Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

Int.Cl.: C07D495/04 (2006.01) A61K31/4365 (2006.01) A61P7/02 (2006.01)

Oversættelsen bekendtgjort den: 2015-01-19

Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: 2014-10-29

Europæisk ansøgning nr.: 06124851.4

Europæisk indleveringsdag: 2004-09-09

Den europæiske ansøgnings publiceringsdag: 2007-04-11

Prioritet: 2003-09-11 GB 0321256

Stamansøgningsnr.: 04768414.7

Designereede stater: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR

Patenthaver: Generics (UK) Limited, Albany Gate, Darkes Lane, Potters Bar, Hertfordshire EN6 1AG, Storbritannien

Opfinder: Arul, Ramakrishnan, Merck Dev. Ctr. Private Ltd, Plot 1A/2, MIDC Taloja, District Raigad, 410 208, Maharashtra, Indien
Rawat, Ajay Singh, Merck Dev. Ctr. Private Ltd, Plot 1A/2, MIDC Taloja, District Raigad, 410 208, Maharashtra, Indien
Rao, Rajesh, Merck Dev. Ctr. Private Ltd, Plot 1A/2, MIDC Taloja, Dist. Raigad, 410 208, Maharashtra, Indien
Pise, Abhinay, Merck Dev. Ctr. Private Ltd, Plot 1A/2, MIDC Taloja, District Raigad, 410 208, Maharashtra, Indien
Gray, Jason, Generics [UK] Limited, Albany Gate, Darkes Lanes, Potters Bar, Hertfordshire EN6 1AG, Storbritannien
Gadakar, Maheshkumar, Merck Dev.Ctr. Private Ltd, Plot 1A/2, MIDC Taloja, Dist Raigad, 410 208, Maharashtra, Indien

Fuldmægtig i Danmark: PATRADE A/S, Fredens Torv 3A, 8000 Århus C, Danmark

Benævnelse: Nye krassilinske polymorfer af clopidogrel

Fremdragne publikationer:
WO-A-03/066637
US-B1-6 180 793
US-B1-6 429 210
Background art

[0001] The present invention relates to a novel crystalline form of the platelet aggregation inhibitor (+)-(S)-methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate, clopidogrel (1), in the form a of hydrogen bromide salt. The present invention further relates to a process for preparing such a form, a pharmaceutical composition comprising such a form, and a use for such a form and composition.

[0002] The pharmaceutical compositions may be used, in particular, for inhibiting platelet aggregation or for treating, preventing or managing thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, or unstable angina.

Technical field

[0003] The manufacturing process for many pharmaceuticals is hindered by the fact that the organic compound, which is the active drug substance, has handling difficulties during the manufacturing process and undesirable properties being imparted to the final drug or dosage form. In addition it can be difficult to control the polymorphic form of the active drug substance throughout the manufacturing process.


[0005] The hydrogen bromide salt of clopidogrel has been reported in EP 0 281 459. However, dopidogrel is currently marketed as the hydrogen sulfate salt and polymorphic forms of this hydrogen sulfate salt have been reported in WO 99/65915.

Summary of the invention

[0006] It is an object of the present invention to provide clopidogrel in a solid crystalline form that affords the compound improved handling properties and/or
improved properties as a pharmaceutical agent and enables control of the polymorphic form during manufacturing.

[0007] Accordingly, a first aspect of the present invention provides clopidogrel hydrogen bromide in polymorph form 3 (anhydrate), having a DSC trace substantially as shown in Figure 1, and an XRPD spectrum substantially as shown in Figure 2 and TGA data substantially as shown in Figure 3.

[0008] Preferably the clopidogrel hydrogen bromide in polymorph form 3 is in particulate form. Preferably the clopidogrel hydrogen bromide in polymorph form 3 is substantially pure.

[0009] In the context of the present application, the term "substantially pure" clopidogrel hydrogen bromide in polymorph form 3 means that the clopidogrel hydrogen bromide in polymorph form 3 comprises less than 20% of other crystalline or amorphous forms of clopidogrel hydrogen bromide, preferably less than 15%, more preferably less than 10%, more preferably less than 5%, more preferably less than 2%, more preferably less than 1%, and even more preferably less than 0.5%. The term "substantially pure" also means that the clopidogrel hydrogen bromide in polymorph form 3 comprises less than 3% of other impurities, preferably less than 2%, more preferably less than 1%, and even more preferably less than 0.5%.

[0010] Preferably the clopidogrel hydrogen bromide in polymorph form 3 is for use as a medicament. Preferably the medicament is for inhibiting platelet aggregation or for treating, preventing or managing thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, or unstable angina.

[0011] A second aspect of the invention provides a process for the preparation of the clopidogrel hydrogen bromide of the first aspect of the invention.

[0012] The compound of the invention is preferably preparable or prepared by a process comprising crystallisation from a solution in an organic solvent or solvents. Said process, in an embodiment, also comprises the step of drying the precipitate to provide a crystalline form in accordance with the first aspect of the invention. The compound can be dried under conventional vacuum drying conditions, for example, under a vacuum of down to 50, 40, 35, 30, 25 or 20 mmHg,
preferably 30 mmHg, and at a temperature of up to 20, 25, 30, 35, 40, 45, 50, 55 or 60°C, preferably 45°C. Preferably the organic solvent is polar, miscible with water, dipolar, and/or aprotic. Optionally the organic solvent comprises a plurality or mixture of solvent compounds. The organic solvent may be 2-propanol, diisopropyl ether, t-butylmethyl ether, dichloromethane, methanol, and/or ethanol.

[0013] Clopidogrel hydrogen bromide in polymorph form 3 is preferably prepared by recrystallisation from a mixture of methanol or ethanol with water, preferably in an alcohol: water ratio of from 5:95 to 20:80, preferably about 10:90. Preferably the recrystallisation is carried out at 2-10°C for 8-20 hours; more preferably the recrystallisation is carried out at 3-8°C for 10-15 hours.

[0014] A compound in accordance with the first aspect of the invention can be used to advantage in the preparation of pharmaceutical dosage or drug forms. Accordingly, in a further aspect, the present invention provides a method of preparing a pharmaceutical dosage form that utilises a compound in accordance with the first aspect of the invention.

[0015] The present invention also provides a pharmaceutical composition prepared or preparable by such a method. The pharmaceutical composition of the present invention may be for immediate, sustained or delayed release. The composition is preferably solid and comprises a compound in accordance with the first aspect of the invention, in addition to one or more conventional pharmaceutically acceptable carrier(s), excipient(s) or diluent(s). Preferred pharmaceutical compositions in accordance with the invention include tablets, capsules and the like.

[0016] The pharmaceutical composition of the present invention can be administered by oral, parental (including intravenous, subcutaneous, intramuscular, intradermal, intratracheal, intraperitoneal, intraarticular, intracranial and epidural), transdermal, airway (aerosol), rectal, vaginal or topical (including buccal, mucosal and sublingual) administration. Preferably the composition is for oral administration.

[0017] For oral administration, the pharmaceutical composition of the invention will generally be provided in the form of tablets, capsules, hard or soft gelatine capsules, caplets, troches or lozenges, as a powder or granules, or as an aqueous solution, suspension or dispersion. Solutions, suspensions and dispersions may be
prepared from powder or granules of clopidogrel hydrogen bromide in polymorph form 3. Preferably the composition is in the form of tablets or capsules.

[0018] Tablets for oral use may include clopidogrel hydrogen bromide in polymorph form 3 mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable excipients are mannitol, macrogol, microcrystalline cellulose, hydrogenated castor oil, and low substituted hydroxypropylcellulose. Tablets can be prepared by conventional techniques, including direct compression, wet granulation and dry granulation. If desired, the tablets may be coated with materials such as hypromellose, lactose, triacetin, and/or carnauba wax.

[0019] Capsules for oral use include hard gelatine capsules in which clopidogrel hydrogen bromide in polymorph form 3 is mixed with a solid diluent, and soft gelatine capsules wherein clopidogrel hydrogen bromide in polymorph form 3 is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

[0020] Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

[0021] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0022] For parenteral use, the compound of the present invention will generally be provided in a sterile aqueous solution or suspension, buffered to an appropriate pH and isotonicity. Such solutions and suspensions may be prepared from powder or granules of clopidogrel hydrogen bromide in polymorph form 3. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride or glucose. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate. The compound of the invention may also be presented as liposome formulations.

[0023] For topical and transdermal administration, the compound of the inven-
ion will generally be provided in the form of ointments, cataplasms (poultices), pastes, powders, dressings, creams, plasters or patches.

[0024] Suitable suspensions and solutions can be used in inhalers for airway (aerosol) administration. Such suspensions and solutions may be prepared from powder or granules of clopidogrel hydrogen bromide in polymorph form 3.

[0025] Preferably the pharmaceutical composition is in unit dosage form comprising clopidogrel hydrogen bromide in polymorph form 3 in an amount of from 1mg to 300mg with respect to the free base, preferably in an amount of from 5mg to 200mg, more preferably in an amount of from 10mg to 125mg, and more preferably in an amount of from 50mg to 100mg.

[0026] The clopidogrel hydrogen bromide of the present invention is effective over a wide dosage range, the actual dose administered being dependent on the condition being treated. For example, in the treatment of adult humans, dosages from 1mg to 300mg, preferably from 10mg to 125mg, more preferably from 50mg to 100mg with respect to the free base per day may be used. The desired dose is normally presented once a day, but may be dosed as two, three, four or more sub-doses administered at appropriate intervals throughout the day.

[0027] Preferably the pharmaceutical composition of the present invention is for inhibiting platelet aggregation or for treating, preventing or managing thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, or unstable angina.

[0028] In a further aspect of the invention, there is provided the use of a compound in accordance with the first aspect of the invention for the manufacture of a medicament for the inhibition of platelet aggregation and consequently the treatment, prevention and/or management of such diseases as thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease or unstable angina.

[0029] The compound in accordance with the first aspect of the invention may also be useful as precursor to other novel or known polymorphic forms of clopidogrel that may be useful in the preparation of pharmaceutical products. Al-
ternatively, the compound in accordance with the first aspect of the invention may be used to prepare other desired polymorphic forms of clopidogrel hydrogen sulfate in a more controllable manner. The present invention therefore provides a process for preparing a polymorphic form of clopidogrel hydrogen sulfate, comprising the step of using clopidogrel hydrogen bromide in polymorph form 3.

[0030] The present invention is illustrated, but in no way limited, by the following examples and figures.

**Brief description of the figures**

[0031]
Figure 1 is a DSC trace of polymorph form 3 clopidogrel hydrogen bromide.
Figure 2 is an XRPD spectrum of polymorph form 3 clopidogrel hydrogen bromide.
Figure 3 shows TGA data for polymorph form 3 clopidogrel hydrogen bromide.

**Detailed description of the invention/ Examples**

(±)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl) acetonitrile

[0032] To a mixture of methanol (2.501) and water (250ml) was charged 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (500g; 2.85mol) with stirring. After stirring for 10 minutes, sodium cyanide (153.0g; 3.12mol) was added and stirred further for 40 minutes. 2-Chlorobenzaldehyde (392.1g; 2.79mol) was added slowly to this reaction mixture between 23-28°C over a period of 1.5 hours. After the addition was over, the flask was heated in an oil bath between 40-50°C and maintained at this temperature for 4.5 hours. After cooling the reaction mixture to 25-30°C, 5% sodium metabisulfite solution (250ml) was added and stirred for 1 hour at this temperature range. To the resulting slurry, water (7.51) was added and stirred for 1 hour at 25-30°C. The off-white solid thus formed was filtered, washed with a 1:1 mixture of methanol: water (2.51) and the wet cake was dried at 75°C under vacuum (pressure: -0.8kg/cm²) for 10 hours to obtain the product as an off-white solid. Yield: 719.0g (87.4%). mp: 124-126.5°C. The product was identified by IR spectrum, 'H and 13C NMR investigation.

(±)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl) acetamide

[0033] (±)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-
yl)acetonitrile (713g; 2.46mol) was added to methanol (3.5051) at 23-28°C with stirring. To this slurry, potassium carbonate (170g; 1.23mol) was added followed by dimethyl sulfoxide (263ml; 3.7mol). The contents were heated between 30-40°C and 30.0% aqueous hydrogen peroxide solution (382ml; 3.70mol) was added between 40-50°C slowly over a period of 3 hours. After the addition was over, the reaction mixture was maintained at this temperature for a further 2 hours, after which the reaction was brought to 20-30°C. 35% Hydrochloric acid (213.0ml) in water (10.71) was added slowly to the reaction mixture over a period of 1 hour 15 minutes. After stirring for 1 hour, the solid formed was filtered and washed with a 1:1 methanol: water mixture (3.5651). The isolated solid was dried in a vacuum oven at 75-80°C for a period of 12 hours. Yield: 716g (94.72%). mp: 124-126°C. The product was identified by IR spectrum, ¹H and ¹³C NMR investigation.

(+)-(1S)-Camphor-10-sulfonic acid salt of (S)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide

[0034]

(a) To a stirred slurry of (±)-2-(2-chlorophenyl)-6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (710g; 2.315mol) in acetone (3.561) and methanol (0.3551) maintained at 23-28°C was added a solution of (+)-(1S)-camphor-10-sulfonic acid (270g; 1.16mol) dissolved in acetone (1.441) over a period of 1 hour. After stirring for another hour, formic acid (98-100%; 53.8g; 1.16mol) was added all at once and stirred for 1 hour, after which the reaction mixture was cooled to 0-10°C and kept at this temperature for another 1 hour 30 minutes. The solid thus formed was filtered and washed with acetone (1.441) and dried in a vacuum oven between 60-65°C for a period of 6 hours. Yield: 470.0g (38% by theory, based on the enantiomer content). mp: 194-208°C. [α]D25: +41.5 (c=1.0g/100ml; methanol).

(b) Isolation of (±)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thienop,2-c]pyrid-5-yl)acetamide from the mother liquor obtained in step (a) To the mother liquor obtained in step (a), 20% aqueous solution of sodium hydroxide (710ml) was added at 26-27°C with stirring. The reaction mixture was heated to 45-50°C and maintained at that temperature for 5 hours. The reaction mixture was concentrated to 1/10 of its volume under vacuum. The resulting slurry was cooled to 30°C and methanol (710ml) was added followed by water (4.91) slowly to the reaction mixture over a period of 30 minutes. The pH of the reaction mass was adjusted to 7-7.5 by the addition of 15% hydrochloric acid solution (1.21). After stirring for an hour, the solid formed was filtered and
washed with water (3.51). The isolated solid was dried in a vacuum oven (pressure: -0.8kg/cm²) between 75-80°C for a period of 14 hours. Yield: 393g. mp: 128-134°C.

(c) (+)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide obtained in step (b) was converted to (+)-(1S)-camphor-10-sulfonic acid salt of (S)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide by following the procedure mentioned in step (a). Yield: 240.0g (36% by theory, based on the enantiomer content). mp: 202-210°C. [α]_D^{25}: +47.5 (c=1.0g/100ml; methanol).

(d) The (+)-(1S)-camphor-10-sulfonic acid salt of (S)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (700g; 1.298mol) obtained was charged into methanol (1.751) with stirring at 23-28°C. The contents were heated to 60°C and the temperature was maintained at this temperature for 2 hours. To this clear solution, acetone (7.01) was added and the temperature was maintained at this temperature for 1 hour. The reaction mixture was cooled between 0-5°C and stirred for another 1 hour and 30 minutes. The solid thus precipitated was filtered, washed with acetone (1.41) and dried between 60-65°C under vacuum (-0.8kg/cm²) for 7 hours. Yield: 545.0g (77.85% by theory). mp: 210-218°C. [α]_D^{25}: +51.69 (c=1.0g/100ml; methanol).

(+)-(S)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide

[0035] The crystallized (+)-(1S)-camphor-10-sulfonic acid salt of (S)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (521.0g; 0.966mol) was charged into methanol (2.6051) with stirring at 23-28°C followed by water (1.0421). To this clear solution, activated carbon (10.42g) was added and the contents were stirred for 1.5 hours at this temperature. The activated carbon was filtered off by passing the contents of the flask through a bed of celite on a Buchner funnel and the residue in the funnel was washed with a water/methanol mixture (3:7; 0.5211). To the combined filtrate, 2% (w/v) aqueous sodium bicarbonate solution (4.1681) was added over a period of 30 minutes and stirred for 1 hour and 30 minutes. The solid precipitated was filtered, washed with methanol: water (2.0841; 1:1 v/v) and dried under vacuum (-0.8kg/cm²) for a period of 8 hours between 70-75°C. Yield: 284.0g (95.8% by theory). mp: 154-156°C. [α]_D^{25}: +39.5 (c=1.0g/100ml; methanol). The product was identified by IR spectrum, ^1H and ^13C NMR investigation.
(+)-(S)-Methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (clopidogrel)

[0036] Concentrated sulfuric acid (~98%; 496ml; 9.30mol) was charged into methanol (1.751) with stirring between 25-38°C followed by dimethyl sulfate (250ml; 2.636mol). The contents were heated to reflux for 3 hours, after which the reaction mixture was cooled to 40-50°C and (+)-(S)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (500g; 1.55mol) was charged. The reaction mixture was heated to 65°C and maintained between 65-66°C for a period of 60 hours. The reaction mixture was cooled to 25-30°C and poured into water (10.01) with stirring. Dichloromethane (5.01) was added, stirred for 1 hour, after which the organic layer was separated. To the aqueous layer dichloromethane (2.51) was added and stirred for 1 hour and the separated organic layer was combined with the earlier separated layer and washed with water (2.51). 5% (w/v) aqueous sodium bicarbonate solution (2.51) was added to this organic layer and stirred for a period of an hour and the separated organic layer was washed with 0.25% sulfuric acid (2.51) followed by water (2.51) and treated with activated carbon (40.0g) for a period of 3 hours with stirring. The activated carbon was removed by filtration through a celite bed and the celite bed was washed with dichloromethane (1.01). This washing was coupled with the filtrate and the solvent removed under vacuum to yield (+)-(S)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetic acid methyl ester as a pale yellow oil. Yield: 380g (73.0% by theory). The product was identified by IR spectrum, 1H and 13C NMR investigation.

(+)-(S)-Methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (clopidogrel) hydrogen bromide polymorph form 3

[0037] Clopidogrel hydrogen bromide polymorph form 3 was prepared by dissolving clopidogrel hydrogen bromide polymorph form 1 (5g) in 5ml of either methanol or ethanol. Once dissolved at room temperature (~22°C), water (40ml) was added to the solution and stirred. The initial precipitate formed was a sticky solid. This solid was filtered off and the remaining solution stored in a refrigerator overnight. The white crystals formed in this chilled solution were then filtered using a Buchner filter funnel and dried at 50°C for one hour.

[0038] The crystals were then characterised using DSC, TGA and XRPD (See Figures 1, 2 and 3).
Patentkrav

1. Fremgangsmåde til fremstilling af clopidogrelbrintbromidanhydrat, omfattende det trin at rekrystallisere clopidogrelbrintbromid af en blanding af metanol eller etanol med vand.


3. Fremgangsmåde ifølge krav 2, hvori blandingen af metanol eller etanol med vand har et alkohol:vand forhold på ca. 10:90.

4. Fremgangsmåde ifølge ethvert af de foregående krav, hvori rekrystalliseringen udføres ved 2-10°C i 8-20 timer.

5. Fremgangsmåde ifølge krav 4, hvori rekrystalliseringen udføres ved 3-8°C i 10-15 timer.

6. Fremgangsmåde ifølge ethvert af de foregående krav, yderligere omfattende det trin at tørre præcipitatet.


8. Clopidogrelbrintbromidanhydrat ifølge krav 7, hvori clopidogrelbrintbromidanhydratet omfatter mindre end 20% andre krøllinske eller amorfe former af clopidogrelbrintbromid, og/eller hvor clopidogrelbrintbromidanhydratet omfatter mindre end 3% andre urenheder.

9. Clopidogrelbrintbromidanhydrat ifølge krav 7 eller 8 til anvendelse som et medikament.

10. Farmaceutisk sammensætning, omfattende clopidogrelbrintbromidanhydrat ifølge ethvert af krav 7 til 9, valgfrit yderligere omfattende en farmaceutisk acceptabel bærer, hjælpestof eller forytnder.

11. Farmaceutisk sammensætning ifølge krav 10, hvori sammensætningen er til oral indgivelse.


14. Farmaceutisk sammensætning ifølge ethvert af krav 10 til 13, hvori sammensætningen er i enhedsdoseringsform omfattende clopidogrelbrintromidanhidrat i en mængde fra 10 mg til 125 mg med hensyn til den fri base.

15. Anvendelse af clopidogrelbrintromidanhidrat ifølge ethvert af krav 7 til 9 til fremstilling af et medicament til hæmning af blodpladeansamling eller til behandling, forebyggelse eller administration af trombose, aterotrombose, en aterotrombotisk begivenhed, iskæmisk slagtifælde, myokardieinfarkt, non-Q-bølge myokardieinfarkt, aterosklrose, perifer arteriesygdom eller ustabil angina.


17. Anvendelse af clopidogrelbrintromidanhidrat ifølge krav 7 eller 8 som forstadie til andre polymorfe former af clopidogrel.
Figure 1

Figure 2