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(54) **Title**: PRASUGREL HYDROCHLORIDE CRYSTALLINE PARTICLES

(57) **Abstract**: The present invention relates to prasugrel hydrochloride crystalline particles having mean particle size of more than about 10 μm, to the methods for the manufacture of said crystalline particles, and to pharmaceutical compositions comprising said crystalline particles.

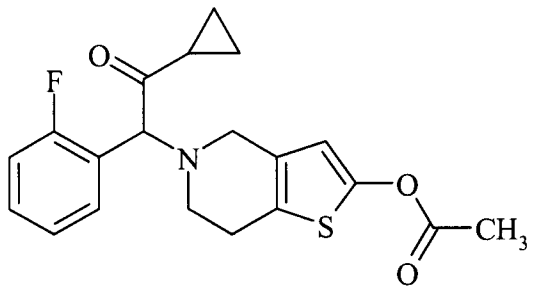
PRASUGREL HYDROCHLORIDE CRYSTALLINE PARTICLES

Filed of the Invention

The present invention relates to prasugrel hydrochloride crystalline particles having a mean particle size of more than about 10 μm, to the methods for the manufacture of said crystalline particles, and to pharmaceutical compositions comprising said crystalline particles.

Background of the Invention

Prasugrel hydrochloride is chemically, 2-acetoxy-5-(α-cyclopropylcarbonyl-2-flurobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride. Prasugrel hydrochloride is represented by the following structure:



.HCl

Prasugrel hydrochloride is a member of the thienopyridine class of ADP receptor inhibitors, like ticloidine and clopidogrel. These agents are believed to reduce the aggregation of platelets by irreversibly binding to P2Y12 receptors. Prasugrel hydrochloride is a novel platelet inhibitor that is expected to be administered as a solid oral dosage form. Prasugrel hydrochloride is undergoing the approval process for acute coronary syndromes planned for percutaneous coronary intervention (PCI).

Prasugrel and its pharmaceutically acceptable salts were disclosed in U.S. patent no. 5,288,726.

U.S. patent no. 6,693,115 disclosed crystal A, crystal B1 and crystal B2 of prasugrel hydrochloride.

PCT publication WO 2009/062044 disclosed crystalline forms C, D, E and amorphous form of prasugrel hydrochloride.

PCT publication WO 2010/070677 (WO'677) disclosed prasugrel hydrochloride having mean particle size of less than about 10 μm.

WO'677 described prasugrel having mean particle size of less than 90 μm, and crystalline forms G1 and G2 of prasugrel hydrochloride.

The prasugrel hydrochloride product prepared by the methods as described in the prior art has a very small particle size i.e., prasugrel hydrochloride crystalline particles with a mean particle size of less than about 10 μm resulting in similarly poor flow properties.

It is well recognized that preparation of tablets with a reproducible composition requires that all the dry ingredients have good flow properties. In cases, where the active ingredient has good flow properties, tablets can be prepared by direct compression of the ingredients. However, in many cases the particle size of the active substance is very small, the active substance is cohesive or has poor flow properties.

Thus, there is a need in the art for prasugrel hydrochloride with a desirable particle size distribution, which has good flow properties, and better dissolution and solubility properties.

Extensive laboratory and full-scale research has resulted in a new and inventive crystallization process for producing prasugrel hydrochloride crystalline particles having a mean particle size of more than about 10 μm. Said particles are useful for the manufacture of directly compressed tablets. Accurate dosing in capsules may also be with such particles.

Thus, an object of the present invention is to provide prasugrel hydrochloride and formulations containing prasugrel hydrochloride particles having a mean particle size of more than about 10 μm, and methods for manufacturing such particles.

Summary of the Invention

In one aspect, the present invention provides crystalline particles of prasugrel hydrochloride having a mean particle size of more than about 10 μm.

In another aspect, the present invention provides a process for the preparation of crystalline particles of prasugrel hydrochloride having a mean particle size of more than about 10 μm, which comprises:

a) providing a solution of prasugrel in an ester solvent;
b) adding hydrochloric acid to the solution obtained in step (a) at a temperature below 30^0C; and
c) isolating prasugrel hydrochloride crystalline particles having a mean particle size of more than about 10 μm.

Yet another aspect, the present invention provides a pharmaceutical composition comprising prasugrel hydrochloride crystalline particles having a mean particle size of more than about 10 μm and one or more pharmaceutically inert excipients.

Detailed description of the Invention

The term "room temperature" refers to temperature at about 20 to 30^0C.

According to one aspect of the present invention, there is provided crystalline particles of prasugrel hydrochloride having a mean particle size of more than about 10 μm.

Preferably, the crystalline particles of prasugrel hydrochloride having a mean particle size distribution (D_{50}) ranges from about 30 to 80 μm, and more preferably having mean particle size ranges from about 35 to 65 μm.

According to another aspect of the present invention, there is provided a process for the preparation of crystalline particles of prasugrel hydrochloride having a mean particle size of more than about 10 μm, which comprises:

a) providing a solution of prasugrel in an ester solvent;
b) adding hydrochloric acid to the solution obtained in step (a) at a temperature below 30^0C; and
c) isolating prasugrel hydrochloride crystalline particles having a mean particle size of more than about 10 μm.

The ester solvent used in step (a) may preferably be a solvent or mixture of solvents selected from ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate and ethyl formate, and more preferable the ester solvent is ethyl acetate.

Hydrochloric acid used in step (b) may be in the form of aqueous hydrochloric acid or in the form of hydrogen chloride gas or hydrogen chloride dissolved in an organic solvent. The organic solvent used for dissolving hydrogen chloride may preferably be

selected from the group consisting of ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate and ethyl formate. Preferably hydrogen chloride dissolved in ethyl acetate may be used.

The addition of hydrochloric acid in step (b) may preferably be carried out at about 20 to 30^0C.

Prasugrel hydrochloride crystalline particles may be isolated in step (c) by methods known such as filtration or centrifugation.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "μm" refers to "micrometer" which is $1x10^{-6}$ meter.

The term "crystalline particles" means any combination of single crystals, aggregates and agglomerates.

The term "Particle Size Distribution (P.S.D.)" means the cumulative volume size distribution of equivalent spherical diameters as determined by laser diffraction at 1 bar dispersive pressure in Sympatec Helos equipment. "Mean particle size distribution, i.e., D_{50}" correspondingly, means the median of said particle size distribution.

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising prasugrel hydrochloride crystalline particles having a mean particle size of more than about 10 μm and one or more pharmaceutically inert excipients.

Preferably, the crystalline particles of prasugrel hydrochloride having a mean particle size distribution (D_{50}) ranges from about 30 to 80 μm, and more preferably mean particle size ranges from about 35 to 65 μm.

Preferable pharmaceutical composition is a solid dosage form or an oral suspension.

The term "solid dosage form" as used herein includes conventional solid dosage forms such as tablet, capsule, granules, sachet, and the like.

Pharmaceutically inert excipients include all physiologically inert excipients used in the pharmaceutical art of dispensing. Examples include binders, diluents, surfactants, disintegrants, lubricants/glidants, coloring agents, and the like.

Specific examples of binders include methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Specific examples of diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like and mixtures thereof.

Surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical dosage forms. These include polyethoxylated fatty acids and its derivatives, for example, polyethylene glycol 400 distearate, polyethylene glycol-20 dioleate, polyethylene glycol 4 – 150 mono dilaurate, and polyethylene glycol – 20 glyceryl stearate; alcohol – oil transesterification products, for example, polyethylene glycol – 6 corn oil; polyglycerized fatty acids, for example, polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example, propylene glycol monocaprylate; mono and diglycerides, for example, glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example, polyethylene glycol – 20 sorbitan monooleate and sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example, polyethylene glycol – 20 cetyl ether and polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example, sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"; ionic surfactants, for example, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine; and the like and mixtures thereof.

Specific examples of disintegrants include low-substituted hydroxypropylcellulose (L-HPC), sodium starch glycollate, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, croscarmellose sodium A-type (Ac-di-sol), starch, crystalline cellulose, hydroxypropyl starch, pregelatinized starch, and the like and mixtures thereof.

Specific examples of lubricants/glidants include colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like and mixtures thereof.

Coloring agents include any FDA approved colors for oral use.

Prasugrel used in the present invention can be prepared by the known process, for example, by

a) reacting the cyclopropyl 2-fluorobenzyl ketone with n-bromosuccinate in a chlorinated solvent to obtain cyclopropyl-2-fluorobenzyl carbonyl bromide;

b) condensing the cyclopropyl-2-fluorobenzyl carbonyl bromide obtained in step (a) with 5,6,7,7a-hexahydrothieno[3,2-c]pyrdin-2(4H)-one hydrochloride in the presence of potassium carbonate and nitrile solvent to obtain a residual mass of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine;

c) reacting the residual mass obtained in step (b) with hydrobromic acid in a ketonic solvent to obtain 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine hydrobromide; and

d) reacting the 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine hydrobromide obtained in step (c) with acetic anhydride in an organic solvent to obtain prasugrel.

The chlorinated solvent used in step (a) may preferably be a solvent or mixture of solvents selected from methylene chloride, chloroform, carbon tetrachloride and ethylene dichloride, and more preferable the chlorinated solvent is ethylene dichloride.

The nitrile solvent used in step (b) may preferably be a solvent or mixture of solvents selected from acetonitrile, propionitrile, butyronitrile and benzonitrile, and more preferable the nitrile solvent is acetonitrile.

Preferably, the ketonic solvent used in step (c) may be a solvent or mixture of solvents selected from acetone, methyl ethyl ketone, methyl isobutyl ketone and diethyl ketone, and more preferable the ketonic solvent is acetone.

The organic solvent used in step (d) may preferably be a solvent or mixture of solvents selected from methylene chloride, chloroform, carbon tetrachloride and ethylene

dichloride, triethylamine and trimethylamine, and more preferable the organic solvents are methylene chloride and triethylamine.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitation on the scope or spirit of the invention.

Examples

Example 1:

Preparation of prasugrel

Step –I: cyclopropyl-2-fluorobenzyl carbonyl bromide

Cyclopropyl 2-fluorobenzyl ketone (50 gm), ethylene dichloride (500 ml), n-bromosuccinate (80 gm) and benzoyl peroxide (1 gm) were added at room temperature. The contents were heated to reflux and maintained for 7 hours at reflux. The reaction mass was cooled to 0^0C and filtered. The solvent was distilled off under vacuum at below 45^0C to obtain residual mass. The residual mass was dissolved in carbon tetrachloride (200 ml) at room temperature and stirred for 30 minutes. The separated solid was filtered and concentrated to obtain 65 gm of cyclopropyl-2-fluorobenzyl carbonyl bromide.

Step –II: Process for preparation of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine hydrobromide

Acetonitrile (1000 ml) was added to 5,6,7,7a-hexahydrothieno[3,2-c]pyrdin-2(4H)-one hydrochloride (90 gm) and then potassium carbonate (187 gm). The contents were stirred for 30 minutes and then cooled to 10^0C. Cyclopropyl-2-fluorobenzyl carbonyl bromide (100 gm) was added to the reaction mass at 10 to 15^0C and maintained for 2 hours 30 minutes at 15^0C. The reaction mass was passed through hi-flo bed and acetonitrile was distilled off under vacuum at below 45^0C to obtain residual mass. The residual mass was dissolved in ethyl acetate (1000 ml) and water (1000 ml). The separated organic layer was dried with sodium sulfate and concentrated at below 45^0C to obtain residual mass. The residual mass was dissolved in methanol (500 ml) and then cooled to 0^0C. The reaction mass was maintained for 20 minutes at 0^0C and then added carbon (10 gm). The reaction mass was passed through hi-flow bed and the solvents was

distilled off under vacuum at below 45^0C to obtain residual mass. The residual mass was dissolved in acetone (360 ml) at room temperature and then cooled to 0^0C. To the reaction mass was added aqueous hydrobromic acid (70 ml) at 0^0C and maintained for 30 minutes at 0^0C. The temperature of the reaction mass was raised to room temperature and stirred for 2 hours 30 minutes at room temperature, filtered. The solid obtained was dried to obtain 60 gm of 5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine hydrobromide.

Step-III: prasugrel

5-(α-Cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno-[3,2-c]pyridine hydrobromide (60 gm) was dissolved in methylene chloride (524 ml) and then added triethylamine (60 gm) at room temperature. The solution was cooled to 0^0C and then added acetic anhydride (60 gm) for 1 hour 30 minutes at 0^0C. The reaction mass was maintained for 2 hours at 0^0C and then added water (500 ml). The temperature of the reaction mass was raised to room temperature and then the layers were separated. The methylene chloride layer was dried with sodium sulfate and concentrated at below 45^0C to obtain residual mass. The residual mass was dissolved in methanol (240 ml) and stirred for 2 hour 30 minutes at room temperature. The separated solid was filtered and dried to obtain 38.5 gm of prasugrel.

Example 2:

Preparation of prasugrel hydrochloride

Prasugrel (2 gm) as obtained in example 1 was dissolved in ethyl acetate (20 ml) and then added hydrochloric acid in ethyl acetate (2.9 ml) at room temperature. The reaction mass was maintained for 4 hours at room temperature and filtered. The solid obtained was dried to obtain 2 gm of prasugrel hydrochloride [High performance liquid chromatography (HPLC) Purity: 99.95%; 10 volume-% of the particles (D_{10}): 2.92 μm, Mean particle size (D_{50}): 53.37 μm and 90 volume-% of the particles (D_{90}): 104.61 μm].

Example 3:

Preparation of prasugrel hydrochloride

Prasugrel (50 gm) was dissolved in ethyl acetate (500 ml) and then added hydrochloric acid in ethyl acetate (72 ml) at room temperature. The reaction mass was maintained for 4 hours at room temperature and filtered. The solid obtained was dried to obtain 49.5 gm of prasugrel hydrochloride (HPLC Purity: 99.62%; D_{10}: 2.99 μm, D_{50}: 53.54 μm and D_{90}: 103.70 μm).

Example 4:

Preparation of prasugrel hydrochloride

Prasugrel (10 gm) was dissolved in ethyl acetate (100 ml) and then added hydrochloric acid in ethyl acetate (14 ml) at room temperature. The reaction mass was maintained for 4 hours at room temperature and filtered. The solid obtained was dried to obtain 9.6 gm of prasugrel hydrochloride (HPLC Purity: 99.66%; D_{10}: 3.02 μm, D_{50}: 52.55 μm and D_{90}: 104.99 μm).

We claim:

1. Crystalline particles of prasugrel hydrochloride having a mean particle size of more than about 10 μm.
2. The crystalline particles of prasugrel hydrochloride as claimed in claim 1, wherein the mean particle size ranges from about 30 μm to 80 μm.
3. The mean particle size as claimed in claim 2, wherein the ranges from about 35 μm to 60 μm.
4. A process for preparation of prasugrel hydrochloride crystalline particles as claimed in claim 1, which comprises:
   a. providing a solution of prasugrel in an ester solvent;
   b. adding hydrochloric acid to the solution obtained in step (a) at a temperature below 30^0C; and
   c. isolating prasugrel hydrochloride crystalline particles having a mean particle size of more than about 10 μm.
5. The process as claimed in claim 4, wherein the ester solvent used in step (a) is a solvent or mixture of solvents selected from ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate and ethyl formate.
6. The process according to claim 5, wherein the ester solvent is ethyl acetate.
7. The process as claimed in claim 4, wherein the hydrochloric acid used in step (b) is in the form aqueous hydrochloric acid or in the form of hydrogen chloride gas or hydrogen chloride dissolved in an organic solvent.
8. The process as claimed in claim 7, wherein the organic solvent is selected from the group consisting of ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate and ethyl formate.
9. The process as claimed in claim 8, wherein the organic solvent is ethyl acetate.
10. The process as claimed in claim 4, wherein the addition of hydrochloric acid in step (b) is carried out at about 20 to 30^0C.
11. A pharmaceutical composition comprising prasugrel hydrochloride crystalline particles having a mean particle size of more than about 10 μm and one or more pharmaceutically inert excipients.

12. The crystalline particles of prasugrel hydrochloride as claimed in claim 11, wherein the mean particle size ranges from about 30 μm to 80 μm.
13. The mean particle size as claimed in claim 12, wherein the ranges from about 35 μm to 60 μm.
14. The pharmaceutical composition as claimed in claim 11, wherein the pharmaceutical composition is selected from a solid dosage form and an oral suspension.
15. The pharmaceutical composition as claimed in claim 14, wherein the solid dosage forms are tablet, capsule, granules and sachet.