric acid, D-lactic acid, D-malic acid, IS-10-camphor sulfonic acid, S-hydratropic acid, (S)-2-methoxy phenyl acetic acid, (R)-2-methoxy-2-trifluoromethyl phenylacetic acid, D-mandelic acid, S(+)-l,l'-binaphthalene-2,2'-dihydrogen phosphate, and mixtures thereof.

4. The process of claim 1, wherein the organic solvent comprises one or more of a water immiscible solvent.

5. The process of claim 4, wherein the water immiscible solvent comprises one or more of dichloromethane, trichloromethane, carbon tetrachloride, dichloroethane, toluene, ethyl acetate, or mixtures thereof.

6. The process of claim 1 further comprising dissolving the clopidogrel base in a suitable organic solvent.

7. The process of claim 6, wherein the suitable organic solvents comprises one or more of alcohols, ketones, esters, ethers, or mixtures thereof.
8. The process of claim 7, wherein the alcohol comprises one or more of methanol, ethanol and isopropanol.

9. The process of claim 7, wherein the ketone comprises one or both of acetone and methyl isobutyl ketone.

10. The process of claim 7, wherein the ester comprises one or both of ethyl acetate and methyl acetate.

11. The process of claim 7, wherein the ether comprises one or more of 2-methoxyethanol, tetrahydrofuran and isopropyl ether.

12. The process of claim 1, wherein the alcoholic hydrochloride comprises one or more of methanolic hydrochloric acid, ethanolic hydrochloric acid, and isopropanolic hydrochloric acid.

13. The process of claim 1, wherein the isolating comprises one or more of filtration, filtration under vacuum, evaporation, decantation and centrifugation.

14. The process of claim 1, further comprising forming the product into a finished dosage form.

15. Pure clopidogrel hydrochloride having purity 99.9% or more by HPLC.

16. A pharmaceutical composition comprising a therapeutically effective amount of pure clopidogrel hydrochloride having a purity of 99.9% or more by HPLC; and one or more pharmaceutically acceptable carriers, excipients or diluents.

17. Clopidogrel hydrochloride having methyl chloride content not more than 100 microgram/gm.

18. The clopidogrel hydrochloride of claim 17, having the methyl chloride content not more than 75 microgram/gm.
19. A pharmaceutical composition comprising a therapeutically effective amount of clopidogrel hydrochloride having less than 100 microgram/gm methyl chloride; and one or more pharmaceutically acceptable carriers, excipients or diluents.

20. The pharmaceutical composition of claim 19 comprising a therapeutically effective amount of clopidogrel hydrochloride having less than 75 microgram/gm methyl chloride; and one or more pharmaceutically acceptable carriers, excipients or diluents.