



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

SOLICITUD
PUBLICADA

Número del expediente: 06-106511
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Apoderado: EMILIO FERRERO
Título de la nueva creación o denominación del signo: "SAL DE CLOPIDOGREL Y SUS FORMAS POLIMOREAS"
Gaceta: 583

③ OPOSICIÓN PRESENTADA POR:

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Número 51'975.664 TP 83823

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Signo opositor: No cumple con los requisitos de patentabilidad.

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

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WO 03/051362

RRT	0.11	0.12	0.14	0.15	0.16	0.55	0.77-0.79	1.00	1.15	1.24	2.25
						AMINO-PREC.		CLD			
FORM IV*								100.0			
FORM VI	0.08	0.12			0.61		0.09	98.6	0.14		0.33
FORM III*		0.23	0.06	0.08	0.72		0.10	98.5	0.28		
FORM V*					0.22			99.4	0.15	0.21**	

NOTE: ONLY PEAKS WITH AREA>0.044% ARE INCLUDED IN THIS TABLE

*SAMPLES AFTER ADDITIONAL DRYING, 24TH AT 60 CELSIUS & 24 H AT 70 CELSIUS.

**PEAK FROM PREVIOUS INJECTION

ALL THE SAMPLES WILL BE INJECTED AGAIN, FOR 120 MINUTES

THE SAMPLE FOR FORM III CORRESPONDS TO EXAMPLE 26, FORM IV TO EXAMPLE 31,
FORM V TO EXAMPLE 39 AND FORM VI TO EXAMPLE 44.

15/15

IMPURITY PROFILE FOR CLOPIDOGREL HYDROGENSULFATE

FIG. 15

PCT/US02/40679

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1 179
at
181

ANEXO 2

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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
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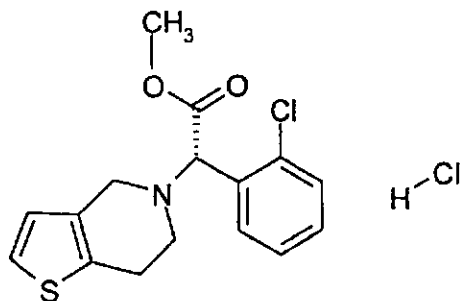
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: POLYMORPHS OF CLOPIDOGREL HYDROCHLORIDE AND THEIR USE AS ANTITHROMBIC COMPOUNDS



(II)

(57) Abstract: The invention relates to crystalline forms I and II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula (I) and hydrates thereof, a process for the preparation thereof and pharmaceutical compositions containing the same. The new polymorphs according to the invention exhibit blood platelet aggregation inhibiting and antithrombotic effect.

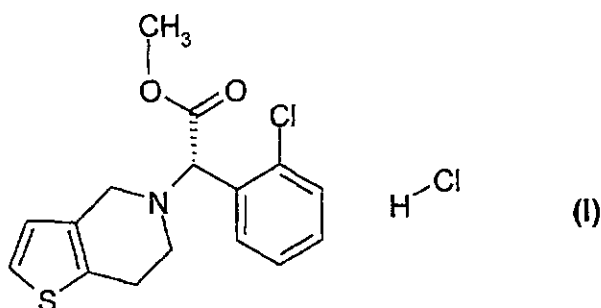
WO 03/066637 A1

POLYMORPHS OF CLOPIDOGREL HYDROCHLORIDE AND THEIR USE AS ANTITHROMBIC COMPOUNDS

FIELD OF THE INVENTION

This invention relates to new polymorphs of clopidogrel hydrochloride, a process for the preparation thereof, pharmaceutical compositions comprising said new polymorphs and the use of the new polymorphs for blood platelet aggregation inhibiting and antithrombotic treatment.

More particularly the invention is concerned with new crystalline forms I and II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula



and hydrates thereof, a process for the preparation of the new polymorphs, pharmaceutical compositions comprising said new

polymorphs and the use of the new polymorphs for blood platelet aggregation inhibiting and antithrombotic treatment.

TECHNICAL BACKGROUND

Methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrogen sulfate is a known blood platelet aggregation inhibitory and antithrombotic pharmaceutical active ingredient having the INN (International Non-Proprietary Name) clopidogrel hydrogen sulfate.

Clopidogrel hydrogen sulfate was first described in EP 281,459 corresponding to HU 197,909. Methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride was also first disclosed in this patent specification. According to said patent the hydrochloride salt is prepared by dissolving clopidogrel base in diethyl ether and precipitating the salt with diethyl ether containing hydrogen chloride. In the patent specification methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride is characterized by its melting point of 117°C and optical rotation of $[\alpha]_D^{20} = +62.23^\circ$ (c=1.82, methanol). The patent is, however, completely silent in disclosing the crystal form of the product and IR or X-ray

powder diffraction data characterizing the crystalline form are not described either.

According to HU 215,957 methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride is prepared in a similar way by dissolving clopidogrel base in diethyl ether and precipitating the salt with diethyl ether containing hydrogen chloride. In the patent the product is characterized by a protracted melting point interval of 130-140°C and an optical rotation of $[\alpha]_D^{20} = +63^\circ$ (c=1, methanol). There is no teaching of the crystal form of the product and IR or X-ray powder diffraction data characteristic of the product are not disclosed either.

According to WO 98/51681, WO 98/51682, WO 98/51689 and WO 2000/27840 methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride is prepared by dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate base in diethyl ether, introducing anhydrous gaseous hydrogen chloride into the solution and isolating the crystals formed by filtration. The hydrogen chloride salt is characterized by a melting point of 130-132°C and an optical rotation of $[\alpha]_D^{20} = +60^\circ$. There is no disclosure of the crystal form of the product, and the IR or X-

ray powder diffraction data characteristic of the product are not mentioned either.

Thus clopidogrel hydrochloride of uniform crystal form has not been described in prior art. On the other hand there is a strong need in pharmaceutical industry for active ingredients of uniform morphology. It is known that various polymorphs differ from each other significantly in their important properties (e.g. dissolution speed, bioavailability, chemical stability). Also from a technological point of view there is a strong need for morphologically uniform pharmaceutical active ingredients which can be produced in a reproducible manner on industrial scale too, because the working-up and processing properties of the various polymorphs (e.g. filtrability, drying, solubility, readiness to be compressed into tablets) differ from each other significantly.

SUMMARY OF THE INVENTION

It is the object of the present invention to provide clopidogrel hydrochloride polymers having uniform morphology meeting the above requirements which can be manufactured in a reproducible manner on industrial scale too.

The above object is solved by the new crystalline methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride polymorphs of the present invention.

The present invention is based on the surprising recognition that two new uniform crystalline forms of clopidogrel hydrochloride } can be prepared in a reproducible manner as described below. The melting point of the new polymorphs of the present invention is significantly different from that of the data disclosed in prior art.

According to the present invention there is provided new crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof characterized by the X-ray powder diffraction pattern expressed in Table 1 and Figure 1.

Table 1
Position of diffraction lines and relative intensities
(> 15 % of polymorph I)

Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]
1	9.64	9.1707	152	21.51	12	21.64	4.1075	107	15.16
2	11.22	7.8873	129	18.25	13	22.90	3.8841	476	67.21

Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]
3	12.98	6.8222	708	100	14	23.13	3.8455	469	66.30
4	13.89	6.3759	161	22.76	15	24.73	3.6006	245	34.67
5	15.05	5.8888	115	16.25	16	25.06	3.5540	302	42.62
6	16.82	5.2697	168	23.66	17	25.41	3.5059	471	66.49
7	17.16	5.1661	189	26.76	18	27.31	3.2655	111	15.73
8	17.65	5.0261	156	22.06	19	27.55	3.2372	179	25.25
9	19.58	4.5336	193	27.33	20	28.78	3.1021	143	20.16
10	19.88	4.4654	393	55.56	21	28.97	3.0822	123	17.39
11	20.57	4.3180	165	23.37	22	32.48	2.7570	190	26.77

According to the present invention there is also provided new crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof characterized by the X-ray powder diffraction pattern expressed in Table 2 and Figure 2.

Table 2
Position of diffraction lines and relative intensities
(> 15 % of polymorph I)

Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]
1	8.85	9.9923	88	15.83	19	22.25	3.9956	184	33.09
2	9.85	8.9800	535	96.22	20	22.58	3.9386	156	28.06
3	11.41	7.7575	358	64.39	21	22.85	3.8920	134	24.10
4	12.97	6.8260	101	18.17	22	23.26	3.8250	523	94.06
5	13.49	6.5640	123	22.12	23	23.80	3.7386	443	79.68
Peak	2*th	D(hkl)	I(abs)	I(rel)	Peak	2*th	D(hkl)	I(abs)	I(rel)

No.	[deg]	[$\bar{L}$]	[cts]	[%]	No.	[deg]	[$\bar{L}$]	[cts]	[%]
6	16.31	5.4362	248	44.60	24	24.21	3.6759	173	31.12
7	16.73	5.2988	182	32.73	25	26.10	3.4143	260	46.76
8	17.01	5.2128	142	25.54	26	26.62	3.3491	388	69.78
9	17.69	5.0139	446	80.22	27	27.14	3.2862	238	42.81
10	17.85	4.9693	556	100	28	27.72	3.2189	350	62.95
11	18.09	4.9039	403	72.48	29	28.09	3.1768	113	20.32
12	18.44	4.8103	123	22.12	30	28.67	3.1141	369	66.37
13	19.53	4.5455	363	65.29	31	29.21	3.0573	123	22.12
14	19.93	4.4547	482	86.69	32	29.54	3.0237	155	27.88
15	20.46	4.3407	140	25.18	33	31.42	2.8475	148	26.62
16	20.92	4.2457	365	65.65	34	32.54	2.7515	117	21.04
17	21.33	4.1662	232	41.73	35	34.13	2.6270	180	32.37
18	21.92	4.0546	401	72.12					

DETAILED DESCRIPTION OF THE INVENTION

The powder diffraction pattern of new crystalline polymorph I is determined under the following conditions:

Equipment: PHILIPS – XPERT PW 3710 powder diffractometer

Radiation: CuK α (λ : 1.54190 $\bar{L}$)

Monochromator: graphite

Exciting voltage: 40 kV

Anode current: 30 Ma

Method:

Standard reference substance: SRM 675

Mica Powder (synthetic fluorographite), Ser. No.: 981307.

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The measurement is continuous: $\Theta/2\Theta$ scan: $4.5^\circ - 35.00^\circ 2\Theta$

Step size: 0.04°

Sample: surface plain, width 0.5 mm, in quartz sample holder, measured and stored at room temperature.

According to the present invention there is also provided a process for the preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof which comprises

- a) dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate in a dipolar aprotic solvent, or in a less polar aprotic solvent, or in a polar solvent or in a mixture thereof, admixing the solution with a solution of hydrogen chloride formed with a dipolar aprotic solvent, or a less polar aprotic solvent, or a polar solvent or a mixture thereof and isolating the crystalline form I polymorph; or
- b) recrystallizing methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride from a dipolar aprotic solvent, or a less polar aprotic solvent or a mixture thereof.

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As dipolar aprotic solvent preferably acetone, acetonitrile, ethyl acetate, or dimethyl formamide or a mixture thereof can be used.

As less polar aprotic solvent preferably dioxane, tetrahydrofuran, diisopropyl ether or a mixture thereof can be used.

As polar solvent preferably lower aliphatic alcohols (e.g. ethanol, n-propanol or 2-propanol) can be used.

According to process a) as solvent particularly advantageously acetone or ethyl acetate or a mixture of acetone and ethyl acetate can be used.

According to process b) as solvent particularly advantageously a mixture of acetone and ethyl acetate can be used.

Process a) can be preferably carried out by dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate base in one of the above solvents and thereafter admixing the solution with a solution of hydrogen chloride formed with one of the above solvents. Salt formation is preferably carried out at room temperature, whereupon the

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mixture is cooled. The precipitated crystalline form I polymorph is isolated by filtration or centrifuging, washed and dried.

Process b) can be carried out by recrystallizing methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride from a dipolar aprotic solvent or a less polar aprotic solvent or a mixture thereof. As starting material methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride morphologically non-uniform or amorphous or having crystalline form II can be used. The dissolving of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride can be carried out under heating, preferably at the boiling point of the reaction mixture. The mixture is filtered, the filtrate cooled to a temperature of about room temperature or allowed to cool. The precipitation of crystals can be optionally promoted by inoculating with a small amount of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride crystals of crystalline form I. One may proceed advantageously by heating the solution of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride to the boiling point, cooling the solution first to room temperature and thereafter to a temperature between -20°C and +15°C, isolating the

precipitated crystals by filtration or centrifuging, washing and drying.

According to a further aspect of the present invention there is provided a process for the preparation of crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof which comprises dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate in a dipolar aprotic solvent or a mixture thereof, admixing the solution with a solution of hydrogen chloride formed with an aprotic solvent or a mixture thereof and isolating the crystalline form II polymorph.

As dipolar aprotic solvent preferably acetone, acetonitrile, ethyl acetate or dimethyl formamide or a mixture thereof can be used.

One may proceed particularly advantageously by carrying out the process in a mixture of acetone and ethyl acetate.

According to a preferable form of realization of the process methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate is dissolved in a dipolar aprotic solvent or a mixture thereof, whereupon a solution of hydrogen chloride formed with a dipolar aprotic solvent or a mixture thereof is

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added. One may proceed particularly advantageously by dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate base in a mixture of acetone and ethyl acetate and adding ethyl acetate containing hydrogen chloride. Salt formation is carried out preferably at room temperature. The precipitated crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride is isolated by filtration or centrifuging, washed and dried.

According to a still further aspect of the present invention there is provided a pharmaceutical composition comprising as active ingredient crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I or a hydrate thereof in admixture with inert solid or liquid pharmaceutical carriers and/or auxiliary agents.

The pharmaceutical compositions according to the present invention can be administered preferably orally or parenterally. The oral compositions may be e.g. tablets, capsules, dragées, solutions, elixirs, suspensions or emulsions. The parenteral pharmaceutical compositions can be preferably intravenous or intramuscular injections.

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The pharmaceutical compositions can contain conventional pharmaceutical carriers and/or auxiliary agents. For this purpose e.g. magnesium carbonate, magnesium stearate, talc, lactose, pectine, dextrine, starch, gelatine, tragacanth, methyl cellulose, sodium carboxy methyl cellulose, lower melting wax, cocoa butter etc. can be used. Soft gelatine capsule can be often prepared without carrier - depending on the properties of the active ingredient - because the wall of the capsule can function as carrier. The oral compositions may be generally tablets, powders, capsules, pilules, cachets and lozenges.

The suppositories contain as carrier e.g. lower melting waxes (e.g. mixtures of fatty acid glycerides or cocoa butter). Suppositories can be prepared by melting the wax and homogenously distributing the active ingredient in the melt wax. The thus obtained melted mixture is poured into moulds of suitable form and size and allowed to solidify under cooling.

The tablets can be prepared by admixing the active ingredient with suitable carriers and pressing the mixture into tablets of suitable form and size.

The powders can be prepared by admixing the finely powdered active ingredient with the finely powdered carrier.

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The liquid compositions can be solutions, suspensions or emulsions from which the active ingredient can also be released in a sustained manner. The aqueous or aqueous-propylene glycol solutions are advantageous. The liquid pharmaceutical compositions suitable for parenteral administration can be preferably prepared in the form of an aqueous polyethylene glycol solution.

The aqueous solutions suitable for oral administration can be prepared by dissolving the active ingredient in water, optionally with the addition of suitable stabilizers, thickening agents, colourants and sweeteners.

Aqueous suspensions suitable for oral administration can be prepared by suspending the active ingredient in the presence of a viscous substance (e.g. natural or artificial gums, resins, methyl cellulose, sodium carboxy methyl cellulose or other suspending agents) in water.

Another type of solid pharmaceutical compositions is converted into a liquid formulation immediately before use and is administered orally as a liquid. The liquid compositions can be solutions, suspensions or emulsions which can optionally contain stabilizers, buffers, colourants, natural or artificial sweeteners, dispersing agents, thickening agents etc.

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The pharmaceutical compositions according to the present invention can be preferably prepared in the form of dosage units which contain the desired amount of the active ingredient. Dosage units can be put on the market in packaged form which contain suitable separated amounts of the active ingredient (e.g. tablets or capsules in packages or vials, or powders in ampoules). The term "dosage unit" encompasses capsules, tablets, lozenges and also the packaging which contains the suitable number of dosage units.

According to a further aspect of the present invention there is provided a process for the preparation of pharmaceutical compositions which comprises admixing crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof with pharmaceutically acceptable solid or liquid carriers and/or auxiliary agents and bringing the mixture to a galenic form.

The pharmaceutical compositions according to the present invention are prepared by methods of pharmaceutical industry known *per se*.

The pharmaceutical compositions according to the present invention may contain in addition to crystalline form I or II

methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof further compatible pharmaceutical active ingredients.

The daily dose of crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride depends on the circumstances of the given case (e.g. the condition and body weight of the patient, the severeness of the condition to be treated, the mode of administration etc.) and is determined by the physician.

According to a further aspect of the present invention there is provided the use of crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof as pharmaceutical active ingredient.

According to a still further aspect of the present invention there is provided the use of crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof as pharmaceutical active ingredient having blood platelet aggregation inhibiting and antithrombotic effect.

According to a still further aspect of the invention there is provided a blood platelet aggregation inhibiting and antithrombotic method of treatment which comprises administering to the patient in need of such treatment a therapeutically effective amount of crystalline form I or II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof.

The advantage of the present invention is that the new methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride polymorphs are of uniform morphology and therefore possess reproducible properties in relation to dissolution velocity, bioavailability, chemical stability, working-up and processing (filtrability, drying, tableting properties etc.). The new polymorphs of the present invention can be prepared by a process which is readily reproducible on industrial scale too.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to said Examples.

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198**Example 1**

Preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride.

3,21 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate are dissolved in 35 ml of tetrahydrofurane whereupon a solution of tetrahydrofurane saturated with gaseous hydrogen chloride is added. The reaction mixture is stirred at room temperature for 2 hours and thereafter allowed to stand in a refrigerator for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold tetrahydrofurane. Thus 2.6 g of the title compound are obtained. Yield 75 %. Mp.: 140-141°C.

Example 2

Preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

3.21 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate are dissolved in a mixture of 4 ml of acetone and 5 ml of ethyl acetate, whereupon 1.3 g of 2-propanol containing hydrogen chloride (31 g HCl/100 g solution) are added. The reaction mixture is stirred at room

temperature for 2 hours and thereafter allowed to stand in a refrigerator for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold ethyl acetate. Thus 2.92 g of the title compound are obtained. Yield 85 %. Mp.: 140-141°C.

Example 3

Preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

3.21 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate are dissolved in 20 ml of ethyl acetate, whereupon 2.5 g of ethyl acetate containing hydrogen chloride are added (14 g HCl/100 g solution). The reaction mixture is stirred at room temperature for 2 hours and thereafter allowed to stand in a refrigerator for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold tetrahydrofurane. Thus 2.92 g of the title compound are obtained. Yield 85 %. Mp.: 140-141°C.

Example 4

Preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

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3 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride are dissolved in 40 ml of boiling tetrahydrofuran. The hot solution is filtered, cooled slowly to room temperature under stirring, then stirred at room temperature for 2 hours and allowed to stand in a refrigerator for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold tetrahydrofuran. Thus 2.5 g of the title compound are obtained. Yield 70 %. Mp.: 140-141°C.

Example 5

Preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

3 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride are dissolved in a boiling mixture of 70 ml of acetone and 30 ml of diisopropyl ether. The hot solution is filtered, cooled slowly to room temperature under stirring, then stirred at room temperature for 2 hours and allowed to stand in a refrigerator for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold ethyl acetate. Thus 2.2 g of the title compound are obtained. Yield 65 %. Mp.: 140-141°C.

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201**Example 6**

Preparation of crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride

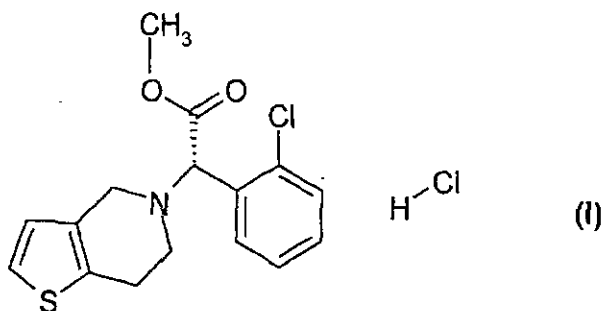
3.21 g of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate are dissolved at room temperature in a mixture of 10 ml acetone and 10 ml of ethyl acetate, whereupon 2.5 g of ethyl acetate containing hydrogen chloride (14 g HCl/100 g solution) are added. The reaction mixture is stirred at room temperature for 16 hours. The precipitated snow-white crystals are filtered off and washed with cold ethyl acetate. Thus 2.2 g of the title compound are obtained. Yield 64 %. Mp.: 143-144°C.

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What we claim is,

1. Crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula



and hydrates thereof characterized by the X-ray powder diffraction pattern expressed in Table 1 and Figure 1.

Table 1
Position of diffraction lines and relative intensities
(> 15 % of polymorph I)

Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]
1	9.64	9.1707	152	21.51	12	21.64	4.1075	107	15.16
2	11.22	7.8873	129	18.25	13	22.90	3.8841	476	67.21
3	12.98	6.8222	708	100	14	23.13	3.8455	469	66.30
4	13.89	6.3759	161	22.76	15	24.73	3.6006	245	34.67

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Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]
5	15.05	5.8888	115	16.25	16	25.06	3.5540	302	42.62
6	16.82	5.2697	168	23.66	17	25.41	3.5059	471	66.49
7	17.16	5.1661	189	26.76	18	27.31	3.2655	111	15.73
8	17.65	5.0261	156	22.06	19	27.55	3.2372	179	25.25
9	19.58	4.5336	193	27.33	20	28.78	3.1021	143	20.16
10	19.88	4.4654	393	55.56	21	28.97	3.0822	123	17.39
11	20.57	4.3180	165	23.37	22	32.48	2.7570	190	26.77

2. Process for the preparation of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof which comprises

- a) dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate in a dipolar aprotic solvent, or in a less polar aprotic solvent, or in a polar solvent or in a mixture thereof, admixing the solution with a solution of hydrogen chloride formed with a dipolar aprotic solvent, or a less polar aprotic solvent, or a polar solvent or a mixture thereof and isolating the crystalline form I polymorph; or
- b) recrystallizing methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride from a dipolar aprotic solvent, or a less polar aprotic solvent or a mixture thereof.

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3. Process according to method a) or b) of Claim 2 which comprises using acetone, acetonitrile, ethyl acetate or dimethyl formamide or a mixture thereof as dipolar aprotic solvent.
4. Process according to method a) or b) of Claim 2 which comprises using dioxane, tetrahydrofurane, or diisopropyl ether or a mixture thereof as less polar aprotic solvent.
5. Process according to method a) of Claim 2 which comprises using a lower aliphatic alcohol, preferably ethanol, n-propanol or 2-propanol as polar solvent.
6. Process according to method a) of Claim 2 which comprises using as solvent acetone and/or ethyl acetate.
7. Process according to method b) of Claim 2 which comprises using a mixture of acetone and ethyl acetate as solvent.
8. Process according to method a) of Claim 2 or Claim 6 which comprises carrying out salt formation at room temperature and thereafter cooling the reaction mixture.

9. Process according to method b) of Claim 2 which comprises carrying out recrystallization by heating the solution of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride and thereafter cooling the solution.

10. Process according to Claim 9 which comprises heating the solution of methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride to the boiling point of the solvent, then cooling to room temperature and thereafter cooling to a temperature between -20°C and +15°C.

11. Pharmaceutical composition comprising as active ingredient crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I or a hydrate thereof in admixture with inert solid or liquid pharmaceutical carriers and/or auxiliary agents.

12. Process for the preparation of pharmaceutical compositions according to Claim 11 which comprises admixing crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof with pharmaceutically acceptable solid or

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liquid carriers and/or auxiliary agents and bringing the mixture to a galenic form.

13. Crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof for use as pharmaceutical active ingredient.

14. Use of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof as pharmaceutical active ingredient having blood platelet aggregation inhibiting and antithrombotic effect.

15. Blood platelet aggregation inhibiting and antithrombotic method of treatment which comprises administering to the patient in need of such treatment a therapeutically effective amount of crystalline form I methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof.

16. Crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof

characterized by the X-ray powder diffraction pattern expressed in Table 2 and Figure 2.

Table 2
Position of diffraction lines and relative intensities
(> 15 % of polymorph I)

Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]	Peak No.	2*th [deg]	D(hkl) [Å]	I(abs) [cts]	I(rel) [%]
1	8.85	9.9923	88	15.83	19	22.25	3.9956	184	33.09
2	9.85	8.9800	535	96.22	20	22.58	3.9386	156	28.06
3	11.41	7.7575	358	64.39	21	22.85	3.8920	134	24.10
4	12.97	6.8260	101	18.17	22	23.26	3.8250	523	94.06
5	13.49	6.5640	123	22.12	23	23.80	3.7386	443	79.68
6	16.31	5.4362	248	44.60	24	24.21	3.6759	173	31.12
7	16.73	5.2988	182	32.73	25	26.10	3.4143	260	46.76
8	17.01	5.2128	142	25.54	26	26.62	3.3491	388	69.78
9	17.69	5.0139	446	80.22	27	27.14	3.2862	238	42.81
10	17.85	4.9693	556	100	28	27.72	3.2189	350	62.95
11	18.09	4.9039	403	72.48	29	28.09	3.1768	113	20.32
12	18.44	4.8103	123	22.12	30	28.67	3.1141	369	66.37
13	19.53	4.5455	363	65.29	31	29.21	3.0573	123	22.12
14	19.93	4.4547	482	86.69	32	29.54	3.0237	155	27.88
15	20.46	4.3407	140	25.18	33	31.42	2.8475	148	26.62
16	20.92	4.2457	365	65.65	34	32.54	2.7515	117	21.04
17	21.33	4.1662	232	41.73	35	34.13	2.6270	180	32.37
18	21.92	4.0546	401	72.12					

17. Process for the preparation of crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-

c]pyridine-5-yl)-acetate hydrochloride of the Formula I and hydrates thereof which comprises dissolving methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate in a dipolar aprotic solvent or a mixture thereof, admixing the solution with a solution of hydrogen chloride formed with an aprotic solvent or a mixture thereof and isolating the crystalline form II polymorph.

18. Process according to Claim 17 which comprises using acetone, acetonitrile, ethyl acetate or dimethyl formamide or a mixture thereof as aprotic solvent.

19. Process according to Claim 18 which comprises using a mixture of acetone and ethyl acetate as solvent.

20. Process according to any of Claims 17-19 which comprises carrying out salt formation at room temperature.

21. Pharmaceutical composition comprising as active ingredient crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride of the Formula I or a hydrate thereof in admixture with inert solid or liquid pharmaceutical carriers and/or auxiliary agents.

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22. Process for the preparation of pharmaceutical compositions according to Claim 21 which comprises admixing crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof with pharmaceutically acceptable solid or liquid carriers and/or auxiliary agents and bringing the mixture to a galenic form.

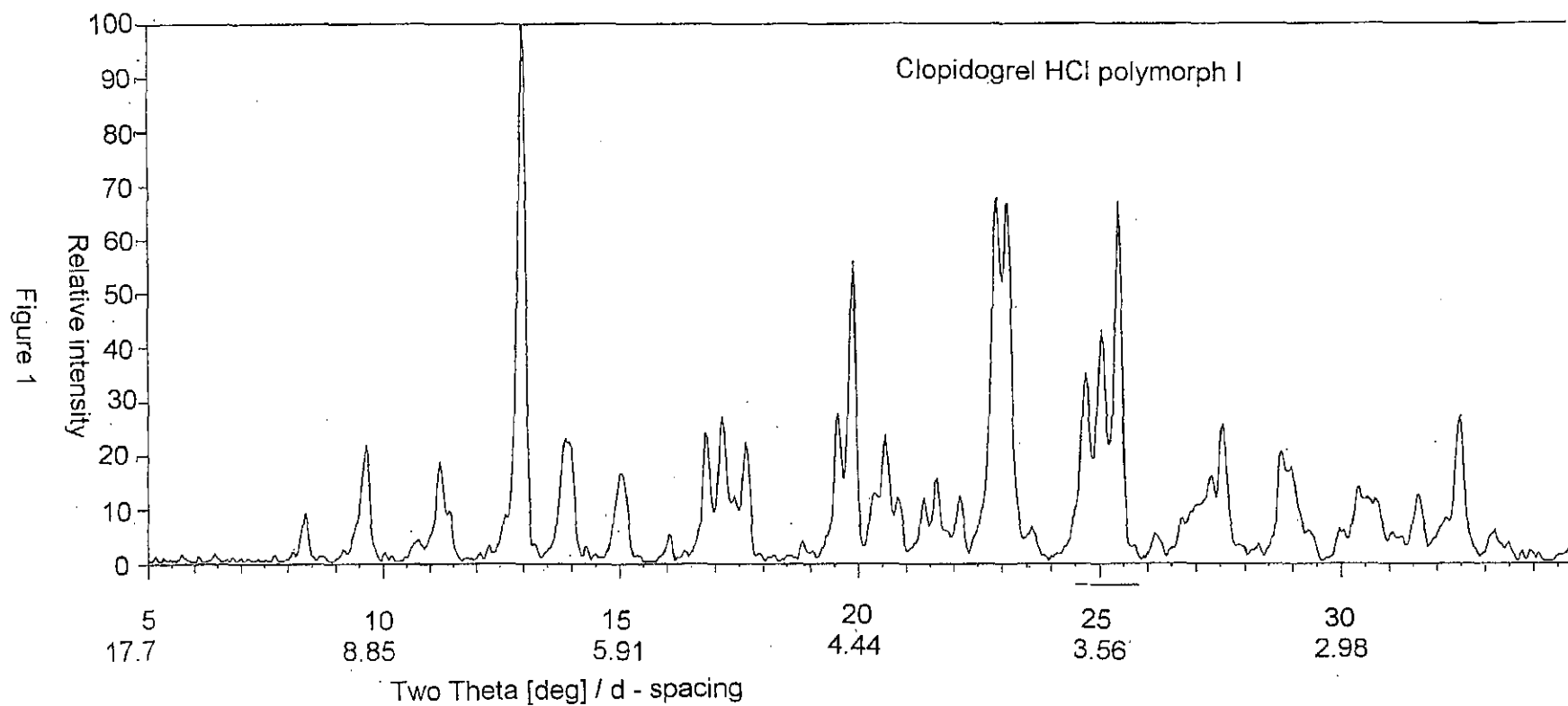
23. Crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof for use as pharmaceutical active ingredient.

24. Use of crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof as pharmaceutical active ingredient having blood platelet aggregation inhibiting and antithrombotic effect.

25. Blood platelet aggregation inhibiting and antithrombotic method of treatment which comprises administering to the patient in need of such treatment a therapeutically effective amount of crystalline form II methyl-(S)-(+)-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridine-5-yl)-acetate hydrochloride or a hydrate thereof.

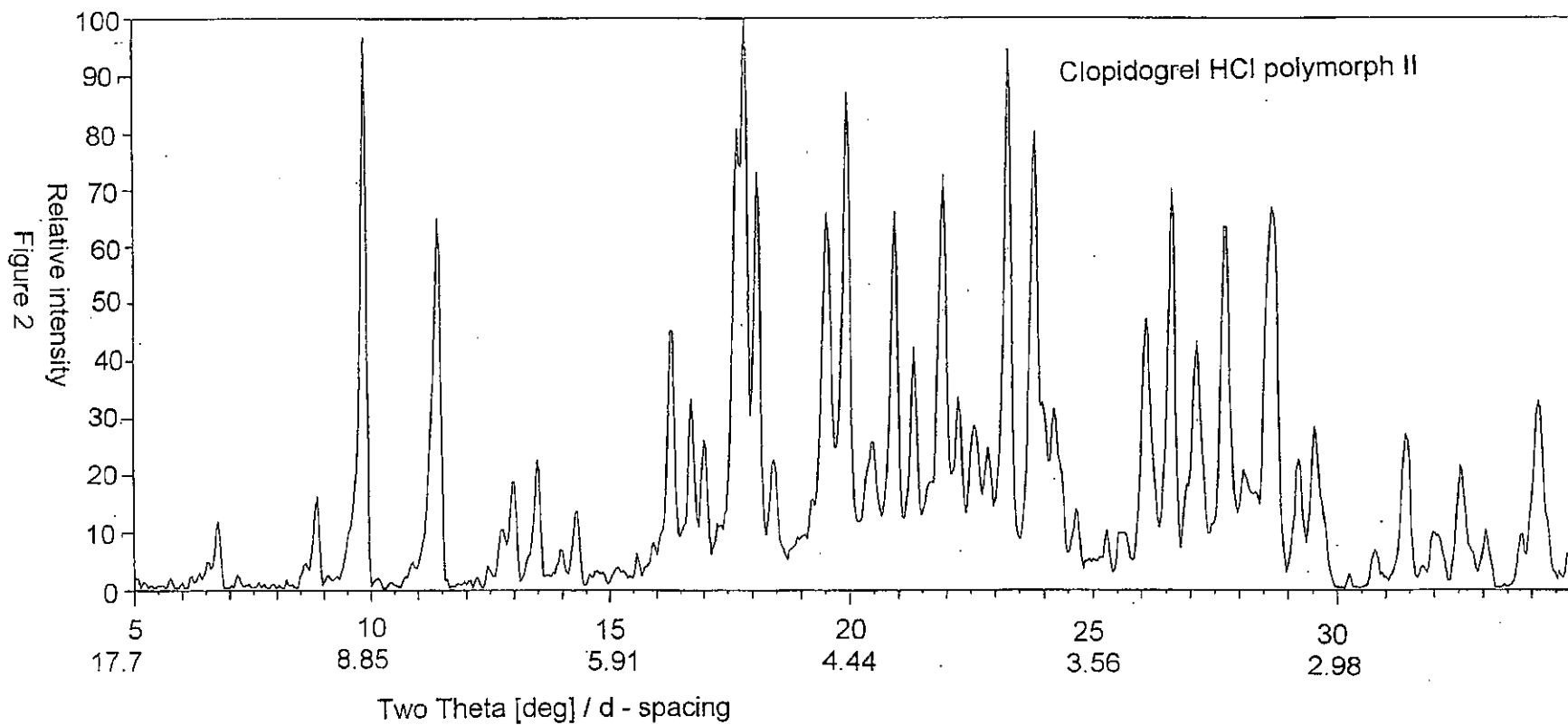
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FileName	Sample Ident.:	Date:	Wavelen	Tube	kV	mA	Step	Range	Max.I
CLOP188	Clopidogrel HCl KF-1	11-14-2001	1.54190	Cu	40	30	0.04	4.5-34.9	708



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in

FileName	Sample Ident.:	Date:	Wavelen	Tube	kV	mA	Step	Range	Max.I
CLOP179	Clopidogrel HCl Sz-6	10-10-2001	1.54190	Cu	40	30	0.04	4.5-34.9	556



INTERNATIONAL SEARCH REPORT

Internal Application No.

PC1/HU 02/00157

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D495/04 A61K31/4365 A61K31/435

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 099 802 A (SANOFI SA) 1 February 1984 (1984-02-01) claims 1,14	1-25
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* 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 document 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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"G" document member of the same patent family

Date of the actual completion of the international search

10 March 2003

Date of mailing of the international search report

18/03/2003

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/HU 02/00157

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HERBERT J-M: "CLOPIDOGREL AND ANTIPLATELET THERAPY" EXPERT OPINION ON INVESTIGATIONAL DRUGS, ASHLEY PUBLICATIONS LTD., LONDON, GB, vol. 3, no. 5, 1 May 1994 (1994-05-01), pages 449-455, XP000607616 ISSN: 1354-3784 the whole document -----	1-25

INTERNATIONAL SEARCH REPORT

national application No.
PCT/HU 02/00157

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 25 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/HU 02/00157

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/HU 02/00157

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ANEXO 3

United States Patent [19]

Badorc et al.

[11] Patent Number: 4,847,265

[45] Date of Patent: Jul. 11, 1989

[54] DEXTRO-ROTATORY ENANTIOMER OF METHYL ALPHA-5 (4,5,6,7-TETRAHYDRO (3,2-C) THIENO PYRIDYL) (2-CHLOROPHENYL)-ACETATE AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING IT

[75] Inventors: Alain Badorc, Roquettes; Daniel Fréhel, Toulouse, both of France

[73] Assignee: Sanofi, France

[21] Appl. No.: 155,550

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[51] Int. Cl.⁴ A61K 31/44; C07D 495/04

[52] U.S. Cl. 514/301; 546/114

[58] Field of Search 546/114; 514/301

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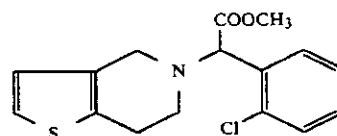
Primary Examiner—Mary C. Lee

Assistant Examiner—Bernard I. Dentz

Attorney, Agent, or Firm—Wegner & Bretschneider

[57] ABSTRACT

The present invention relates to the dextro-rotatory enantiomer of Formula



and its pharmaceutically acceptable salts with platelet aggregation inhibiting activity.

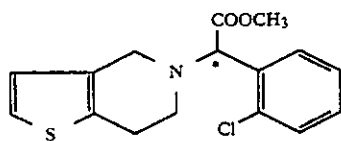
The invention also relates to a process for the preparation of this compound starting from the racemate and the pharmaceutical compositions containing it.

7 Claims, No Drawings

**DEXTRO-ROTATORY ENANTIOMER OF
METHYL ALPHA-5(4,5,6,7-TETRAHYDRO (3,2-C)
THIENO PYRIDYL)
(2-CHLOROPHENYL)-ACETATE AND THE
PHARMACEUTICAL COMPOSITIONS
CONTAINING IT**

The present invention relates to the dextro-rotatory enantiomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate, a process for its preparation and pharmaceutical compositions containing it.

The compound of the invention corresponds to the following formula (I):



in which the C* is an asymmetric carbon atom. In fact, this formula represents both the dextro-rotatory molecule claimed as well as its levo-rotatory enantiomer. The racemic mixture corresponding to this formula was described in the French patent application published under the No. 2 530 247. Hereafter the dextro-rotatory enantiomer claimed according to the invention will be designated by I_d and the levo-rotatory enantiomer by I_l .

It is known that the optical rotatory power of a compound depends on the solvent in which it is measured and on its concentration in this solvent. The optical rotatory power of the dextro-rotatory isomer according to the invention is positive in methanolic solution.

In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers.

The invention also relates to the addition salts of the compounds of formula (I_d) with pharmaceutically acceptable mineral or organic acids.

The compound (I_d) is an oil whereas its hydrochloride exists as a white powder. The oily products are usually difficult to purify and it is preferable to use for the preparation of pharmaceutical compositions crystalline products which can usually be purified by recrystallization.

However, it has been observed in the present case that some of the salts of compound (I_d) usually precipitate in an amorphous form and/or that they are hygroscopic, a property which makes them difficult to handle on an industrial scale. Thus, the salts of carboxylic acid and sulfonic acids classically used in pharmacy have been prepared, acids such as acetic, benzoic, fumaric, maleic, citric, tartaric, gentisic, methane-sulfonic, ethanesulfonic, benzenesulfonic and laurylsulfonic acids as well as the salts of dobesilic acid (m.p. = 70° C.) and para-toluenesulfonic acid (m.p. = 51° C.), the purification of which proved to be difficult.

Among the mineral and organic acid salts of the dextro-rotatory isomer of the compound of Formula (I_d) salts have been found which crystallize easily, are not hygroscopic and are sufficiently water-soluble as to make their use as active medicinal principles particularly advantageous.

The present invention thus relates more particularly to the hydrogen sulfate, the taurocholate and the hydrobromide of the dextro-rotatory enantiomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate.

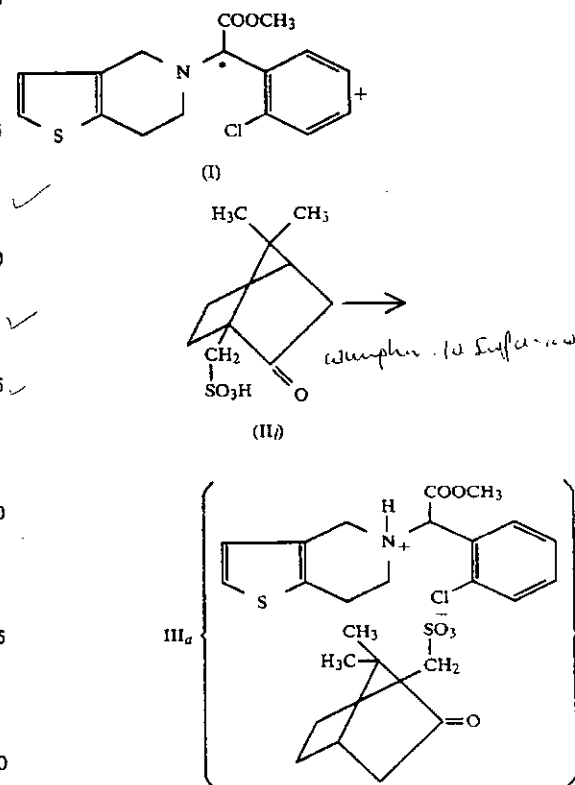
These salts are prepared in a standard manner by the action of the corresponding acid on the base in solution in a solvent from which they precipitate spontaneously or after addition of a non-solvent of the salt.

The dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate can be prepared by forming the salt of the racemic compound with an optically active acid in a solvent, repeated recrystallizations of the salt until a product of constant optical rotatory power is obtained, followed by the liberation of the dextro-rotatory isomer from its salts by a base; if required, a salt is formed between the dextro-rotatory isomer and a pharmaceutically acceptable acid.

The optically active acid may advantageously be levo-rotatory camphor-10-sulfonic acid.

One and the same solvent may be used for salt formation and recrystallization: acetone is ideally suited in this case.

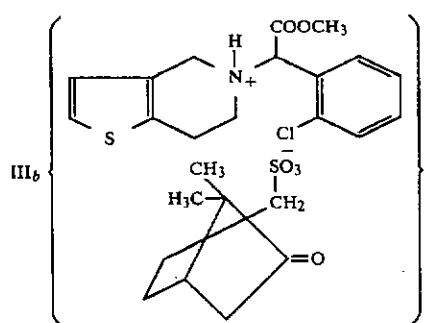
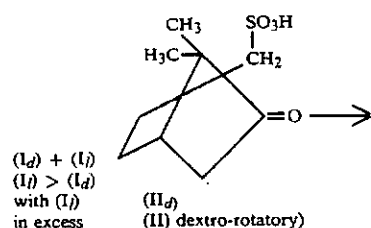
The chiral, levo-rotatory camphor-10-sulfonic acid of Formula (II₁) is allowed to react in an inert solvent with the racemic mixture of Formula (I) according to the following reaction scheme:



Salt formation may be carried out in solvents such as alcohols, ketones, dimethylformamide. The salt precipitates spontaneously or is isolated by salting out or evaporation of the solvent. A mixture of two diastereoisomers of Formula (IIIa) is formed. By repeated recrystallizations from a solvent such as acetone the precipitate

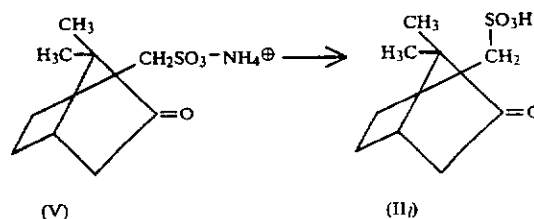
is enriched in the salt of the dextro-rotatory isomer of compound (I). After each recrystallization the optical rotatory power $[\alpha]_D^{20}$ of the precipitate is measured at 20° C. in methanol at a concentration varying between 1.5 and 2 g/100 ml. When the $[\alpha]_D^{20}$ stops increasing the base of Formula (I_D) is liberated from the salt (III_a) by the action of a base such as sodium or potassium hydrogen carbonate in aqueous media at temperatures varying between 5° C. and 20° C. Evaporation of the filtrate of the first recrystallization IV after the crystals of the precipitated salt (III_a) have been filtered off, gives a mixture enriched in the salt of (I_l) enantiomer. The basification of this mixture of diastereoisomeric salts with a weak base such as sodium or potassium hydrogen carbonate in aqueous solution at temperatures varying between 5° C. and 20° C. leads to a mixture of the two enantiomers (I_d) plus (I_l) enriched in the levo-rotatory enantiomer (I_l).

This mixture (I_d) + (I_l) enriched in enantiomer (I_l) is allowed to react with dextro-rotatory camphor-10-sulfonic acid which will be designated as (II_d) in a solvent according to the following reaction scheme:



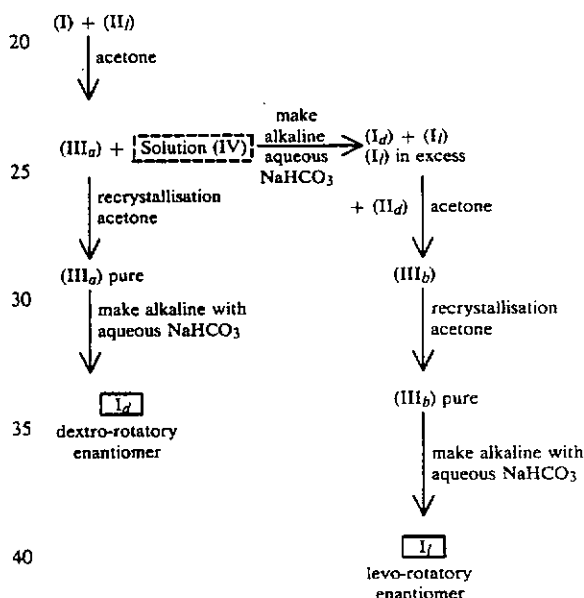
The crystalline mixture of diastereoisomeric salts (III_b) obtained is recrystallized from acetone until the optical rotatory power $[\alpha]_D^{20}$ of the precipitate remains constant. As previously mentioned the optical rotatory power $[\alpha]_D^{20}$ of the diastereoisomeric salt (III_b) is determined after each recrystallization.

The liberation of the stereoisomeric (I_l) from its salt is carried out in a standard manner, like that for compound (I_d). Levo-rotatory camphor-10-sulfonic acid (II_l) may be obtained from commercially available ammonium camphor-10-sulfonate of Formula (V) according to the reaction scheme:



An aqueous solution of the ammonium salt (V) is chromatographed on an Amberlite IRN-77 resin. After lyophilization of the eluate camphor-10-sulfonic acid of Formula (II_l) is recovered.

The entire sequence of the process is shown schematically below:



Each of the pure enantiomers (I_d) and (I_l) may be converted into a salt by means of the standard methods; for example, the hydrochlorides are prepared by the addition of a solution of hydrogen chloride gas in diethyl ether to a solution of (I_d) or (I_l) in diethyl ether.

DETERMINATION OF THE ENANTIOMERIC PURITY OF THE DEXTRO-ROTATORY (I_d) AND LEVO-ROTATORY (I_l) ENANTIOMERS

Two methods have been used:

proton NMR spectroscopy with the addition of a chiral rare earth high pressure liquid chromatography using a chiral stationary phase.

(a) Proton NMR spectroscopy with the addition of a chiral rare earth. The enantiomeric purity (optical purity) was determined by ¹H 60 MHz NMR spectroscopy in the presence of a rare earth chiral complex according to the method described by G. M. WHITESIDES et al. (J. Am. Chem. Soc. 1974, 96, 1038).

In the racemic product (I), the hydrogen attached to the asymmetric centre in the α position to the ester function appears as a singlet (chemical shift δ=4.87 ppm in CDCl₃ as solvent. The addition of the rare earth complex Eu(tfc)₃ [tris 3-(trifluoromethyl) hydroxyme-

thylene)-d-camphorato europium (III)] to the probe containing a solution of the racemate (I) in CDCl_3 leads to the resolution of the initial singlet into two, well-separated singlets corresponding to the proton of each of the two enantiomers (I_d) and (I_l). When the molar ratio of rare earth complex/compound (I)=0.4, the separation between the two singlets is about 6 Hz.

With each of the two enantiomers prepared, (I_d) and (I_l), the same procedure was used as for the racemate (I). The smaller chemical shift corresponds to the proton of the dextro-rotatory enantiomer (I_d) and the larger chemical shift to the levo-rotatory enantiomer (I_l).

The precision of the method was determined by comparing the ^1H (60 MHz) NMR spectra obtained with and without addition of the rare earth complex for each of the two enantiomers (I_d) and (I_l) in the pure state or as mixtures containing increasing quantities of one of the enantiomers. It was observed that it was possible to detect easily more than 5% by weight of one enantiomer in the presence of the other.

(b) High pressure liquid chromatography using a chiral stationary phase The study was conducted with a liquid chromatograph HP-1084 using a UV detector at 215 nm. The chiral stationary phase was DEAE silica (10 microns) onto which was grafted alpha-1 acid glycoprotein (0.4×100 mm) (ENANTIOPAC R-LKB). The mobile phase consisted of an aqueous phosphate buffer mixture 8 mM ($\text{NaH}_2\text{PO}_4/\text{Na}_2\text{HPO}_4$) containing 0.1M of NaCl, adjusted to pH=7.4, and 15% of isopropanol (v/v). The flow rate was fixed at 0.3 ml/minute and the temperature of the column was maintained at $18^\circ\text{--}20^\circ\text{C}$. Under these conditions, the dextro-rotatory enantiomer (I_d) has a retention time of 45 minutes and the levo-rotatory enantiomer (I_l) has a retention time of 35 minutes.

The precision of the determination of the optical purity of the two enantiomers was estimated by chromatographing each of the two enantiomers (I_d) and (I_l) prepared either alone or as a mixture containing increasing amounts of one of the enantiomers. It was observed that it was easy to detect:

2% (weight/weight) of enantiomer (I_d) in enantiomer (I_l)

4% (weight/weight) of enantiomer (I_l) in enantiomer (I_d).

Under these conditions it may be concluded that the optical purity of the two enantiomers (I_d) and (I_l) obtained according to the examples is at least equal to 96% for the dextro-rotatory enantiomer (I_d) and at least equal to 98% for the levo-rotatory enantiomer (I_l).

The following examples are non-restrictive and are presented to illustrate the present invention.

EXAMPLE 1

Salts of dextro-rotary methyl-alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate

(a) levo-rotatory camphor-10-sulfonic acid

A column of Amberlite IRN-77 resin is prepared and tested by passing 1N hydrochloric acid through it and then by washing this column of acidified resin abundantly with water. Levo-rotatory ammonium camphor-10-sulfonate is dissolved in a minimum of water and applied to the column of resin previously prepared. Elution is carried out with water. The eluted fractions containing the acid are lyophilized.

White crystals, m.p.= 198°C ; $[\alpha]_D^{20} = -20.53$ ($c=2.075$ g/100 ml water).

(b) Camphor-10-sulfonic acid salt of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990 B).

32 g (0.0994 mole) of racemic methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate are dissolved in 150 ml of acetone. 9.95 g (0.0397 mole) of levo-rotary camphor-10-sulfonic acid monohydrate are added. The clear solution is left to stand at room temperature. After 48 hours some crystals have formed. The reaction mixture is concentrated to 50 ml and left to stand at room temperature for 24 hours. The crystals obtained are filtered off, washed with acetone and dried (yield: 55% on the basis of the starting racemate).

White crystals, m.p.= 165°C , $[\alpha]_D^{20} = +24.67$ ($c=1.58$ g/100 ml; methanol).

The crystals obtained above are redissolved in the minimum of boiling acetone (50 ml). The crystals obtained after cooling are filtered off, washed with acetone and dried (yield: 88%).

White crystals, m.p.= 165°C , $[\alpha]_D^{20} = +24.75$ ($c=1.68$ g/100 ml; methanol).

(c) Dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate.

12 g (0.022 mole) of the pure product obtained in (b) are dissolved in a minimum of water. After cooling to 5°C , the aqueous solution obtained is made alkaline with a saturated aqueous solution of sodium hydrogen carbonate. The alkaline aqueous phase is extracted with dichloromethane. The organic extracts are dried over anhydrous sodium sulfate. On evaporation of the solvent a colorless oil is obtained (quantitative yield). Oil, $[\alpha]_D^{20} = +51.52$ ($c=1.61$ g/100 ml; methanol).

(d) The hydrochloride of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (dextro-rotatory) (SR 25990 A).

7 g (0.0228 mole) of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate are dissolved in 100 ml of diethyl ether. 30 ml of a solution of 1N HCl in diethyl ether are added and the crystals obtained are filtered off. The crystals are washed with diethyl ether and dried (yield: 94%).

White crystals, m.p.= 117°C , $[\alpha]_D^{20} = +62.23$ ($c=1.82$ g/100 ml; methanol).

(e) The hydrogen sulfate of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990 C).

800 ml of a saturated aqueous solution of sodium bicarbonate are added to a suspension of 200 g of SR 25990 B in 800 ml of dichloromethane. After vigorous shaking, the organic phase is separated, dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is dissolved in 500 ml of ice-cold acetone and 20.7 ml of concentrated sulfuric acid (93.64%, $d=1.83$) are added drop-wise. The precipitate formed is isolated by filtration and washed with 1,000 ml of acetone, then dried in a vacuum oven at 50°C .

139 grams of analytically pure white crystals are thus obtained with a melting point of 184°C . Empirical formula: $\text{C}_{16}\text{H}_{16}\text{ClNO}_2\text{S} \cdot \text{H}_2\text{SO}_4$ $[\alpha]_D^{20} = +55.10$ ($c=1.891$ g/100 ml; methanol).

(f) The hydrobromide of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990D).

150 ml of an aqueous solution of sodium bicarbonate are added to a suspension of 20 g of SR 25990 B in 200

ml of dichloromethane. The residue obtained after separation of the organic phase, drying and evaporation of the solvent is dissolved in 150 ml of diethyl or diisopropyl ether, and 4.4 ml of a 48% (wt/v) aqueous solution of hydrobromic acid are added drop-wise. The precipitate formed is isolated. After drying, 14.4 g of crystals are obtained with a melting point of 111° C. (yield 99%).

13.4 g of these crystals are recrystallized from a mixture of isopropyl ether (100 ml) and isopropanol (150 ml) to give 10.2 g of analytically pure hydrobromide: m.p. = 140° C.; empirical formula: $C_{16}H_{16}ClNO_2S \cdot HBr$ $[\alpha]_D^{20} = +59.23$ (c = 2.09 g/100 ml; methanol).

(g) The taurocholate of dextro-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25990E).

The sodium salt of taurocholic acid is chromatographed on Amberlite IRN-77 resin by eluting with water. The fractions obtained are lyophilized.

3 g (0.0054 mole) of SR 25990B are treated with a saturated aqueous solution of sodium bicarbonate and the mixture is extracted with dichloromethane. The organic phase is separated, dried over sodium sulfate and evaporated to dryness. The free base obtained is taken up in 30 ml of isopropanol; 2.8 g (0.0054 mole) of taurocholic acid dissolved in 100 ml of isopropanol are added to this solution. The mixture is stirred overnight at room temperature, then evaporated to dryness. The residue solidified on being triturated with ether. 3.5 g of beige crystals are obtained. m.p. = 120° C. $[\alpha]_D^{20} = +39.53$ (c = 1.791 g/100 ml of methanol). $C_{16}H_{16}ClNO_2S \cdot C_{26}H_{45}NO_7S$; C, H, N analyses in agreement with theory.

EXAMPLE 2

Salts of levo-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate

(a) Salt of d-camphor-10-sulfonic acid (SR 25989 B)

After separation of SR 25990 B in Example 1-b the solvent is evaporated from the acetone filtrate obtained.

The residue is taken up in water and diethyl ether. The ethereal phase is decanted. The aqueous phase is cooled to 5° C. and made alkaline with a saturated aqueous solution of sodium bicarbonate. The aqueous alkaline phase is extracted with diethyl ether. The ethereal extracts are pooled and dried over anhydrous sodium sulfate.

On evaporation of the solvent an oil is obtained which is purified by filtration through a bed of silica (eluant: diethyl ether). A colourless oil is recovered consisting of a mixture of about 65% of the levo-rotatory enantiomer and 35% of the dextro-rotatory enantiomer, proportions determined by means of 1H (60 MHz) NMR spectroscopy after the addition of chiral, rare earth complex.

16.66 g (0.0517 mole) of the mixture thus obtained are dissolved in 70 ml of acetone. 7.77 g (0.0310 mole) of dextro-rotatory camphor-10-sulfonic acid monohydrate are added. The homogeneous mixture is left to stand overnight at room temperature. The crystals obtained are filtered off, washed with acetone and dried (yield: 44% based on the mixture).

The crystals obtained are dissolved in a minimum of refluxing acetone (60 ml). The precipitate obtained on cooling to room temperature is filtered off, washed with

acetone and dried. White crystals, m.p. = 167° C., $[\alpha]_D^{20} = -24.85$ (c = 1.79 g/100 ml; methanol).

(b) Levo-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate.

11.3 g (0.0204 mole) of the camphor-10-sulfonate obtained in (a) are dissolved in a minimum of water. The aqueous solution obtained is cooled to 5° C. and made alkaline with a saturated aqueous solution of sodium hydrogen carbonate. The alkaline aqueous phase is extracted with dichloromethane. The organic solution is dried and the solvent is evaporated. A colourless oil is isolated (quantitative yield).

Oil $[\alpha]_D^{20} = -50.74$ (c = 1.58 g/100 ml; methanol).

(c) The hydrochloride of levo-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25989 A).

Prepared according to the method described in Example 1(d). Yield: 94%.

White crystals, m.p. = 117° C., $[\alpha]_D^{20} = -62.56$ (c = 1.80 g/100 ml; methanol).

(d) The hydrogen sulfate of levo-rotatory methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate (SR 25989 C).

70 g (0.126 mole) of the camphor sulfonate SR 25989 B obtained are treated as described in (a) above with a saturated aqueous solution of sodium bicarbonate in the presence of dichloromethane. The organic phase is separated, dried over sodium sulfate and evaporated to dryness. The residue is taken up in 300 ml of acetone and 7.2 ml (0.126 mole) of concentrated sulfuric acid are added drop-wise. After being stirred the crystals formed are filtered off and washed with acetone. 47.8 g of white crystals are obtained. m.p. = 182° C. $[\alpha]_D^{20} = -51.61$ (c = 2.044 g/100 ml; methanol). The analysis (C,H,N) are in agreement with theory.

PHARMACOLOGICAL STUDY

The platelet aggregation inhibiting activity and the toxicity of these new compounds were compared to those of the racemic mixture described in the French Pat. No. 82.12599 (Publication No. 2 530 247).

A description will now be given of the results of this study which demonstrates another advantage of the invention, namely that the salts of the dextro-rotatory isomer have a better therapeutic index than the salt of the racemic mixture; in fact, the levo-rotatory isomer exhibits almost no platelet aggregation inhibiting activity and its toxicity is markedly higher than that of its dextro-rotatory homologue.

The platelet aggregation inhibiting activities and the antithrombotic activities of the compounds were studied in the rat by standard methods.

The activity on the aggregation of plates induced by ADP or collagen was determined ex-vivo.

The products dissolved in ethanol (200 mg/ml) and diluted in water containing gum arabic (5%-wt/v) were administered by the oral route to groups of five female rats of the CD-COBS strain, weighing 250-300 g, in amounts of 10 ml of suspension per kilogram two hours before blood samples were taken.

The blood samples were taken from animals anesthetized with diethyl ether by puncture of the abdominal aorta and placed over a 3.8% aqueous solution of sodium citrate (1 vol/9 volumes of blood). The platelet-rich plasma was then isolated by centrifugation at 200 g for 10 minutes.

Aggregation is induced by the addition of 2 μ l of aggregating solution to 400 μ l of platelet-rich plasma.

The aggregating solutions used were: a 500 μ M aqueous solution of ADP marketed by Boehringer Mannheim (final concentration 2.5 μ M), and a solution of collagen marketed by Sigma (type 1) at a concentration of 0.25 g/100 ml in 3% acetic acid (v/v) (final concentration 12.5 μ g/ml).

The aggregation of the platelets was monitored as described in the method by G. V. R. Born in Nature 194, p. 927 (1967) using a Coultronics® aggregometer at a temperature of 37° C. and agitation of 900 rpm.

For aggregation with ADP, the aggregometer generates a curve representing a platelet aggregation as measured by a change in optical density. The height of this curve is defined as the height of aggregation. The percentage of aggregation is the relation between the aggregation height measured and the height corresponding to 100% aggregation $\times 100$. The percentage of inhibition is determined by the relation:

$$\frac{\text{Control aggregation height} - \text{produced aggregation height}}{\text{Control aggregation height}} \times 100$$

The results obtained for the aggregation with ADP for the hydrochloride of the racemic mixture (PCR 4099), the hydrogen sulfates of the dextro-rotatory (SR 25990 C) and levo-rotatory (SR 25989 C) isomers on the one hand, and for PCR 4099 and the hydrochlorides of the dextro-rotatory (SR 25990 A) and levo-rotatory (SR 25989 A) on the other, are shown in Table I; they demonstrate that the levo-rotatory isomer is inactive and that the dextro-rotatory isomer is at least as active as the racemate.

TABLE I

PRO-DUCT	DOSE mg/Kg P.O.	QUANTITY of base administered	% IN-HIBITION	P**
% AGGREGATION				
Controls			42.4 $\pm$ 1.5	
PCR 4099	4.48	3.84	29.8 $\pm$ 2.4	30 0.01
(racemate)	8.97	7.69	17.2 $\pm$ 2.2	59 0.001
	17.9	15.38	11.1 $\pm$ 2.3	74 0.001
SR 25989C	20	15.38	41.0 $\pm$ 1.5	3 n.s.
	40	30.76	37.1 $\pm$ 1.7	13 n.s.
SR 25990C	1.25	0.96	39.4 $\pm$ 1.3	7 n.s.
	2.5	1.92	28.4 $\pm$ 2.3	33 0.01
	5	3.84	14.0 $\pm$ 1.6	67 0.001
	10	7.69	8.5 $\pm$ 1.6	80 0.001
Controls			33.8 $\pm$ 2.3	
SR 25990E	10	3.84	9.6 $\pm$ 3	72 0.001
	20	7.69	4 $\pm$ 1.6	88 0.001
AGGREGATION HEIGHT				
Controls			103 $\pm$ 5	
PCR 4099	2.5	2.14	86 $\pm$ 5	17 0.05
(racemate)	5	4.28	72 $\pm$ 8	30 0.05
	12.5	10.71	32 $\pm$ 9	69 0.001
SR 25989A	25	22.46	101 $\pm$ 1	2 n.s.
SR 25990A	2.5	2.25	67 $\pm$ 7	35 0.01
	5	4.49	26 $\pm$ 5	75 0.001
	12.5	11.23	19 $\pm$ 4	82 0.001
	25	22.46	11 $\pm$ 1	89 0.001

*mean of results $\pm$ standard error of the mean (SEM)

**Student test

***aggregation height in mm: mean $\pm$ SEM (n = 5)

n.s. not significant

For the aggregation with collagen, the percentage of inhibition is the difference of the slopes of the curves representing the variation of the optical density as a function of time for the control and the product to be tested divided by the slope of the control multiplied by

100. The results shown in Table II demonstrate again that only the dextro-rotatory isomer is active whereas the salts have comparable activities.

TABLE II

PRO-DUCT	DOSE mg/Kg P.O.	QUANTITY of base administered	SLOPE	% IN-HIBITION	P**
Controls			4.8 $\pm$ 0.3		
PCR 4099	4.48	3.84	3.6 $\pm$ 0.2	25	0.05
(racemate)	8.97	7.69	2.7 $\pm$ 0.3	44	0.01
	17.9	15.38	1.5 $\pm$ 0.3	69	0.001
SR 25989C	20	15.38	4.3 $\pm$ 0.2	10	n.s.
	40	30.76	4.0 $\pm$ 0.2	17	n.s.
SR 25990C	1.25	0.96	4.5 $\pm$ 0.3	6	n.s.
	2.5	1.92	4.1 $\pm$ 0.2	15	n.s.
	5	3.84	2.3 $\pm$ 0.1	52	0.001
	10	7.69	1.7 $\pm$ 0.3	65	0.001
Controls			3.5 $\pm$ 0.1		
SR 25990E	10	3.84	2.1 $\pm$ 0.5	40	0.05
	20	7.69	1.4 $\pm$ 0.4	60	0.01
Controls			3.97 $\pm$ 0.29		
PCR 4099	2.5	2.14	3.13 $\pm$ 0.33	21	n.s.
(racemate)	5	4.28	2.94 $\pm$ 0.34	26	0.05
	12.5	10.71	2.19 $\pm$ 0.42	45	0.01
SR 25989A	25	22.46	4.32 $\pm$ 0.29	10	n.s.
SR 25990A	2.5	2.25	3.05 $\pm$ 0.19	23	0.05
	5	4.49	1.24 $\pm$ 0.22	69	0.001
	12.5	11.23	0.86 $\pm$ 0.14	78	0.001
	25	22.46	0.74 $\pm$ 0.13	81	0.001

**Student test
n.s. not significant

The antithrombotic activity of these compounds has also been studied in the test of venous thrombosis on a screw thread described by Kumada T. et al. in Thromb. Res 18 p. 189 (1980).

Female rats of the same type as those previously described, in groups of 10 animals, were anesthetized with diethyl ether and their vena cava was isolated after abdominal incision.

A metallic screw thread 21 mm long consisting of a dentist's drill, marketed by Dyna (France) size No. 30, was introduced into the lumen of this vein just below the renal bifurcation descending towards the iliac veins, without damaging the wall; 19 to 20 mm of the length of the screw thread are implanted and the remaining 1 mm protrudes through the closed stomach into the exterior.

The thrombi formed rapidly and five hours later, under pentobarbital anesthesia, the abdomen is reopened and ligatures are placed above and below the screw thread which is withdrawn after longitudinal incision of the vein and the isolated thrombus is weighed.

The results which are presented in Table III show that the levo-rotatory isomer is inactive in this test, in contrast to the dextro-rotatory isomer and the racemate.

TABLE III

PRO-DUCT	DOSE mg/Kg P.O.	QUANTITY of base admin.	WEIGHT of thrombi*	VARIATION %	P**
Controls			3.9 $\pm$ 0.3		
PCR 4099	4.48	3.84	2.17 $\pm$ 0.24	44	0.001
(racemate)	8.97	7.69	1.39 $\pm$ 0.15	64	0.001
	17.9	15.38	1.00 $\pm$ 0.19	74	0.001
SR 25989C	40	30.76	4.17 $\pm$ 0.42	-7	n.s.
SR 25990C	1.25	0.96	3.11 $\pm$ 0.32	20	n.s.
	2.5	1.92	2.29 $\pm$ 0.22	41	0.01
	5	3.84	1.71 $\pm$ 0.24	56	0.01
	10	7.69	1.26 $\pm$ 0.19	67	0.01
	20	15.38	1.20 $\pm$ 0.13	69	0.01

TABLE III-continued

PRO- DUCT	DOSE mg/Kg P.O admin.	QUAN- TITY of base	WEIGHT of thrombi*	VARIA- TION %	P**
Controls			3.78 +/- 0.36		
SR 25990E	10	3.84	1.48 +/- 0.15	60	0.001
	20	7.69	1.18 +/- 0.15	68	0.001

* = weight of thrombi in mg +/- standard error of the mean

P = U test of Kruskal - Wallis

For the toxicological study, the compounds were administered by the oral route in the form of a suspension in the same volume of water made up to 10% (wt/v) with gum arabic to groups of 10 fasted female rats of the Sprague Dawley strain weighing 120 to 135 grams.

The number of dead animals was determined 14 days after the administration of the compound under study. The lethal doses thus determined, expressed in weight of the salt administered, are presented in Table IV; these results show on the one hand that the toxicity of the racemic mixture is similar to that of the levo-rotatory isomer whereas the dextro-rotatory isomer is markedly less toxic, and, on the other hand, that the toxicity depends on the nature of the acid used to form the salt.

TABLE IV

PRODUCTS	D 10	D 50 ()	D 90	ABSOLUTE-LETHAL DOSE
PCR 4099 (racemate)	1318	1615 (1448-1747)	1979	2000
SR 25989 A	1259	1702 (1443-1797)	2299	2000
SR 25990 A	3055	4316 (3569-5705)	6137	5000
SR 25990 C	2257	2591 (2372-2805)	2974	4000
SR 25990 D	2634	4268 (3581-6012)	6914	5000

() = confidence interval

The pharmacological study just presented has demonstrated the interesting inhibitory properties towards platelet aggregation of the compound Id and the absence of any activity of its isomer II.

The medicine of the invention can be made available for oral administration in the form of tablets, sugar-coated tablets, capsules, drops, granules or a syrup. It can also be made available for rectal administration in the form of suppositories or for parenteral administration in the form of an injectable solution.

Each unit dose contains advantageously from 0.001 g to 0.100 g of the derivative of the invention, and the daily doses to be administered may vary from 0.001 g to 0.500 g of active ingredient depending on the age of the patient and the severity of the disorder to be treated. Some pharmaceutical formulations of the medicine of

the invention will be given below as non-restrictive examples.

(1) Tablets

Active ingredient: 0.010 g

5 Excipient: lactose, powdered sugar, rice-starch, alginic acid, magnesium stearate

(2) Sugar-coated tablets

Active ingredient: 0.005 g

10 Excipient: magnesium stearate, maize starch, gum arabic, shellac, white sugar, glucose, white wax, carnauba wax, paraffin, cochineal.

(3) Capsules

Active ingredient: 0.025 g

Excipient: magnesium stearate, maize starch, lactose.

15 (4) Injectable solution

Active ingredient: 0.050 g

Isotonic saline q.s.p. 3 ml.

(5) Suppositories

Active ingredient: 0.030 g

20 Semi-synthetic triglycerides q.s.p. 1 suppository.

On account of its interesting inhibitory properties towards platelet aggregation and its interference in the mechanism of formation of arterial and venous thromboses, the medicine of the invention can be usefully administered in the treatment and prevention of platelet disorders due to extracorporeal blood circuits or the consequence of complications in atheroma.

We claim:

1. Dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer and its pharmaceutically acceptable salts.

2. Hydrochloride of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

3. Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

4. Hydrobromide of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

5. Taurocholate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

6. Pharmaceutical composition which comprises an effective platelet aggregation inhibiting amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

7. Composition according to claim 6, comprising unit doses containing from 0.001 g to 0.100 g of active ingredient.

* * * * *

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clopidogrel hydrogensulfate crystal Form IV.

Example 31 - Preparation of clopidogrel hydrogensulfate Form IV

5 Clopidogrel base (2.96g) was dissolved in isopropanol (45 mL). Aqueous sulfuric acid (98%, 0.50ml) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and stirred at this temperature for an additional 2 hours to obtain a white precipitate. The solid was collected by filtration, washed with isopropanol (2x10ml) and dried at 50°C in a vacuum oven for 28 hours to obtain 2.78g (71%) of clopidogrel hydrogensulfate crystal
10 Form IV.

Example 32 - Preparation of clopidogrel hydrogensulfate Form IV

15 Clopidogrel base (2.91g) was dissolved in isopropanol (IPA) (44ml). Ninety eight percent aqueous sulfuric acid (0.32ml) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and stirred at this temperature for an additional 2 hours to obtain a white precipitate. The solid was collected by filtration, washed with IPA (2x10ml) and dried at 50°C in a vacuum oven for 26 hours to obtain 3.04g (80%) of clopidogrel hydrogensulfate crystal Form IV.

Example 33 - Preparation of clopidogrel hydrogensulfate Form IV

20 Clopidogrel base (2.93g) was dissolved in isopropanol (45ml). Sixty percent aqueous sulfuric acid (0.99 mL) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and stirred at this temperature for an additional 2.5 hours to obtain a white precipitate. The
25 solid was collected by filtration, washed with isopropanol (2x10ml) and dried at 50°C in a vacuum oven for 15 hours to obtain 2.22g (58%) of clopidogrel hydrogensulfate crystal Form IV.

Example 34 - Preparation of clopidogrel hydrogensulfate Form IV

30 Clopidogrel base (2.98g) was dissolved in isopropanol (45 mL). Sixty percent aqueous

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sulfuric acid (0.67ml) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and stirred at this temperature for additional 2 hours to obtain a white precipitate. The solid was collected by filtration, washed with IPA (2x10ml) and dried at 50°C in a vacuum oven for 15 hours to obtain 0.93g (24%) of clopidogrel hydrogensulfate crystal Form IV.

Example 35 - Preparation of clopidogrel hydrogensulfate Form IV

Clopidogrel base (2.85g) was dissolved in isopropanol (43 mL). Forty percent aqueous sulfuric acid (1.67 mL) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and stirred at this temperature for additional 3.5 hours to obtain a white precipitate. The solid was collected by filtration, washed with IPA (2x10ml) and dried at 50°C in a vacuum oven for 14.5 hours to obtain 1.47g (40%) of clopidogrel hydrogensulfate crystal Form IV.

Example 36 - Preparation of clopidogrel hydrogensulfate Form IV

Clopidogrel base (2.95g) was dissolved in isopropanol (45ml). Forty percent aqueous sulfuric acid (1.15 mL) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and stirred at this temperature for an additional 3.5 hours to obtain a white precipitate. The solid was collected by filtration, washed with IPA (2x10 mL) and dried at 50°C in a vacuum oven for 14.5 hours to obtain 0.49g (13%) of clopidogrel hydrogensulfate crystal Form IV.

Example 37 - Preparation of clopidogrel hydrogensulfate Form IV

Clopidogrel base (2.89g) was dissolved in isopropanol (44 mL). Eighty percent aqueous sulfuric acid (0.42 mL) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. The solution was cooled to room temperature and stirred at this temperature for an additional 5 hours. Then half of the solvent was removed by evaporation under reduced pressure and the resulting solution was stored at room temperature for 45 minutes to obtain a white precipitate. The solid was collected by filtration, washed with IPA (3x10ml) and dried at 50°C in a vacuum oven for 15 hours to

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obtain 1.24g (33%) of clopidogrel hydrogensulfate crystal Form IV.

Example 38 - Preparation of clopidogrel hydrogensulfate Form IV

Clopidogrel base (2.96g) was dissolved in isopropanol (IPA) (45 mL). Eighty percent
5 aqueous sulfuric acid (0.65 mL) was added to the solution at 20°C. The reaction mixture
was heated to reflux temperature for 2 hours. Then, the solution was cooled to room
temperature and stirred at this temperature for an additional 1.5 hours to obtain a white
precipitate. The solid was collected by filtration, washed with IPA (2x10ml) and dried at
10 50°C in a vacuum oven for 15 hours to obtain 3.24g (84%) of clopidogrel hydrogensulfate
crystal Form IV.

Example 39 - Preparation of clopidogrel hydrogensulfate Form V

Clopidogrel hydrogensulfate (3 grams) was dissolved in 2-butanol (9 mL) at reflux
temperature. The resulting solution was cooled to room temperature and methyl tert-
15 butylether (MTBE) (40 mL) was added drop wise. The obtained mixture was stirred at
room temperature for 72 hours. The solid was then filtered and dried at 50°C in a vacuum
oven for 24 hours to give 3.15g of clopidogrel hydrogensulfate crystal Form V.

Example 40 - Preparation of clopidogrel hydrogensulfate Form V

Clopidogrel hydrogensulfate (3 grams) was dissolved in 2-butanol (8 mL) at reflux
temperature. The resulting solution was cooled to room temperature and the solvent was
20 evaporated to dryness under reduced pressure. Then diethylether (DEE) (26 mL) was
added drop wise and the obtained mixture was stirred at room temperature for 24 hours.
The solid was then filtered and dried at 50°C in a vacuum oven for 24 hours to give 3.08g
25 of clopidogrel hydrogensulfate crystal Form V.

Example 41 - Preparation of clopidogrel hydrogensulfate Form V

Clopidogrel hydrogensulfate (3 grams) was dissolved in 2-butanol (14 mL) at reflux
30 temperature. The resulting solution was cooled to room temperature. Then MTBE (35 mL)
was added drop wise and the obtained mixture was stirred at room temperature for 16

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hours. Additional MTBE (11 mL) was added and the suspension was stirred at room temperature for additional 2 hours. The solid was filtered, washed with MTBE (25 mL) and dried at 65°C in a vacuum oven for 24 hours to give 2.95g (98%) of clopidogrel hydrogensulfate crystal Form V.

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Example 42 - Preparation of clopidogrel hydrogensulfate Form V

Clopidogrel base (2.98g) was dissolved in 2-butanol (23 mL). Ninety eight percent aqueous sulfuric acid (0.50 mL) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. The solution was cooled to room temperature and stirred at this temperature for an additional 3 hours. Then the solvent was evaporated to dryness under reduced pressure to obtain an oil. Then tert-butyl methyl ether (MTBE) (44 mL) was added to the oily residue and the resulting mixture was stirred at room temperature for 16 hours. The precipitate was collected by filtration, washed with MTBE (2x10ml) and dried at 50°C in a vacuum oven for 22.5 hours to obtain 3.38g (87%) of clopidogrel hydrogensulfate crystal Form V.

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Example 43 - Preparation of clopidogrel hydrogensulfate Form V

Clopidogrel base (2.94g) was dissolved in 2-butanol (23 mL). Ninety eight percent aqueous sulfuric acid (0.43mL) was added to the solution at 20°C. The reaction mixture was heated to reflex temperature for 2 hours. The solution was cooled to room temperature and stirred at this temperature for additional 1.5 hours. Then the solvent was evaporated to dryness under reduced pressure to obtain oil. Then diethyl ether (DEE) (40ml) was added to the oily residue and the resulting mixture was stirred at room temperature for 16 hours. The precipitate was collected by filtration, washed with DEE (2x10 mL) and dried at 50°C in a vacuum oven for 19 hours to obtain 2.11 g (55%) of clopidogrel hydrogensulfate crystal Form V.

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Example 44 - Preparation of clopidogrel hydrogensulfate Form VI

Clopidogrel base (2.86g, 1 eq.) was dissolved in 1-Propanol (22.6 mL). Eighty percent aqueous sulfuric acid (0.59 mL, 0.66eq.) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and stirred at this temperature for additional 16 hours. The solvent was

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5 evaporated to dryness under reduced pressure to obtain an oily residue. To the residue, MTBE (50 mL) was added and the resulting mixture was stirred at room temperature for 24 hours during which a massive precipitate was formed. The white solid was collected by filtration, washed with MTBE (2x10 mL) and dried at 50°C in a vacuum oven for 30 hours to obtain 2.58g (69%) of clopidogrel hydrogensulfate crystal Form VI.

10 Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to, limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications. Polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Sciences, Volume 95 can be used as a guidance. All references mentioned herein are
15 incorporated in their entirety.

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153**CLAIMS**

What is claimed is:

- 5 1. Clopidogrel hydrogensulfate characterized by data selected from the group consisting of: a powder X-ray diffraction pattern with peaks at about 8.1, 8.7, 14.3, 15.4, 20.1, 22.3, 22.5, 23.5, and 24.1 ± 0.2 degrees two-theta, a differential scanning calorimetric thermogram having an endothermic peak at about 105°C and a FTIR spectrum with peaks at about 581, 707, 755, 971, 1057, 1196, 1252, 1436,
10 1476, 1748, 2590, 2670 and 2963 cm^{-1} .
2. The clopidogrel hydrogensulfate of claim 1 characterized by a differential scanning calorimetric thermogram having an endothermic peak at about 105°C .
- 15 3. The clopidogrel hydrogensulfate of claim 1 or 2 characterized by a FTIR spectrum with peaks at about 581, 707, 755, 971, 1057, 1196, 1252, 1436, 1476, 1748, 2590, 2670 and 2963 cm^{-1} .
4. The clopidogrel hydrogensulfate of claim 3 further characterized by a FTIR
20 spectrum peaks at about 886, 1323, 1594 cm^{-1} .
5. The clopidogrel hydrogensulfate of claim 4 characterized by a FTIR spectrum as substantially depicted in Fig. 3.
- 25 6. The clopidogrel hydrogensulfate of claim 1, 2, 3, 4 or 5, having a powder X-ray diffraction pattern with peaks at about 8.1, 8.7, 14.3, 15.4, 20.1, 22.3, 22.5, 23.5, and 24.1 ± 0.2 degrees two-theta.
7. The clopidogrel hydrogensulfate of claim 6 further characterized by a powder
30 X-ray diffraction pattern as substantially depicted in Fig 1.

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8. A process for preparing clopidogrel hydrogensulfate of claim 1, 2, 3, 4, 5, 6 or 7 comprising the steps of:
- a) preparing a solution of clopidogrel hydrogensulfate in 1-butanol;
 - b) removing the 1-butanol from the solution to obtain a residue;
 - 5 c) admixing an antisolvent with the residue to precipitate clopidogrel hydrogensulfate; and
 - d) separating the clopidogrel hydrogensulfate.
9. The process of claim 8, further comprising a step of drying the clopidogrel hydrogensulfate.
10. Clopidogrel hydrogensulfate characterized by data selected from the group consisting of: a PXRD pattern as substantially depicted in Fig. 4. and a FTIR spectrum with peaks at about 583, 723, 762, 846, 1040, 1167, 1223, 1438, 1478, 15 1638, 1752, 2585 and 2960 cm^{-1} .
11. The clopidogrel hydrogensulfate of claim 10 characterized by a FTIR spectrum with peaks at about 583, 723, 762, 846, 1040, 1167, 1223, 1438, 1478, 1638, 1752, 2585 and 2960 cm^{-1} .
12. The clopidogrel hydrogensulfate of claim 11 having a FTIR spectrum as substantially depicted in Fig. 5.
13. The clopidogrel hydrogensulfate of claim 10, 11 or 12 characterized by a PXRD pattern as substantially depicted in Fig. 4.
14. A process for preparing clopidogrel hydrogensulfate of claim 10, 11, 12 or 13, comprising the steps of:
- a) preparing a solution of clopidogrel hydrogensulfate in an alcohol selected from the group consisting of methanol and ethanol;
 - 30 b) admixing the solution with an antisolvent to precipitate clopidogrel

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hydrogensulfate, and

c) separating the clopidogrel hydrogensulfate.

5 15. The process of claim 14, wherein admixing involves adding the solution to the antisolvent.

16. The process of claim 14 or 15, wherein a portion of the precipitate, when ether is used an anti-solvent, is converted into Form I before separation.

10 17. A process for preparing clopidogrel hydrogensulfate of claim 10, 11, 12 or 13, comprising the steps of:

a) preparing a solution of clopidogrel hydrogensulfate in an alcohol selected from the group consisting of methanol and ethanol;

b) removing the alcohol from the solution to obtain a residue;

15 c) admixing an antisolvent with the residue to precipitate clopidogrel hydrogensulfate; and

d) separating the clopidogrel hydrogensulfate.

20 18. The process of claim 17, wherein a portion of the precipitate, when ether is used as an antisolvent, is converted into Form I before separating the ether.

19. A process for preparing clopidogrel hydrogensulfate of claim 10, 11, 12 or 13 comprising the steps of:

25 a) preparing a solution of clopidogrel hydrogensulfate in an alcohol selected from the group consisting of methanol and ethanol;

b) admixing the solution with an antisolvent; and

c) removing the alcohol and the antisolvent.

30 20. The process of claim 19, wherein admixing involves adding the solution to the antisolvent.

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21. The process of claim 19 or 20, further comprising a step of concentrating the solution before admixing the antisolvent.
22. The process of claim 19, 20 or 21, wherein the antisolvent is a one ring aromatic hydrocarbon.
23. The process of claim 22, wherein the one ring aromatic hydrocarbon is selected from the group consisting of xylene, toluene and benzene.
24. The process of claim 23, wherein the one ring aromatic hydrocarbon is toluene.
25. A process for preparing clopidogrel hydrogensulfate of claim 10, 11, 12 or 13 comprising the steps of:
- a) preparing a solution of clopidogrel hydrogensulfate in acetone; and
 - b) removing the acetone.
26. A process for preparing clopidogrel hydrogensulfate Form I comprising contacting amorphous clopidogrel hydrogensulfate with an ether, and separating the clopidogrel hydrogensulfate Form I.
27. The process of claim 26, wherein each alkyl radical of the ether is independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, 1-butyl, 2-butyl and t-butyl.
28. The process of claim 27, wherein the ether is selected from the group consisting of diethyl ether and methyl t-butyl ether.
29. The process of claim 26, wherein the amorphous clopidogrel hydrogensulfate is suspended in ether.
30. The process of claim 29, wherein the clopidogrel hydrogensulfate is suspended in

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ether for more than about 1 hour.

31. The process of claim 30, wherein the amorphous clopidogrel hydrogensulfate is suspended in ether for more than about 4 hours to obtain substantially Form 1.

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32. Clopidogrel hydrogensulfate characterized by data selected from the group consisting of: a PXRD pattern with peaks at about 22.0, 25.9, 26.9, 27.4, 28.1, 28.6 and 28.9 ± 0.2 degrees two theta, a DSC thermogram with an endothermic peak at about 160-170°C and a FTIR spectrum with peaks at about 618, 769, 842, 893, 935, 974, 1038, 1116, 1370, 1384 cm^{-1} .

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33. The clopidogrel hydrogensulfate of claim 32 further characterized by a DSC thermogram with an endothermic peak at about 160-170°C.

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34. The clopidogrel hydrogensulfate of claim 32 or 33 characterized by a FTIR spectrum with peaks at about 618, 769, 842, 893, 935, 974, 1038, 1116, 1370, 1384 cm^{-1} .

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35. The clopidogrel hydrogensulfate of claim 34, further characterized by a FTIR spectrum as substantially depicted in Fig 8.

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36. The clopidogrel hydrogensulfate of claim 32, 33, 34 or 35 characterized by a PXRD pattern with peaks at about 22.0, 25.9, 26.9, 27.4, 28.1, 28.6 and 28.9 ± 0.2 degrees two theta.

37. The clopidogrel hydrogensulfate of claim 36 further characterized by a PXRD pattern with peaks at about 11.0, 12.5, 13.3, 14.0, 17.6, 18.2, 18.8, 20.5, 22.9, 24.1 ± 0.2 degrees two theta.

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38. The clopidogrel hydrogensulfate of claim 37, further characterized by a PXRD pattern as substantially depicted in Fig. 6.

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39. A process for preparing clopidogrel hydrogensulfate of claim 32, 33, 34, 35, 36, 37 or 38 comprising the steps of:
- a) preparing a solution of clopidogrel hydrogensulfate in isopropanol;
 - b) precipitating clopidogrel hydrogensulfate; and
 - c) separating the clopidogrel hydrogensulfate.
40. A process for preparing clopidogrel hydrogensulfate of claim 32, 33, 34, 35, 36, 37 or 38 comprising the steps of:
- a) preparing a solution of clopidogrel hydrogensulfate in isopropanol; and
 - b) removing the isopropanol.
41. Clopidogrel hydrogensulfate characterized by data selected from the group consisting of: a PXRD diffraction pattern with peaks at about 25.5, 26.6, 27.8 and 28.5 ± 0.2 degrees two theta, a DSC profile with an endothermic peak at about 126-132°C and a FTIR spectrum with peaks at about 623, 743, 802, 817, 843, 963, 972, 1028 and 1374 cm^{-1} .
42. The clopidogrel hydrogensulfate of claim 41 characterized by a DSC profile with an endothermic peak at about 126-132°C.
43. The clopidogrel hydrogensulfate of claim 41 or 42 characterized by a FTIR spectrum with peaks at about 623, 743, 802, 817, 843, 963, 972, 1028 and 1374 cm^{-1} .
44. The clopidogrel hydrogensulfate of claim 43, characterized by a FTIR spectrum as substantially depicted in Fig 11.
45. The clopidogrel hydrogensulfate of claim 41, 42, 43 or 44 characterized by a PXRD diffraction pattern with peaks at about 25.5, 26.6, 27.8 and 28.5 ± 0.2 degrees two theta.

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46. The clopidogrel hydrogensulfate of claim 45 further characterized by a PXRD pattern with peaks at about 11.0, 12.4, 13.1, 13.8, 15.2, 17.5, 18.1±0.2 degrees two theta.

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47. The clopidogrel hydrogensulfate of claim 46 further characterized by a PXRD pattern as substantially depicted in Fig. 9.

48. A process for preparing clopidogrel of claim 41, 42, 43, 44, 45, 46 or 47 comprising the steps of:

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- a) preparing a solution of clopidogrel hydrogensulfate in 2-butanol;
- b) admixing an antisolvent with the solution to precipitate clopidogrel hydrogensulfate; and
- c) separating the clopidogrel hydrogensulfate.

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49. The process of claim 48, wherein admixing involves addition of the antisolvent to the solution.

50. A process for preparing clopidogrel of claim 41, 42, 43, 44, 45, 46 or 47 comprising the steps of:

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- a) preparing a solution of clopidogrel hydrogensulfate in 2-butanol;
- b) removing the 2-butanol from the solution to obtain a residue;
- c) admixing an antisolvent with the residue to precipitate clopidogrel hydrogensulfate; and
- d) separating the clopidogrel hydrogensulfate.

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51. Clopidogrel hydrogensulfate characterized by data selected from the group consisting of: a powder X-ray diffraction pattern with peaks at about 8.3, 9.1, 23.2, 23.6 ±0.2 degrees two-theta, a differential scanning calorimetric thermogram having an endothermic peak at about 136°C and a FTIR spectrum with peaks at about 959, 1061, 1430, 1751, 1757 and 3119 cm⁻¹.

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52. Clopidogrel hydrogensulfate of claim 51 characterized by a differential scanning calorimetric thermogram having an endothermic peak at about 136°C.
- 5 53. Clopidogrel hydrogensulfate of claim 51 or 52 having a FTIR spectrum with peaks at about 959, 1061, 1430, 1751, 1757 and 3119 cm^{-1} .
54. The clopidogrel hydrogensulfate of claim 53 further characterized by a FTIR spectrum as substantially depicted in Fig. 14.
- 10 55. Clopidogrel hydrogensulfate having of claim 51, 52, 53 or 54 having a powder X-ray diffraction pattern with peaks at about 8.3, 9.1, 23.2, 23.6 ± 0.2 degrees two-theta.
- 15 56. The clopidogrel hydrogensulfate of claim 55 further characterized by a powder X-ray diffraction pattern as substantially depicted in Fig. 12.
57. A process for preparing clopidogrel hydrogensulfate of claim 51, 52, 53, 54, 55 or 56 comprising the steps of:
- 20 a) preparing a solution of clopidogrel hydrogensulfate in 1-propanol,
b) removing the 1-propanol from the solution to obtain a residue;
c) admixing an antisolvent with the residue to precipitate clopidogrel hydrogensulfate; and
d) separating the clopidogrel hydrogensulfate.
- 25 58. The process of claim 8, 17, 19, 25, 40, 50 and 57, wherein removing is carried out by evaporation.
59. The clopidogrel hydrogensulfate prepared by the process of claim 8, 14, 17, 19, 25,
30 39, 40, 48, 50 or 57.

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60. The process of claim 8, 39, 40, 48, 50 or 57, wherein the process results in a clopidogrel hydrogensulfate with a purity of at least about 99% as measured by area percentage with HPLC.

5 61. A process for preparing clopidogrel hydrogensulfate Form II comprising the steps of:

- a) preparing a solution of clopidogrel hydrogensulfate in a solvent selected from the group consisting of dichloromethane, 1,4-dioxane, toluene, chloroform, ethyl acetate, methylethyl ketone and t butylmethyl ether;
- 10 b) precipitating clopidogrel hydrogensulfate from the solution; and
- c) separating the clopidogrel hydrogensulfate.

62. The process of claim 61, wherein the solvent is dichloromethane.

15 63. The process of claim 61, wherein the solvent is 1,4-dioxane.

64. The process of claim 61, wherein the solvent is toluene.

65. The process of claim 61, wherein the solvent is chloroform.

20 66. The process of claim 61, wherein the solvent is ethyl acetate.

67. The process of claim 61, wherein the solvent is methylethyl ketone.

25 68. The process of claim 61, wherein the solvent is t-butylmethyl ether.

69. A process for preparing clopidogrel hydrogensulfate Form II comprising the steps of:

- a) preparing a solution of clopidogrel hydrogensulfate in acetonitrile;
- 30 b) admixing the solution with an antisolvent to precipitate clopidogrel hydrogensulfate; and

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c) separating the precipitate.

70. The process of claim 69, wherein the admixing involves addition of the solution to the antisolvent.

5

71. The process of claim 69, wherein the clopidogrel hydrogensulfate used to prepare the solution is amorphous clopidogrel hydrogensulfate.

72. The process of claim 8, 14, 17, 48, 50, 57 or 69, wherein the antisolvent is an ether.

10

73. The process of claim 72, wherein each alkyl radical of the ether is independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, 1-butyl, 2-butyl and t-butyl.

15

74. The process of claim 73, wherein the ether is diethyl ether.

75. The process of claim 8, 14, 17, 19, 25, 39, 40, 48, 50, 57, 61 or 69, wherein preparing a solution includes converting clopidogrel base to clopidogrel hydrogensulfate by contact with hydrosulfuric acid in solvent of the resulting solution.

20

76. A pharmaceutical composition comprising clopidogrel hydrogensulfate Form III, and a pharmaceutically acceptable excipient.

25

77. A pharmaceutical composition comprising clopidogrel hydrogensulfate Form IV, and a pharmaceutically acceptable excipient.

78. A pharmaceutical composition comprising clopidogrel hydrogensulfate Form V, and a pharmaceutically acceptable excipient.

30

79. A pharmaceutical composition comprising clopidogrel hydrogensulfate Form VI,

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and a pharmaceutically acceptable excipient.

80. A pharmaceutical composition comprising clopidogrel hydrogensulfate amorphous form, and a pharmaceutically acceptable excipient.

5

81. A method of inhibiting platelet aggregation comprising administering the pharmaceutical composition of claim 76, 77, 78, 79 or 80.

82. Clopidogrel hydrogensulfate 1-butanol solvate.

10

83. The clopidogrel hydrogensulfate of claim 82, wherein the 1-butanol content is about 7% to about 8% by weight.

84. Clopidogrel hydrogensulfate isopropanol solvate.

15

85. The clopidogrel hydrogensulfate of claim 84, wherein the isopropanol content is about 3% to about 9% by weight.

86. Clopidogrel hydrogensulfate 2-butanol solvate.

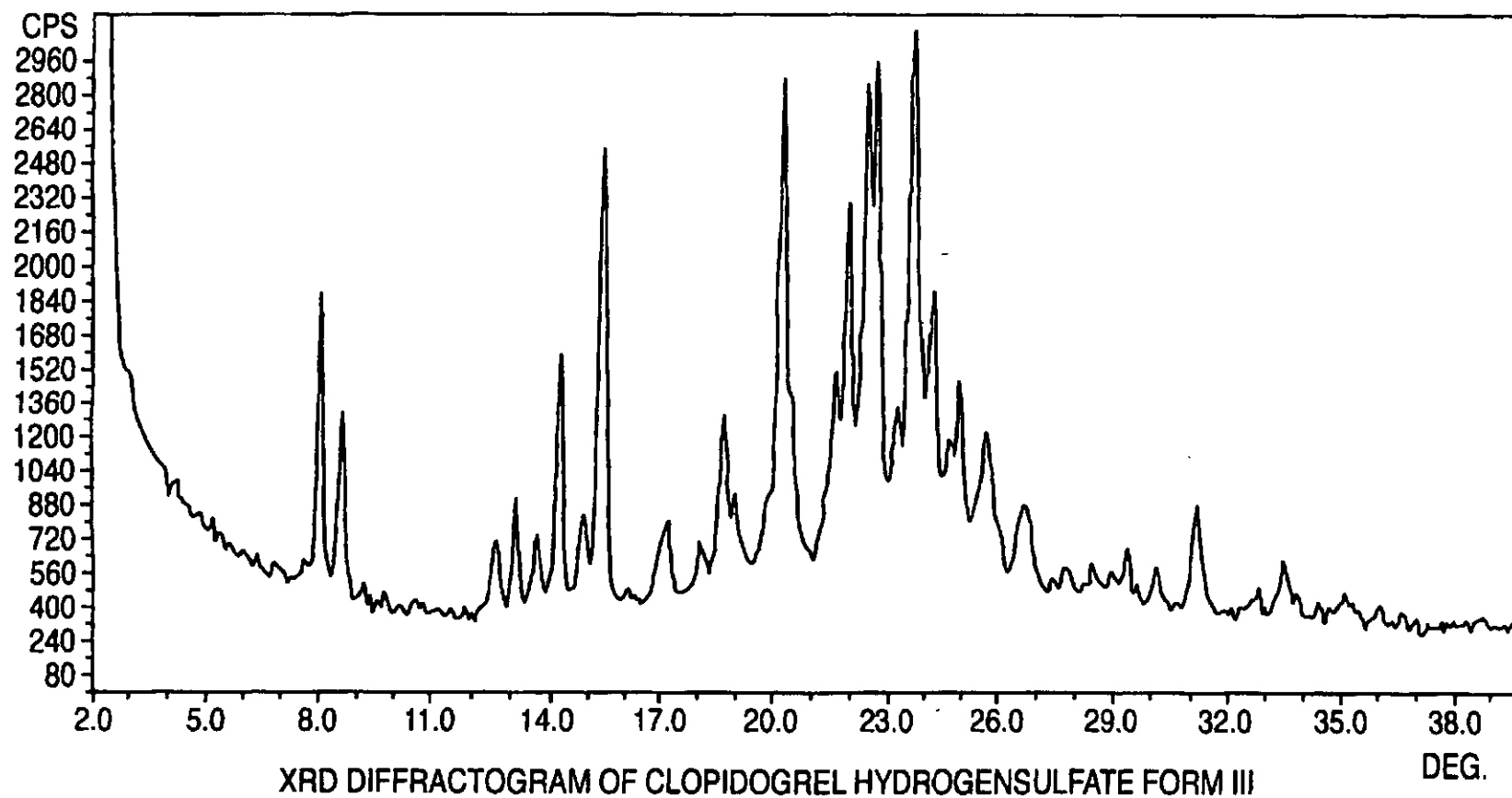
20

87. The clopidogrel hydrogensulfate of claim 86, wherein the 2-butanol content is about 9% to about 10% by weight.

88. Clopidogrel hydrogensulfate 1-propanol solvate.

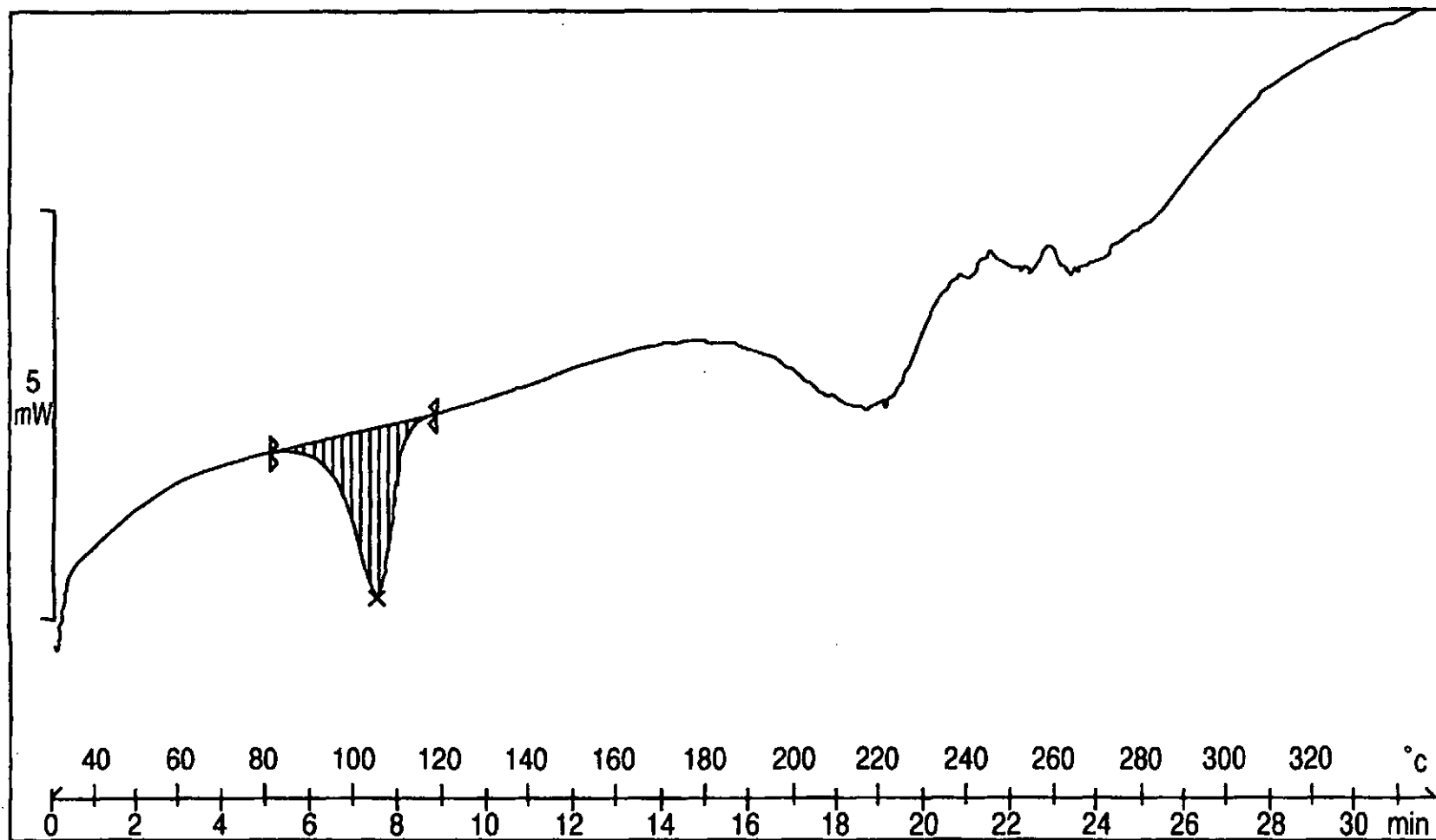
25

89. The clopidogrel hydrogensulfate of claim 88, wherein the 1-propanol content is about 6% by weight.



XRD DIFFRACTOGRAM OF CLOPIDOGREL HYDROGENSULFATE FORM III

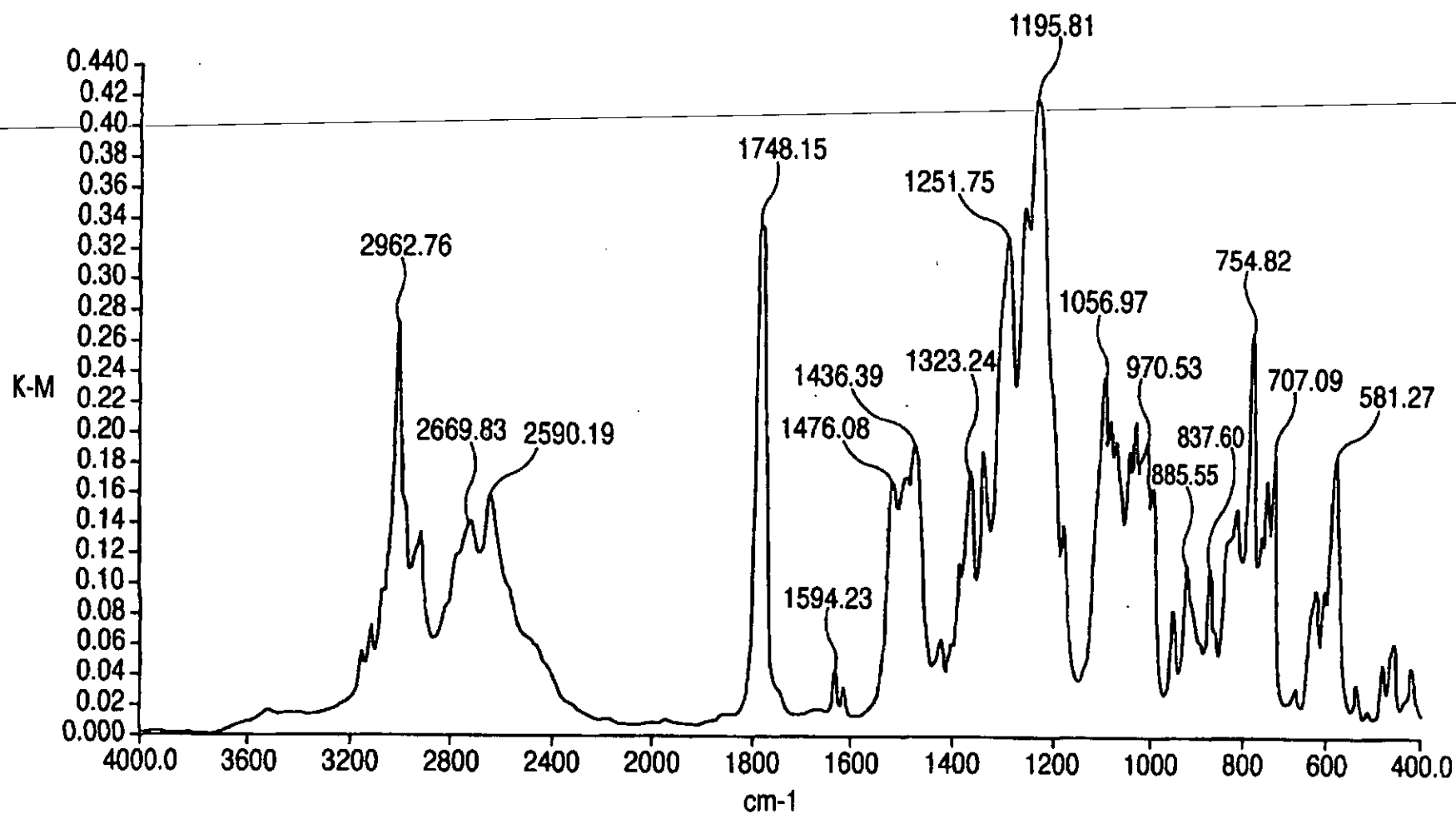
FIG. 1



DSC THERMOGRAM OF CLOPIDOGREL HYDROGENSULFATE FORM III

FIG. 2

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FTIR SPECTRUM OF CLOPIDOGREL HYDROGENSULFATE FORM III

FIG. 3

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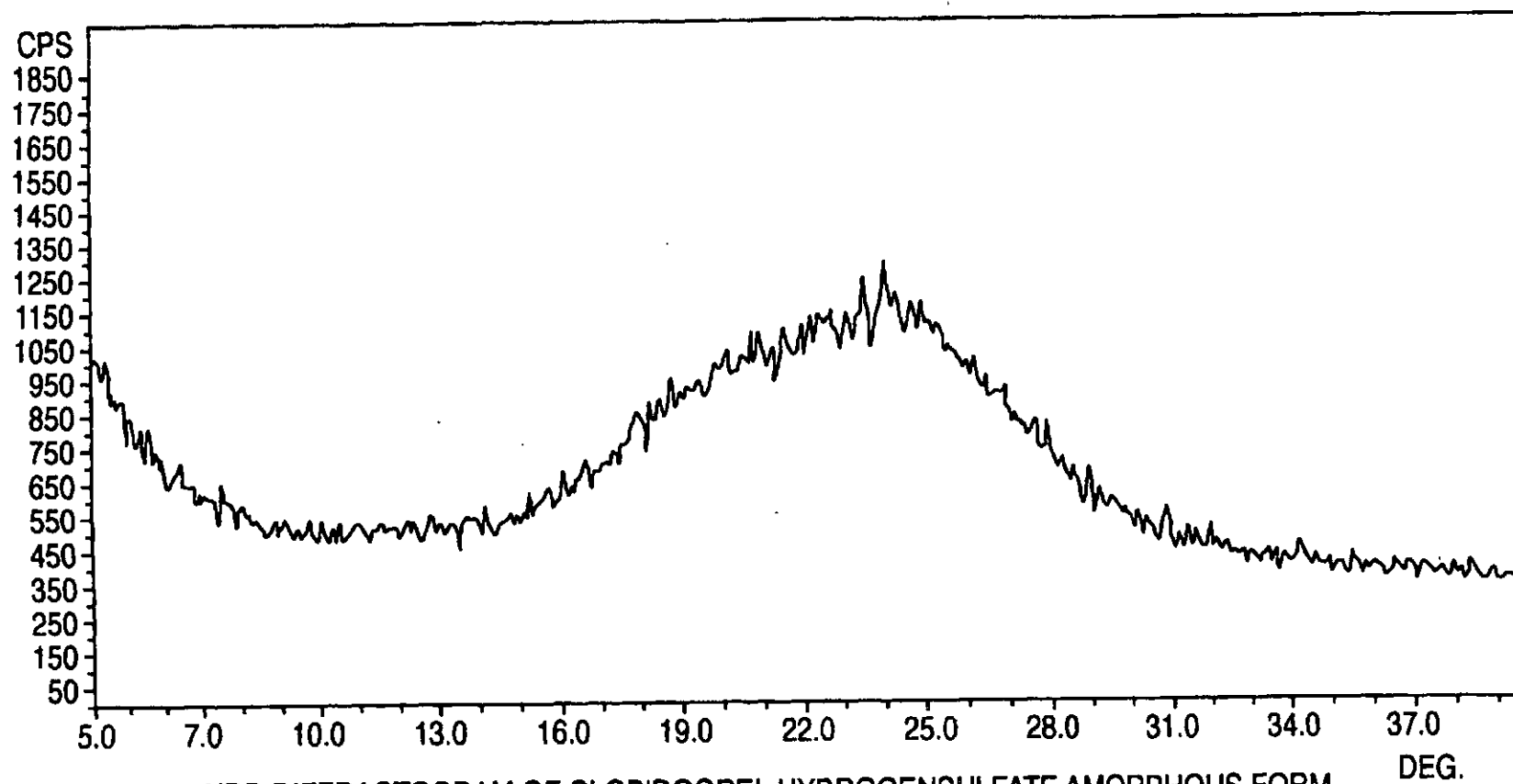
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XRD DIFFRACTOGRAM OF CLOPIDOGREL HYDROGENSULFATE AMORPHOUS FORM

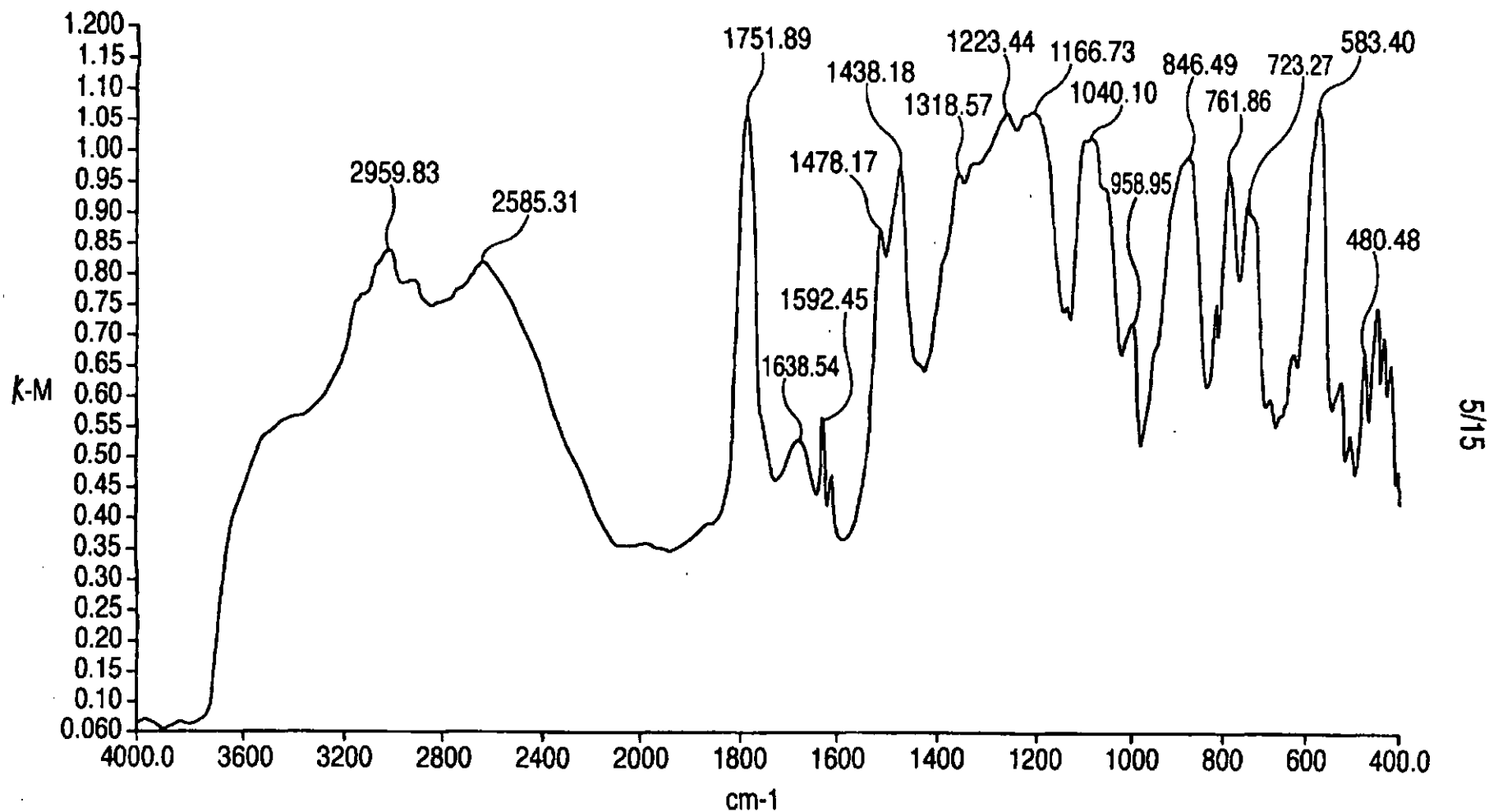
FIG. 4

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FTIR SPECTRUM OF CLOPIDOGREL HYDROGENSULFATE AMORPHOUS FORM

FIG. 5

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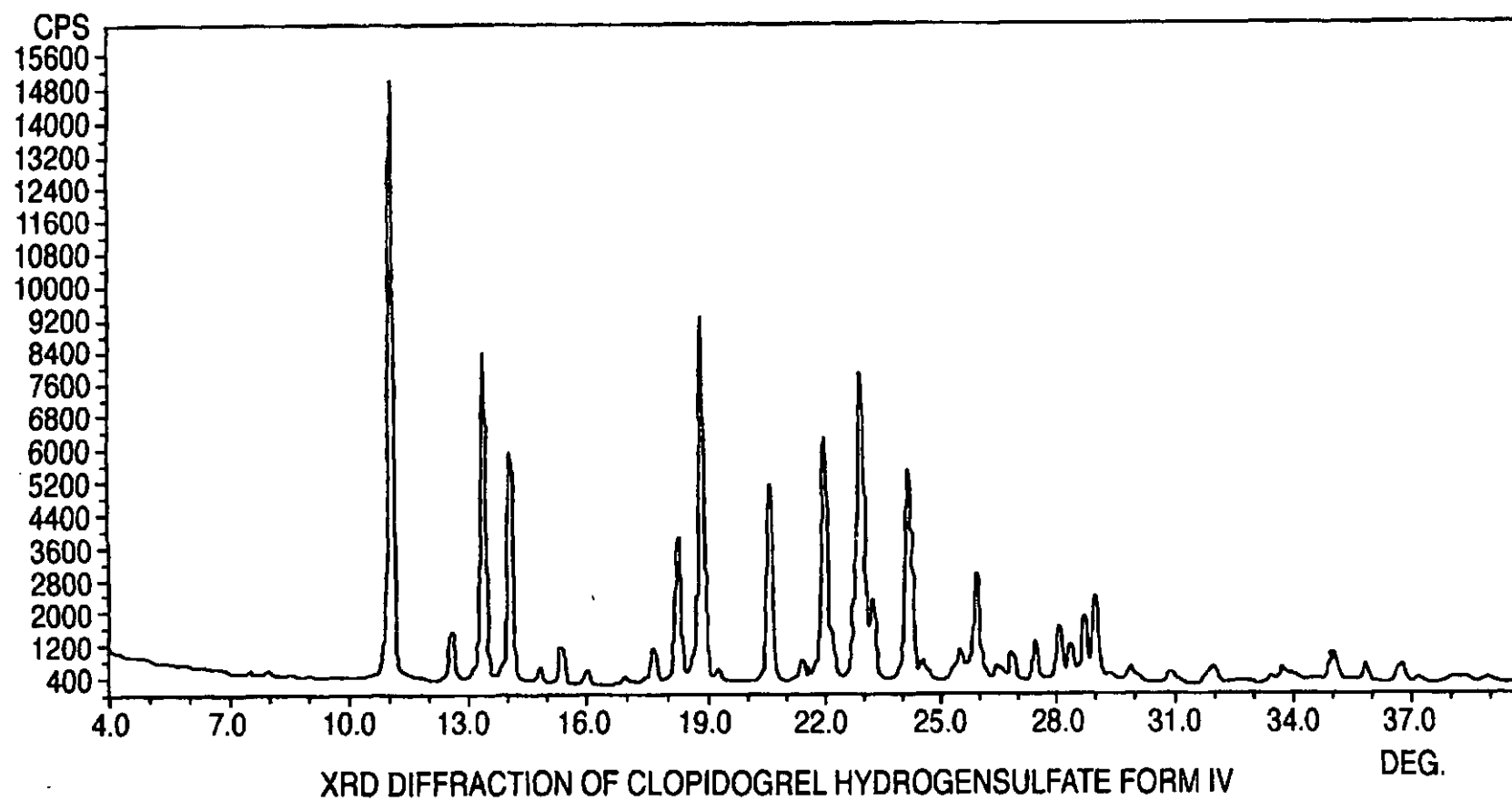


FIG. 6

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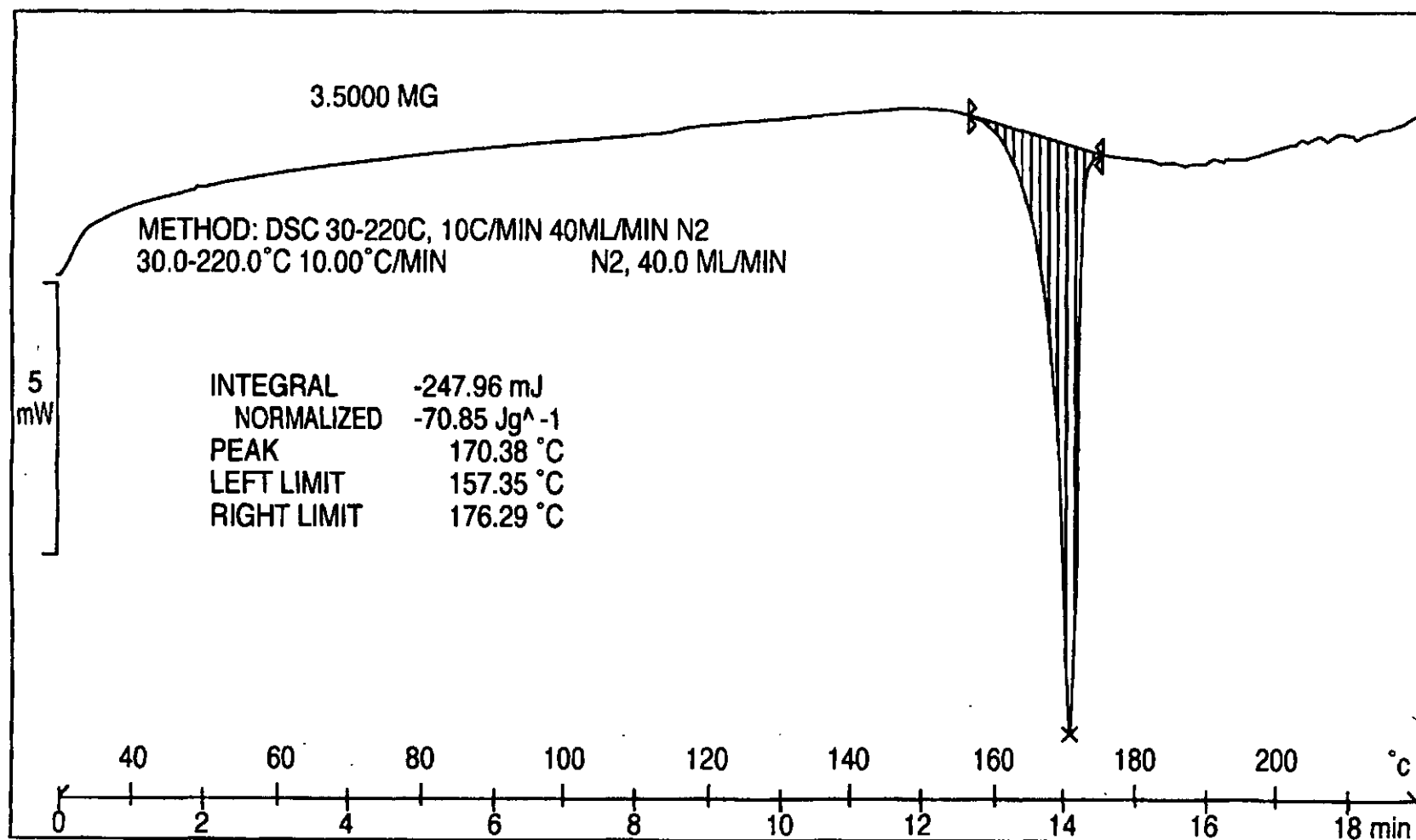


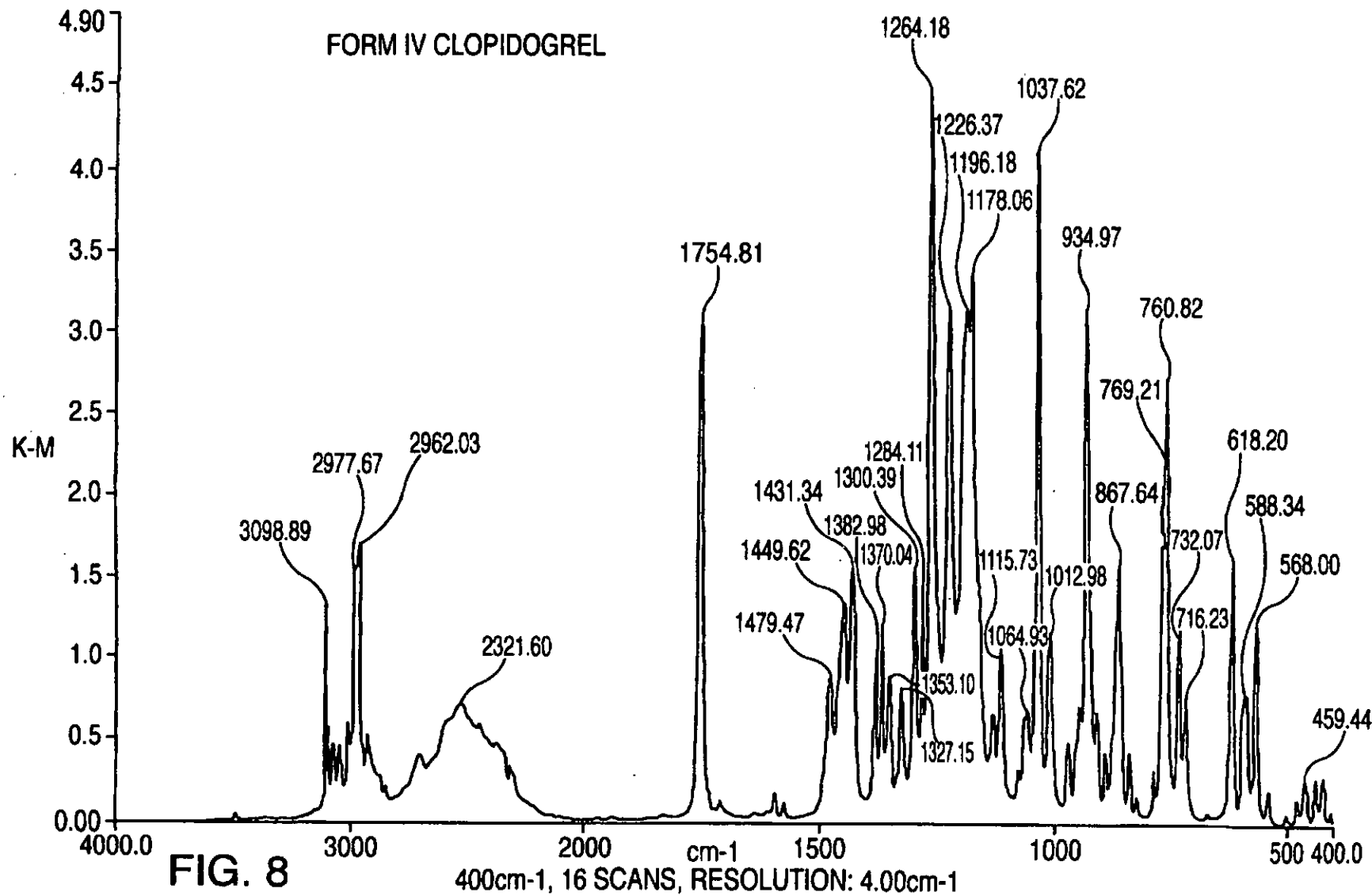
FIG. 7

METTLER TOLEDO STAR® SYSTEM

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FORM IV CLOPIDOGREL



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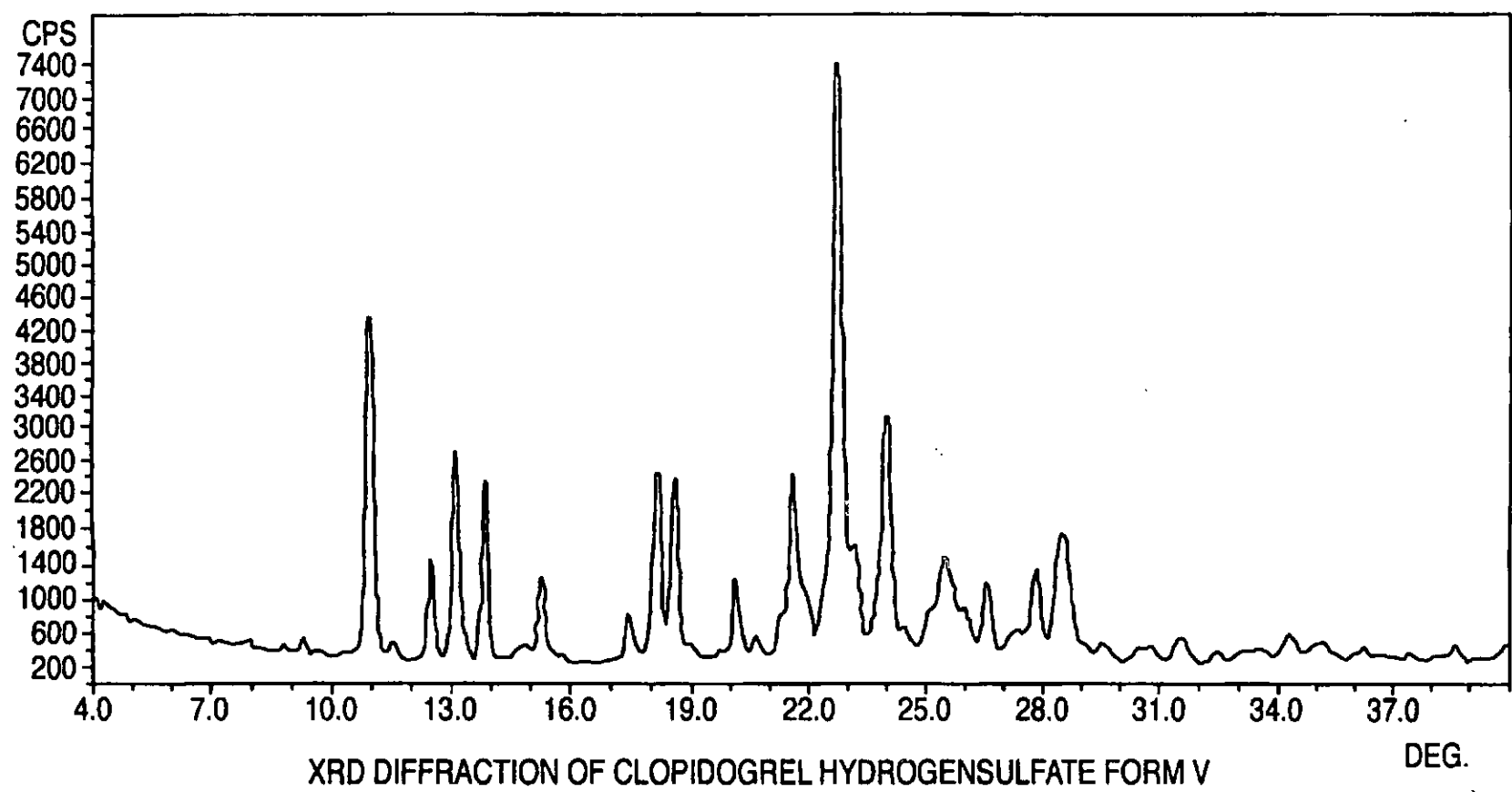


FIG. 9

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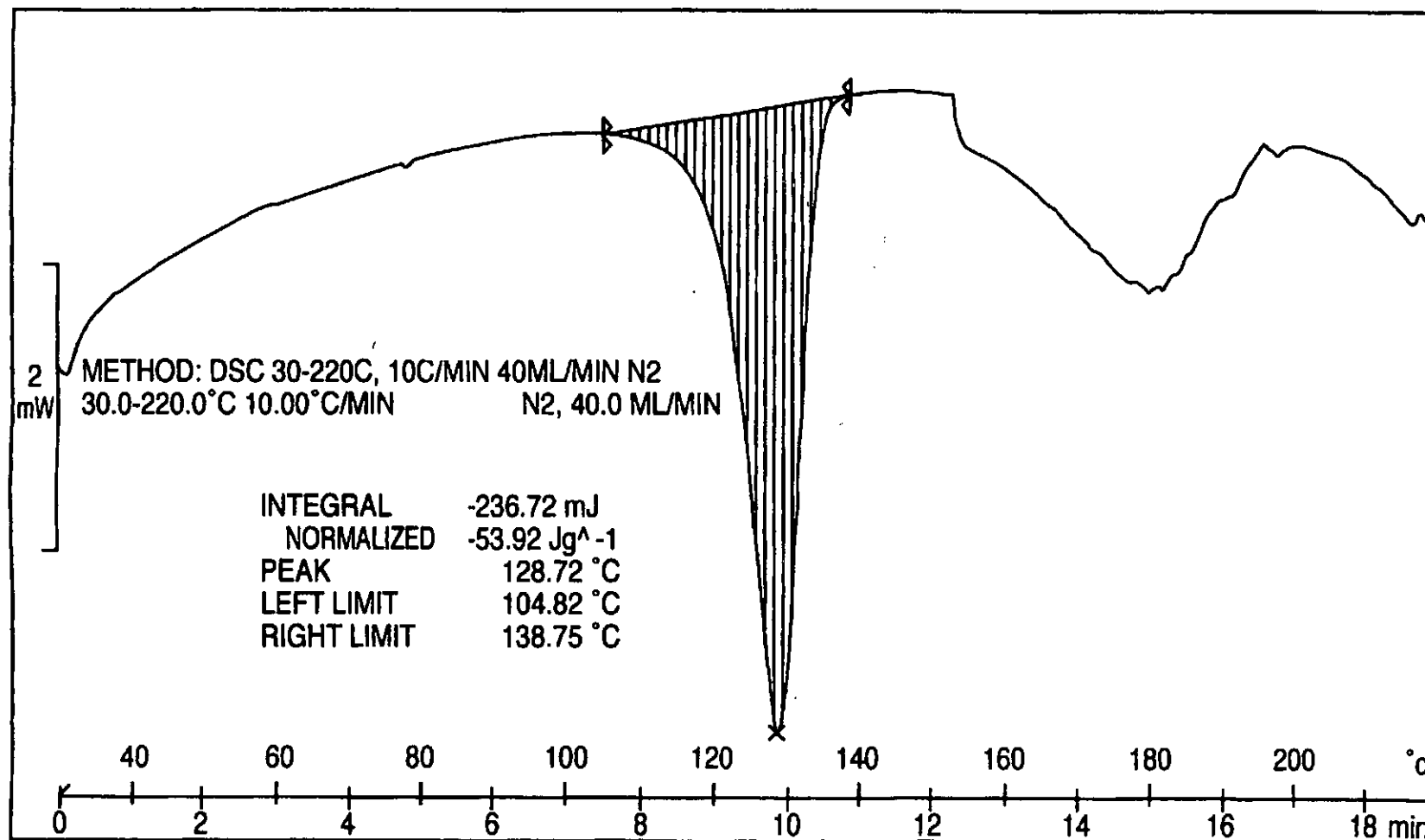
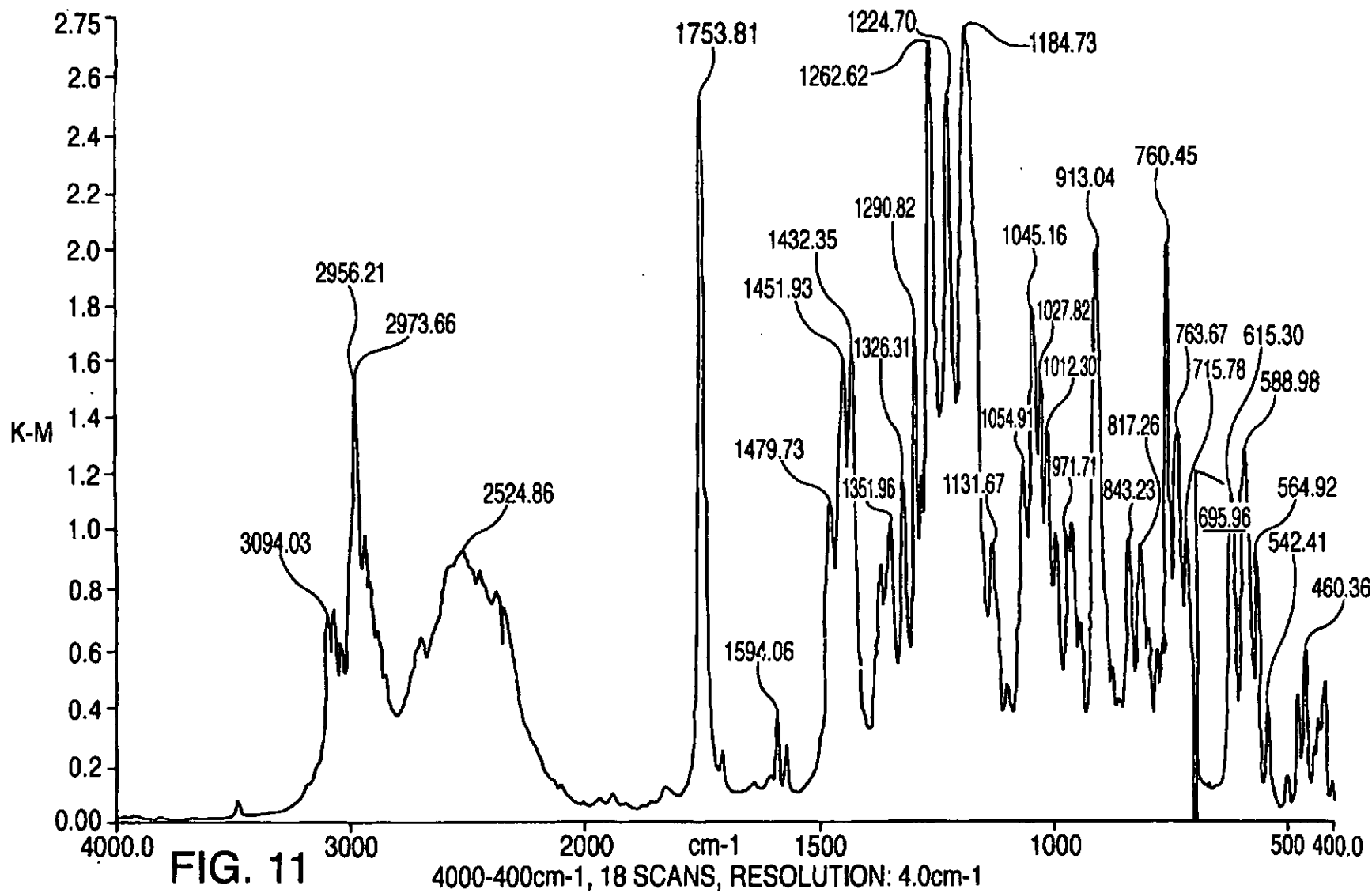


FIG. 10

METTLER TOLEDO STAR^e SYSTEM

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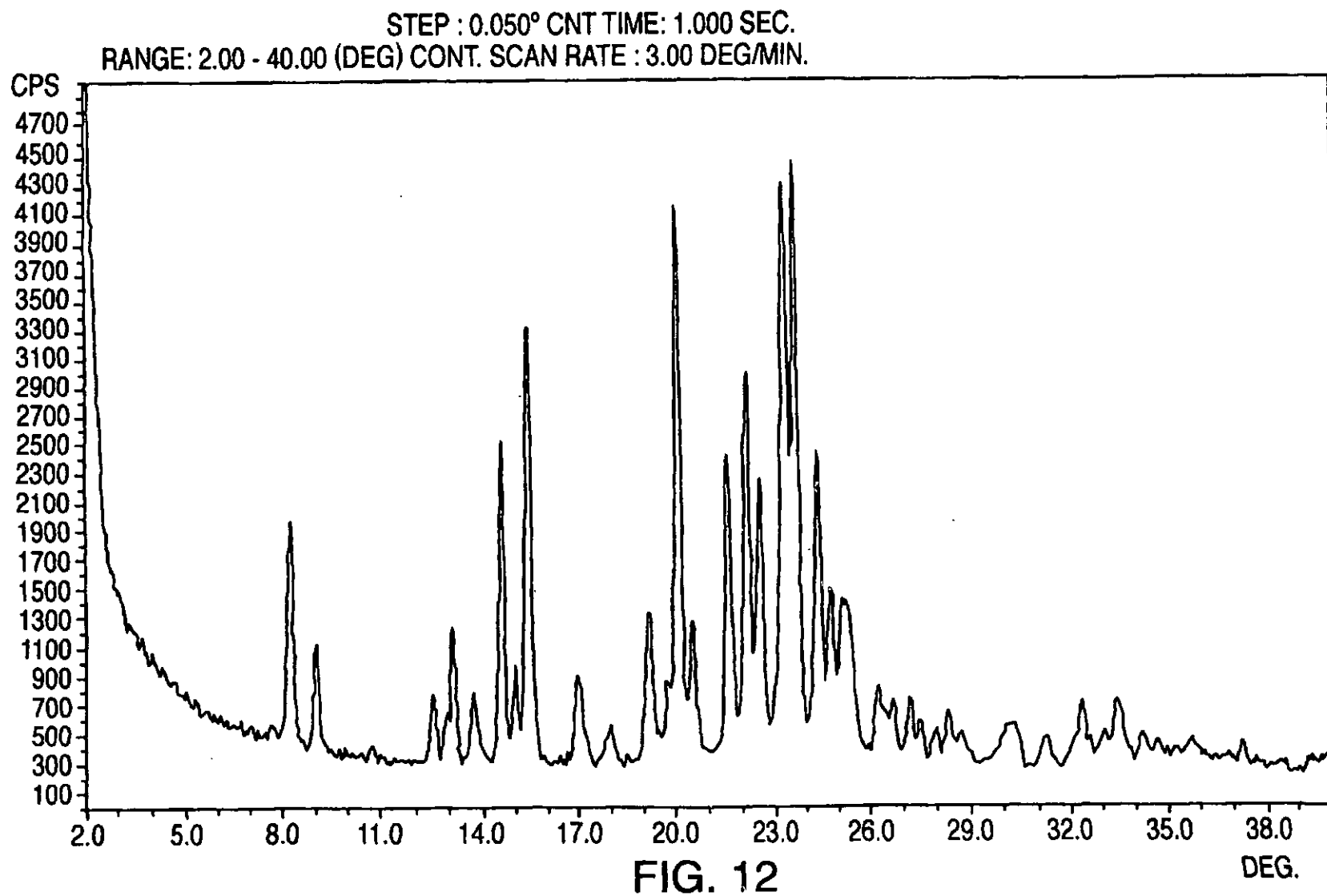
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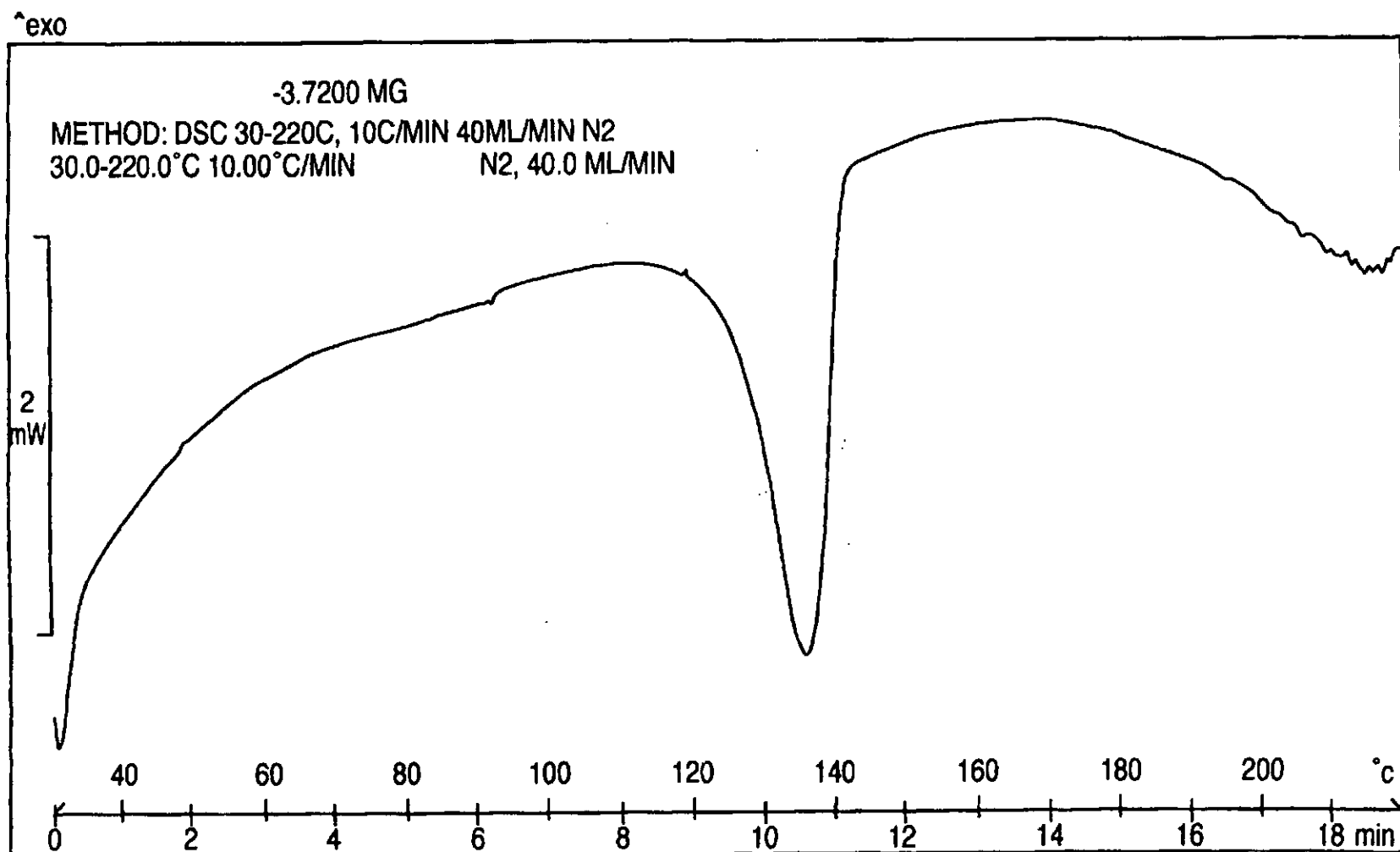


FIG. 13

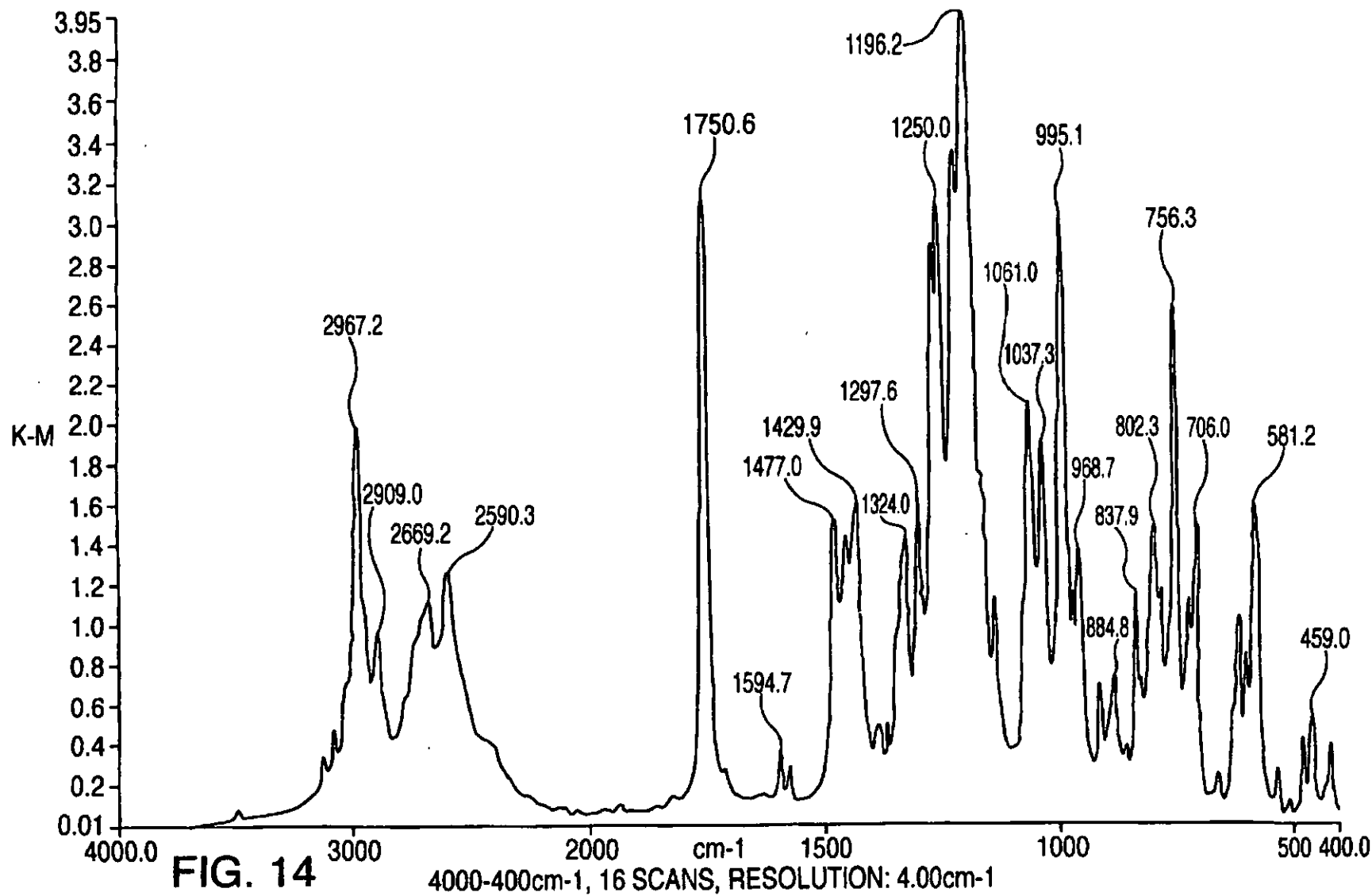
METTLER TOLEDO STAR^e SYSTEM

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As the examples illustrate, one skilled in the art would appreciate that the optimal conditions for crystallizing clopidogrel hydrogensulfate Form II from these solvents is solvent dependent. The conditions used for crystallization may vary from one solvent to another.

5

Typically, clopidogrel hydrogensulfate is dissolved in one of the solvents and is preferably heated to obtain a complete solution. Preferably the solution is heated for about a few hours.

10

After dissolution, the solution is cooled. Preferably, the solution is cooled to about room temperature. The solutions may precipitate under slightly different conditions depending on the solvent used. The solution may be concentrated by partially removing the solvent, such as by evaporation. The solution may be stirred from about a few hours to about a few days. After precipitation, the precipitate may be separated by techniques well known in the art, such as by filtration.

15

Preferably the precipitate is dried. The precipitate may be heated or the pressure reduced to accelerate the drying process. Preferably the precipitate is heated from about 40°C to about 60°C, with about 50°C being the most preferred. A vacuum oven known in the art may be used for about one or two days to dry the precipitate.

20

The present invention further provides a process for preparing clopidogrel hydrogensulfate Form II comprising the steps of preparing a solution of clopidogrel hydrogensulfate in acetonitrile, admixing the solution with an antisolvent to precipitate clopidogrel hydrogensulfate and separating the clopidogrel hydrogensulfate. Preferably, the solution is added to the antisolvent.

25

Preferably, the solution is prepared by mixing amorphous clopidogrel hydrogensulfate with acetonitrile. Preferably the solution is kept at about room temperature. The solution is then added to an antisolvent to precipitate clopidogrel hydrogensulfate. Preferably, the solution is added slowly to the antisolvent.

30

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The antisolvent is preferably an ether. More preferably, each alkyl radical of the ether is independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, 1-butyl, 2-butyl and t-butyl. Most preferably, the ether is diethyl ether.

5 After addition of the solution to an antisolvent, a precipitate forms. The suspension may be stirred, preferably for about a day. The precipitate is then separated by techniques well known in the art, such as by filtration.

10 Preferably the precipitate is dried. The precipitate may be heated or the pressure reduced to accelerate the drying process. Preferably the precipitate is heated from about 50°C to about 70°C, with about 65°C being the most preferred. A vacuum oven known in the art may be used.

15 The new crystalline forms of clopidogrel hydrogensulfate are solvates of various solvents. Clopidogrel hydrogensulfate Form III is a solvate of 1-butanol, and contains about 7 to about 8% 1-butanol by weight. Form IV is considered a solvate of isopropanol, and contains about 3% to about 9% isopropanol by weight. Form V is a solvate of 2-butanol and contains about 9% to about 10% 2-butanol by weight. Form VI is a solvate of 1-propanol, and contains about 6% propanol by weight.

20 One skilled in the art may appreciate that the processes of the present invention may use clopidogrel free base rather than clopidogrel hydrogensulfate as a starting material. After preparing a solution of an alcohol and the free base, the free base may be treated with sulfuric acid to obtain the hydrogensulfate form. The solution is then preferably heated to
25 reflux for a few hours. Preferably, the sulfuric acid used is about 20% to about 98% aqueous sulfuric acid, most preferably about 80% aqueous sulfuric acid. The molar equivalent of sulfuric acid to clopidogrel base used is preferably from about .66 equivalents to about 1.1 equivalents.

30 One skilled in the art would appreciate that the conditions and the yield may vary when starting with clopidogrel base rather than clopidogrel hydrogensulfate.

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The yield and the conditions may further vary according to the molar ratio and the concentration of the sulfuric acid used. The examples of the present invention provide guidance to one skilled in the art regarding the optimal conditions.

5 One skilled in the art may also appreciate that the scope of the disclosure is not limited by the order of the additions in adding an antisolvent. For example, a mixture may be added to an antisolvent or vice versa, though an embodiment may prefer one over the other. Usually the crystallization of clopidogrel is better when a solution is added to the antisolvent, but operationally it is often more convenient to add the antisolvent to the solution. When
10 adding an antisolvent to a residue, the order of addition is of minimal relevance.

One of skill in the art appreciates the use of an anti-solvent to cause precipitation of a compound. In one embodiment, an anti-solvent is added to a solution to decrease the solubility for a particular compound in a particular solvent, thus resulting in precipitation.
15 In another embodiment, an anti-solvent is added to an oily residue or a gummy material, wherein the low solubility of the anti-solvent for a particular compound results in precipitation of that compound.

Many processes of the present invention involve crystallization out of a particular solvent.
20 One skilled in the art would appreciate that the conditions concerning crystallization can be modified without affecting the form of the polymorph obtained. For example, when mixing clopidogrel hydrogensulfate in a solvent to form a solution, warming of the mixture can be necessary to completely dissolve the starting material. If warming does not clarify the mixture, the mixture can be diluted or filtered. To filter, the hot mixture can be passed
25 through paper, glass fiber or other membrane material, or a clarifying agent such as celite. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature crystallization.

The conditions can also be changed to induce/accelerate precipitation. A preferred way of
30 inducing precipitation is to reduce the solubility of the solvent. The solubility of the solvent can be reduced, for example, by cooling the solvent.

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Another manner to accelerate crystallization is by seeding with a crystal of the product or scratching the inner surface of the crystallization vessel with a glass rod. Other times, crystallization can occur spontaneously without any inducement. The present invention covers both embodiments where crystallization or precipitation occurs spontaneously, or is
5 induced/accelerated, unless if such inducement is critical for obtaining a particular polymorph.

As a platelet inhibitor, clopidogrel is effective at suppressing the lethal effects of blood clotting. Platelet aggregation often occurs around damaged blood vessels. The blood
10 vessels may only have minor fissures or plaques to induce platelet aggregation.

Platelet aggregation leads to the blockage of arteries, thus increasing the risk of primary and secondary strokes and heart attacks. By inhibiting platelet aggregation, clopidogrel hydrogensulfate reduces the risk of heart attacks and strokes. Clopidogrel is particularly
15 effective in the secondary prevention of ischemic events, which are defined in the art as a decrease in the blood supply to a bodily organ, tissue, or part caused by constriction or obstruction of the blood vessels.

Pharmaceutical compositions of the present invention contain clopidogrel hydrogensulfate
20 Forms III, IV, V, VI and the amorphous form, optionally in mixture with other Form(s) or amorphous clopidogrel and/or active ingredients. The clopidogrel hydrogensulfate Forms III, IV, V and VI obtained by the processes of the present invention are ideal for pharmaceutical composition in that they have a purity of at least about 90%, more preferably at least about 95%, and most preferably at least about 99%. (Area percentage as
25 measured by HPLC). In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients. Excipients are added to the composition for a variety of purposes.

Diluents increase the bulk of a solid pharmaceutical composition, and may make a
30 pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline

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cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrans, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered
5 cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions
10 include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium
15 alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition.

Disintegrants include alginic acid, carboxymethylcellulose calcium,
20 carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrillin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered

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composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, clopidogrel hydrogensulfate and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the

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gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

According to the present invention, a liquid composition may also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium lactate, sodium citrate or sodium acetate.

Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories,

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sachets, troches and lozenges, as well as liquid syrups, suspensions and elixirs.

The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tableted, or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

A tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention may comprise any of the aforementioned blends

THO
138%

and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

5 Capsules, tablets and lozenges, and other unit dosage forms preferably contain a base equivalent of about 75 mg, which is about 98 grams of clopidogrel hydrogensulfate Form III, IV, V, VI or the amorphous form. The unit dosage form as used herein refers to the amount of the various forms of clopidogrel contained in the vehicle of administration, such as a tablet or a capsule. In a preferred embodiment, the unit dosage in a tablet for oral administration contains a base equivalent of about 25 mg to 150 mg. Most preferably, it is
10 about 75 mg base equivalent. One skilled in the art would appreciate that other unit dosages may be made as necessary in a routine fashion.

Instruments Used:

15 **PXRD**

Powder X-ray diffraction patterns were obtained by methods known in the art using a Scintag X-ray powder diffractometer model X'TRA, a variable goniometer, an X-Ray tube with Cu target anode and a solid state detector. A round standard aluminum sample holder with a round zero background quartz plate was used. Scans were performed over a range of
20 2 to 40 degrees two-theta, continuously, with a scan rate of 3 degrees/min.

DSC

The DSC thermogram was obtained using a DSC Mettler 821e Star[®]. The temperature range of scans was 30-350°C at a rate of 10°C/min. The weight of the sample was 3-5 mg.
25 The sample was purged with nitrogen gas at a flow rate of 40 mL/min. Standard 40 μ l aluminum crucibles having lids with three small holes were used.

FTIR

To obtain the FTIR results, a Perkin-Elmer Spectrum One FTIR spectrometer with the
30 diffuse reflectance technique was used. The sample was finely ground with potassium bromide, and the spectrum was recorded using potassium bromide background in a

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diffused reflectance accessory. The spectrum was recorded from 4000-400 cm^{-1} . Sixteen scans were taken at a resolution of 4.0 cm^{-1} .

For FTIR, KBr tablets were not used. In the prior art, Form II was characterized by FTIR using KBr tablets. As disclosed, Applicants performed FTIR by diffuse reflectance technique ("DRIFT"). Clopidogrel hydrogensulfate Form I and Form II were analyzed both by DRIFT technique and by KBr tablet technique. Similar pattern were obtained for the same crystal form by the different techniques.

HPLC

Column and Packing: Keystone, Betasil C 18, 250 x 4.6

Eluent: 70% methanol, 30% buffer 10.01M K₂HP04, pH=7.5 with H₃PO₄

Flow Rate: 1 ml/min

Column Temp: 30°C

Detection wavelength = 230 nm

Diluent: 70% methanol/30%water

Sample: 10 mg/ 10 ml diluent

Injection volume: 20 micro liters, Instrument: Varian

The following examples further illustrate the present invention:

EXAMPLES

Example 1 - Preparation of clopidogrel hydrogensulfate Form II

Clopidogrel base (5.01g, 1eq.) was dissolved in methylethyl ketone (MEK) (39.5 mL).

Eighty percent aqueous sulfuric acid (0.74 mL, 0.66eq.) was added to the solution at 20°C.

The reaction mixture was heated to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and half of the amount of the solvent was evaporated under

reduced pressure during which a precipitate was formed. The white solid was collected by

filtration, washed with MEK (2 x 10ml) and dried at 50°C in a vacuum oven for 24 hours

to obtain 3.55g (54%) of clopidogrel hydrogensulfate crystal Form II.

TH2 140
\$12**Example 2 - Preparation of clopidogrel hydrogensulfate Form II**

Clopidogrel base (4.27g, 1 eq.) was dissolved in methylethyl ketone (MEK) (33.7ml). Eighty percent aqueous sulfuric acid (1.03ml, 1.1eq.) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and stirred at this temperature for additional 67 hours during which a precipitate was formed. The white solid was collected by filtration, washed with MEK (2x10 mL) and dried at 50°C in a vacuum oven for 24 hours to obtain 4.59g (82%) of clopidogrel hydrogensulfate crystal Form II.

Example 3 - Preparation of clopidogrel hydrogensulfate Form II

Clopidogrel base (3.73g, 1eq.) was dissolved in dichloromethane (29.4 mL). Eighty percent aqueous sulfuric acid (0.55ml, 0.66eq.) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours during which a precipitate was formed. Then, the solution was cooled to room temperature and half of the amount of the solvent was evaporated under reduced pressure. The white solid was collected by filtration, washed with dichloromethane (2x10ml) and dried at 50°C in a vacuum oven for 24 hours to obtain 1.42g (30%) of clopidogrel hydrogensulfate crystal Form II.

Example 4 - Preparation of clopidogrel hydrogensulfate Form II

Clopidogrel base (4.37g, 1 eq.) was dissolved in dichloromethane (34.5 mL). Eighty percent aqueous sulfuric acid (1.06 mL, 1.1eq.) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours during which a turbid solution was formed. Then, the solution was cooled to room temperature and stirred at this temperature for an additional 16 hours during which a massive precipitate was formed. The white solid was collected by filtration, washed with dichloromethane (2x10ml) and dried at 50°C in a vacuum oven for 24 hours to obtain 2.76g (48%) of clopidogrel hydrogensulfate crystal Form II.

Example 5 - Preparation of clopidogrel hydrogensulfate Form II

Clopidogrel base (4.29g, 1 eq.) was dissolved in toluene (33.8 mL). Eighty percent aqueous sulfuric acid (1.04 mL, 1.1eq.) was added to the solution at 20°C. The reaction

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mixture was heated to reflux temperature for 3 hours. Then, the solution was cooled to room temperature and stirred at this temperature for an additional 16 hours during which a massive precipitate was formed. The white solid was collected by filtration, washed with toluene (2x10ml) and dried at 50°C in a vacuum oven for 24 hours to obtain 4.59g (82%) of clopidogrel hydrogensulfate crystal Form II.

Example 6 - Preparation of clopidogrel hydrogensulfate Form II

Clopidogrel base (4.24g, leq.) was dissolved in chloroform (33.4 mL). Eighty percent aqueous sulfuric acid (0.62 mL, 0.66eq.) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours during which a precipitate was formed. Then, the solution was cooled to room temperature and half of the amount of the solvent was evaporated under reduced pressure. The white solid was collected by filtration, washed with chloroform (2x10 mL) and dried at 50°C in a vacuum oven for 24 hours to obtain 3.14g (56%) of clopidogrel hydrogensulfate crystal Form II.

Example 7- Preparation of clopidogrel hydrogensulfate Form II

Clopidogrel base (4.37g, leq.) was dissolved in chloroform (34.5 mL). Eighty percent aqueous sulfuric acid (1.06ml, 1.1 eq.) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours during which a precipitate was formed. Then, the solution was cooled to room temperature and stirred at this temperature for an additional 16 hours during which a massive precipitate was formed. The white solid was collected by filtration, washed with chloroform (2x10ml) and dried at 50°C in a vacuum oven for 24 hours to obtain 5.01g (88%) of Clopidogrel hydrogensulfate crystal Form II.

Example 8 - Preparation of clopidogrel hydrogensulfate Form II

Clopidogrel base (4.03g, 1 eq.) was dissolved in ethyl acetate (31.8 mL). Eighty percent aqueous sulfuric acid (0.59 mL, 0.66eq.) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 3 hours during which a sticky precipitate was formed. Then, the solution was cooled to room temperature and stirred at this temperature for an additional 16 hours during which a massive precipitate was formed. The white solid

was collected by filtration, washed with ethyl acetate (2x10ml) and dried at 50°C in a vacuum oven for 24 hours to obtain 2.59g (49%) of clopidogrel hydrogensulfate crystal Form II.

5 **Example 9 - Preparation of clopidogrel hydrogensulfate Form II**

Clopidogrel base (5.31 g, 1eq.) was dissolved in ethyl acetate (41.9 mL). Eighty percent aqueous sulfuric acid (1.29 mL, 1.1eq.) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours during which a massive precipitate was formed. Then, the solution was cooled to room temperature and stirred at this
10 temperature for an additional 3 hours. The white solid was collected by filtration, washed with ethyl acetate (2x10ml) and dried at 50°C in a vacuum oven for 24 hours to obtain 4.60g (66%) of clopidogrel hydrogensulfate crystal Form II.

15 **Example 10 - Preparation of clopidogrel hydrogensulfate Form II**

Clopidogrel base (4.39g, 1eq.) was dissolved in tert-butylmethyl ether (MTBE) (34.6ml). Eighty percent aqueous sulfuric acid (0.64ml, 0.66eq.) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 3 hours during which a sticky precipitate was formed. Then, the solution was cooled to room temperature and stirred at this temperature for an additional 2 hours. The obtained white solid was collected by
20 filtration, washed with MTBE (2x10 mL) and dried at 50°C in a vacuum oven for 24 hours to obtain 2.96g (52%) of clopidogrel hydrogensulfate crystal Form II.

25 **Example 11 - Preparation of clopidogrel hydrogensulfate Form II**

Clopidogrel base (4.17g, 1eq.) was dissolved in 1,4-Dioxane (32.9 mL). Eighty percent aqueous sulfuric acid (0.61ml, 0.66eq.) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours during which a massive precipitate was formed. Then, the solution was cooled to room temperature and stirred at this temperature for additional 2 hours. The white solid was collected by filtration, washed with 1,4-dioxane (2x10mL) and dried at 50°C in a vacuum oven for 24 hours to obtain
30 2.61 g (48%) of clopidogrel hydrogensulfate crystal Form II.

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145**Example 12 - Preparation of clopidogrel hydrogensulfate Form II**

Amorphous clopidogrel hydrogensulfate (1g) was dissolved in acetonitrile (6 mL) at room temperature. The resulting solution was added to DEE (350ml) drop wise and the obtained suspension was stirred at room temperature for 19 hours. The white solid was collected by filtration, washed with DEE (15 mL) and dried at 65°C in a vacuum oven for 24 hours to obtain 0.71 g (71 %) of clopidogrel hydrogensulfate crystal Form II.

Example 13 - Preparation of clopidogrel hydrogensulfate amorphous form

Clopidogrel hydrogensulfate (3 grams) was dissolved in methanol (6 mL). Toluene (350mL) was separately heated to reflux temperature. The methanolic solution of clopidogrel hydrogensulfate was added dropwise to the boiling toluene. The resulting solution was refluxed for an additional 20 minutes. The solution was cooled to room temperature and was stirred at this temperature for 16 hours. The solvent was evaporated under reduced pressure to dryness to obtain a creamy foam (1.26 grams, 42%), which characterization data showed to be the amorphous form.

Example 14 - Preparation of clopidogrel hydrogensulfate amorphous form

Clopidogrel hydrogensulfate (2 grams) was dissolved in methanol (4 mL). The resulting solution was added dropwise to diethyl ether (350 mL). The suspension was stirred at RT for about forty five minutes. The solid was filtered and dried at about 50°C in a vacuum oven for 24 hours to give 1.12 grams (56%) of clopidogrel hydrogensulfate, which characterization data showed to be the amorphous form.

Example 15 - Preparation of clopidogrel hydrogensulfate amorphous form

Clopidogrel hydrogensulfate (1 gram) was dissolved in methanol (3 mL) at room temperature. The resulting solution was added drop wise to diethylether (DEE) (350 mL). The obtained mixture was stirred at room temperature for 0.5 hour. The solid was then filtered and dried at 50°C in a vacuum oven for 16 hours to give 0.86g (86%) of amorphous clopidogrel hydrogensulfate.

Example 16 - Preparation of clopidogrel hydrogensulfate amorphous form

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Clopidogrel base (3.42g) was dissolved in acetone (27 mL). Aqueous sulfuric acid (20%, 4.57 mL) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. The solution was cooled to room temperature and stirred at this temperature for additional 1.5 hours. Then the solvent was evaporated to dryness under reduced pressure to obtain powder (3.59g, 78%) which characterization data showed to be the amorphous form.

Example 17 - Preparation of clopidogrel hydrogensulfate amorphous form

Clopidogrel base (2.88g) was dissolved in acetone (23 mL). Aqueous sulfuric acid (20%, 2.56 mL) was added to the solution at 20°C. The reaction mixture was heated to reflux temperature for 2 hours. The solution was cooled to room temperature and stirred at this temperature for an additional 2 hours. Then the solvent was evaporated to dryness under reduced pressure to obtain powder (3.08g, 82%) which characterization data showed to be the amorphous form.

Example 18 - Preparation of clopidogrel hydrogensulfate Form I

Clopidogrel hydrogensulfate (2 grams) was dissolved in methanol (4 mL). The resulting solution was added to methyl t-butyl ether (300 mL) dropwise. The suspension was stirred at RT for 16 hours. The resulting precipitate was filtered and dried at 65 ° C in a vacuum oven for 24 hours to obtain crystals (1.5 grams, 75%). Subsequent analysis confirmed that the crystals were clopidogrel hydrogensulfate Form I.

Example 19 - Preparation of clopidogrel hydrogensulfate Form I

Clopidogrel hydrogensulfate (3 grams) was dissolved in absolute ethanol (9 mL) at reflux temperature to obtain a clear solution. The solution was then cooled to room temperature and the solvent was evaporated to dryness under reduced pressure to obtain oil. Then methyl t-butyl ether or diethylether (28 mL) were added dropwise to the oily residue and the resulting mixture was stirred at room temperature for 24 hours. The white product was filtered and dried at 50°C in a vacuum oven for 24 hours to give 2.6 grams (87%) of clopidogrel hydrogensulfate crystal Form I.

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5**Example 20 - Preparation of clopidogrel hydrogensulfate Form I**

Clopidogrel hydrogensulfate (3 grams) was dissolved in methanol (4 mL) at reflux temperature to obtain a clear solution. The solution was then cooled to room temperature and the solvent was evaporated to dryness under reduced pressure to obtain oil. Then tert-Butyl methylether or diethylether (30 mL) was added dropwise to the oily residue and the resulting mixture was stirred at room temperature for 16 hours. The white product was filtered and dried at 50°C in a vacuum oven for 24 hours to give 2.65 grams (88%) of clopidogrel hydrogensulfate crystal Form I.

Example 21 - Preparation of clopidogrel hydrogensulfate Form I and amorphous form

Clopidogrel base (3.85 g) was dissolved in absolute ethanol (30.4 mL). Eighty percent aqueous sulfuric acid (0.56 mL) was added to the solution. The reaction mixture was heated to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and the solvent was evaporated to dryness under reduced pressure leaving a white foam. The foam was stirred in methyl t-butyl ether (MTBE) (70ml) for 3 hours at room temperature. Approximately half of the MTBE was evaporated under reduced pressure and a solid was recovered by filtration. The solid was dried at 50°C in a vacuum oven to obtain 2.82g (56%) of a mixture of clopidogrel hydrogensulfate crystal Form I and amorphous clopidogrel hydrogensulfate.

Example 22 - Preparation of clopidogrel hydrogensulfate Form I

Clopidogrel hydrogensulfate (1 gram) was dissolved in methanol (3 mL) at room temperature. The resulting solution was added drop wise to diethylether (DEE) (350 mL). The obtained mixture was stirred at room temperature for 1 hour. The solid was then filtered and dried at 50°C in a vacuum oven for 19.5 hours to give 0.76g (76%) of clopidogrel hydrogensulfate crystal Form I.

Example 23 - Preparation of clopidogrel hydrogensulfate Form I

Clopidogrel hydrogensulfate (1 gram) was dissolved in methanol (3 mL) at room temperature. The resulting solution was added drop wise to diethylether (DEE) (350 mL).

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The obtained mixture was stirred at room temperature for 5 hours. The solid was then filtered and dried at 50°C in a vacuum oven for 14 hours to give 0.74g (74%) of clopidogrel hydrogensulfate crystal Form I.

5 **Example 24 - Preparation of clopidogrel hydrogensulfate Form I**

Clopidogrel hydrogensulfate (1 gram) was dissolved in methanol (3 mL) at room temperature. The resulting solution was added drop wise to diethylether (DEE) (350 mL). The obtained mixture was stirred at room temperature for 8 hours. The solid was then filtered and dried at 50°C in a vacuum oven for 13 hours to give 0.78g (78%) of
10 clopidogrel hydrogensulfate crystal Form I.

Example 25 - Preparation of clopidogrel hydrogensulfate Form I

Clopidogrel hydrogensulfate (1 gram) was dissolved in methanol (3 mL) at room temperature. The resulting solution was added drop wise to diethylether (DEE) (350 mL).
15 The obtained mixture was stirred at room temperature for 19.5 hours. The solid was then filtered and dried at 50°C in a vacuum oven for 23 hours to give 0.74g (74%) of clopidogrel hydrogensulfate crystal Form I.

Example 26 - Preparation of clopidogrel crystal Form III

20 A suspension of clopidogrel hydrogensulfate (3 grams) in 1-butanol (5 mL) was heated to reflux temperature for 30 minutes to obtain a clear solution. The solution was cooled to room temperature (RT) and the solvent was evaporated under reduced pressure to obtain an oily residue. Diethyl ether (30 mL) was added to the residue. The resulting mixture was stirred at room temperature for 24-48 hours. A white product precipitated from the
25 mixture, and was then filtered, and washed with diethyl ether (2 x 10 mL). The white product was dried at 65°C in a vacuum oven for 24 hours to give 2.91 grams of crystalline clopidogrel hydrogensulfate (97%), which was identified as Form III by PXRD.

Example 27 - Preparation of clopidogrel crystal Form III

30 Clopidogrel base (4.28g) was dissolved in 1-butanol (16.9ml). Eighty percent aqueous sulfuric acid (0.63ml) was added to the solution at 20°C. The reaction mixture was heated

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to reflux temperature for 2 hours. Then, the solution was cooled to room temperature and the solvent was evaporated to dryness under reduced pressure leaving yellow oil. The oil was stirred in methyl t-butyl ether (MTBE) (125ml) for 96 hours at room temperature to obtain a precipitate. The solid was collected by filtration, washed with MTBE (2x10ml) and dried at 50°C in a vacuum oven for 24 hours to obtain 3.33g (60%) of clopidogrel hydrogensulfate crystal Form III.

Example 28 - Preparation of clopidogrel crystal Form III

Clopidogrel hydrogensulfate crystal Form I (1g) was dissolved in 1-butanol (5 mL) at reflux temperature. When a clear solution was obtained, the solution was cooled to room temperature and the solvent was evaporated to dryness under reduced pressure to obtain an oily residue. Then diethyl ether (DEE) (7 mL) was added to the residue and the resulting mixture was stirred at room temperature for 24 hours during which a precipitate was formed. The white solid was collected by filtration, washed with DEE (25 mL) and dried at 60°C in a vacuum oven for 20 hours to obtain 0.86g (86%) of clopidogrel hydrogensulfate crystal Form III.

Example 29 - Preparation of clopidogrel hydrogensulfate Form IV

Clopidogrel hydrogensulfate (3 grams) was dissolved in isopropanol (IPA) (32 mL (~11 vol.)) at reflux temperature. The resulting solution was cooled to room temperature and stirred at this temperature for 1 hour. The solid was then filtered and dried at 50°C in a vacuum oven for 16 hours to give 1.66g (55%) of clopidogrel hydrogensulfate crystal Form IV.

Remark: The volume of the solvent can be increased up to 21 volumes/ 1g of clopidogrel hydrogensulfate.

Example 30 - Preparation of clopidogrel hydrogensulfate Form IV

Clopidogrel hydrogensulfate (3 grams) was dissolved in isopropanol (IPA) (60ml (20 vol.)) at reflux temperature. The resulting solution was cooled to room temperature and the solvent was evaporated to dryness under reduced pressure to give 2.0g (67%) of

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then distilled and cooled, followed by subsequent crystallization. The crystals are washed and dried to obtain Form I.

According to *Chemical Abstract* Accession No. 1999:811251, Form II is prepared by addition of a solution of 50 g of clopidogrel camphorsulfonate in 100 mL of dichloromethane to a solution of 9.1 g of potassium carbonate in 70 mL of water. The organic phase was separated, concentrated and dissolved in 229 mL of acetone. The acetone solution was refluxed with 7.4 g of 80% sulfuric acid under nitrogen for 2 h. The solvent was then removed to yield Form II.

Form II may also be prepared from Form I by storing aqueous mother liquor from the crystallization of Form I for 3-6 months.

The present invention also provides for clopidogrel hydrogensulfate 1-butanolate, isopropanolate, 2-butanolate and 1-propanolate.

Four new crystal forms of clopidogrel hydrogensulfate, designated Forms III, IV, V and VI plus the amorphous form of clopidogrel hydrogensulfate, and a novel process for their preparation, and preparation of Form I and II of clopidogrel have now been discovered.

SUMMARY OF THE INVENTION

In one aspect the present invention provides for clopidogrel hydrogensulfate characterized by data selected from the group consisting of a powder X-ray diffraction pattern with peaks at about 8.1, 8.7, 14.3, 15.4, 20.1, 22.3, 22.5, 23.5, and 24.1 ± 0.2 degrees two-theta, a differential scanning calorimetric thermogram having an endothermic peak at about 105°C and a FTIR spectrum with peaks at about 581, 707, 755, 971, 1057, 1196, 1252, 1436, 1476, 1748, 2590, 2670 and 2963 cm^{-1} . Said solid crystalline form denotes Form III.

In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate having at least one of the characteristics of Form III (such as the PXRD peaks and/or FTIR peaks and/or DSC peaks disclosed herein) comprising the steps of

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preparing a solution of clopidogrel hydrogensulfate in 1-butanol, removing the 1-butanol from the solution to obtain a residue, admixing an antisolvent with the residue to precipitate clopidogrel hydrogensulfate and separating the clopidogrel hydrogensulfate. The wet sample is preferably dried.

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In another aspect, the present invention provides for clopidogrel hydrogensulfate characterized by data selected from the group consisting of: a PXRD pattern as substantially depicted in Fig. 4. and a FTIR spectrum with peaks at about 583, 723, 762, 846, 1040, 1167, 1223, 1438, 1478, 1638, 1752, 2585 and 2960 cm^{-1} . Said solid form is amorphous form.

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In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate having at least one of the characteristics of amorphous form comprising the steps of preparing a solution of clopidogrel hydrogensulfate in an alcohol selected from the group consisting of methanol and ethanol, admixing the solution with an antisolvent to precipitate clopidogrel hydrogensulfate and separating the clopidogrel hydrogensulfate.

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In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate having at least one of the characteristics of amorphous form comprising the steps of preparing a solution of clopidogrel hydrogensulfate in an alcohol selected from the group consisting of methanol and ethanol, removing the alcohol from the solution to obtain a residue, admixing an antisolvent with the residue to precipitate clopidogrel hydrogensulfate and separating the clopidogrel hydrogensulfate.

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In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate having at least one of the characteristics of amorphous form comprising the steps of preparing a solution of clopidogrel hydrogensulfate in an alcohol selected from the group consisting of methanol and ethanol, admixing the solution with an antisolvent and removing the alcohol and the antisolvent.

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In another aspect, the present invention provides a process for preparing clopidogrel

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hydrogensulfate having at least one of the characteristics of amorphous form comprising the steps of preparing a solution of clopidogrel hydrogensulfate in acetone and removing the acetone.

5 In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate Form I comprising contacting amorphous clopidogrel hydrogensulfate with an ether, and separating the clopidogrel hydrogensulfate Form I. Preferably, the amorphous clopidogrel hydrogensulfate is suspended in ether.

10 In another aspect, the present invention provides for clopidogrel hydrogensulfate characterized by data selected from the group consisting of: a PXRD pattern with peaks at about 22.0, 25.9, 26.9, 27.4, 28.1, 28.6 and 28.9 ± 0.2 degrees two theta, a DSC thermogram with an endothermic peak at about 160-170°C and a FTIR spectrum with peaks at about 618, 769, 842, 893, 935, 974, 1038, 1116, 1370, 1384 cm^{-1} . Said solid
15 crystalline form denotes Form IV.

In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate of having at least one of the characteristics of Form IV comprising the steps of preparing a solution of clopidogrel hydrogensulfate in isopropanol, precipitating
20 clopidogrel hydrogensulfate and separating the clopidogrel hydrogensulfate.

In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate having at least one of characteristics of Form IV comprising the steps of preparing a solution of clopidogrel hydrogensulfate in isopropanol and removing the
25 isopropanol.

In another aspect, the present invention provides for clopidogrel hydrogensulfate characterized by data selected from the group consisting of: a PXRD diffraction pattern with peaks at about 25.5, 26.6, 27.8 and 28.5 ± 0.2 degrees two theta, a DSC profile with an
30 endothermic peak at about 126-132°C and a FTIR spectrum with peaks at about 623, 743, 802, 817, 843, 963, 972, 1028 and 1374 cm^{-1} . Said Solid crystalline form denotes Form V.

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In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate having at least one of the characteristics of Form V comprising the steps of preparing a solution of clopidogrel hydrogensulfate in 2-butanol, admixing an antisolvent with the solution to precipitate clopidogrel hydrogensulfate and separating the clopidogrel hydrogensulfate.

In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate having at least one of the characteristics of Form V comprising the steps of preparing a solution of clopidogrel hydrogensulfate in 2 butanol, removing the 2-butanol from the solution to obtain a residue, admixing an antisolvent with the residue to precipitate clopidogrel hydrogensulfate and separating the clopidogrel hydrogensulfate.

In another aspect, the present invention provides for clopidogrel hydrogensulfate characterized by data selected from the group consisting of a powder X-ray diffraction pattern with peaks at about 8.3, 9.1, 23.2, 23.6 ± 0.2 degrees two-theta, a differential scanning calorimetric thermogram having an endothermic peak at about 136°C and a FTIR spectrum with peaks at about 959, 1061, 1430, 1751, 1757 and 3119 cm^{-1} . Said crystalline form denotes Form VI.

In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate comprising the steps of preparing a solution of clopidogrel hydrogensulfate in 1-propanol, removing the 1-propanol from the solution to obtain a residue, admixing an antisolvent with the residue to precipitate clopidogrel hydrogensulfate and separating the clopidogrel hydrogensulfate.

Preferably, removing is carried out in the processes of the present invention by evaporation.

In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate Form II comprising the steps of preparing a solution of clopidogrel hydrogensulfate in a solvent selected from the group consisting of dichloromethane,

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1,4-dioxane, toluene, chloroform, ethyl acetate, methylethyl ketone and t-butylmethyl ether, precipitating clopidogrel hydrogensulfate from the solution and separating the clopidogrel hydrogensulfate.

5 In another aspect, the present invention provides a process for preparing clopidogrel hydrogensulfate Form II comprising the steps of preparing a solution of clopidogrel hydrogensulfate in acetonitrile, admixing the solution with an antisolvent to precipitate clopidogrel hydrogensulfate and separating the precipitate.

10 Preferred anti-solvents are C₂ to C₈ ethers.

The present invention also provides for pharmaceutical compositions and their method of administration to inhibit platelet aggregation.

15 **BRIEF DESCRIPTION OF THE FIGURES**

Fig. 1 is a powder X-ray diffraction pattern of clopidogrel hydrogensulfate Form III.

Fig. 2 is a differential scanning calorimetric (DSC) thermogram of clopidogrel hydrogensulfate Form III.

20 Fig. 3 is a FTIR spectrum of clopidogrel hydrogensulfate Form III.

Fig. 4 is a powder X-ray diffraction (PXRD) pattern of clopidogrel hydrogensulfate amorphous form.

25 Fig. 5 is a FTIR spectrum of clopidogrel hydrogensulfate amorphous form.

Fig. 6 is a PXRD pattern of clopidogrel hydrogensulfate Form IV.

30 Fig. 7 is a DSC thermogram of clopidogrel hydrogensulfate Form IV.

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Fig. 8 is a MR spectrum of clopidogrel hydrogensulfate Form IV.

Fig. 9 is a PXRD pattern of clopidogrel hydrogensulfate Form V.

5 Fig. 10 is a DSC thermogram of clopidogrel hydrogensulfate Form V.

Fig. 11 is a FTIR spectrum of clopidogrel hydrogensulfate Form V.

10 Fig. 12 is a PXRD pattern of clopidogrel hydrogensulfate Form VI.

Fig. 13 is a DSC thermogram of clopidogrel hydrogensulfate Form VI.

Fig. 14 is a FTIR spectrum of clopidogrel hydrogensulfate Form VI.

15 Fig. 15 is an area analysis of impurities using HPLC.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the terms "IPA", "isopropanol", "isopropyl alcohol" and "2-propanol" refer to the same alcohol.

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As used herein, the terms "crystallization" and "precipitation" are synonymous.

The present invention provides new polymorphs of clopidogrel hydrogensulfate and novel amorphous form. The various forms are obtained *inter alia* by using different alcohols.

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In a first aspect, the present invention provides a new crystalline form of clopidogrel hydrogensulfate, designated Form III. Clopidogrel hydrogensulfate Form III is characterized by a powder X-ray diffraction pattern (Fig. 1) with peaks at about 8.1, 8.7, 14.3, 15.4, 20.1, 22.3, 22.5, 23.5, and 24.1 ± 0.2 degrees two-theta.

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Clopidogrel hydrogensulfate Form III produces a differential scanning calorimetric (DSC)

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thermogram (Fig. 2) having a maximum endotherm of about 105°C.

Clopidogrel hydrogensulfate Form III produces a FTIR spectrum (Fig. 3) with characteristic absorption bands at about 581, 707, 755, 971, 1057, 1196, 1252, 1436, 1476,
5 1748, 2590, 2670 and 2963 cm^{-1} . The FTIR spectrum of clopidogrel hydrogensulfate Form III has additional absorption bands at about 838, 886 and 1594 cm^{-1} .

The present invention further provides a process for preparing clopidogrel hydrogensulfate Form III comprising the steps of preparing a solution of clopidogrel hydrogensulfate and
10 1-butanol, removing the 1-butanol to obtain a residue, admixing an antisolvent with the residue to precipitate clopidogrel hydrogensulfate and separating the clopidogrel hydrogensulfate.

In the process, clopidogrel hydrogensulfate is mixed with a sufficient amount of alcohol to
15 dissolve the clopidogrel hydrogensulfate at or below the reflux temperature of the alcohol. To fully dissolve the clopidogrel hydrogensulfate, the mixture may be heated to a temperature up to reflux of the alcohol. Preferably, the mixture is refluxed for about 30 minutes. When preparing the solution with clopidogrel base and sulfuric acid, the solution is preferably refluxed for longer periods of time, such as about 2 hours. One skilled in the
20 art may appreciate that minor differences in the temperature and times may produce the same result, and other temperatures and times may produce the same result under other conditions.

In the most preferred embodiment, the alcohol is evaporated under ambient or reduced
25 pressure after cooling, with intermediate cooling optional. Preferably, the solution is cooled to room temperature and the alcohol is evaporated under reduced pressure. A residue remains after evaporation.

An antisolvent is then added to the residue. Preferably, the antisolvent is ether. More
30 preferably, each one of the ether's alkyl radical groups connected to the oxygen atom is independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl,

1-butyl, 2-butyl and t-butyl. Most preferably, the ether is diethyl ether or methyl t-butyl ether.

The mixture of residue and antisolvent may then be stirred for one or two days, preferably for longer times when starting with clopidogrel base. A precipitate begins to form. The precipitate is then separated from the mixture. One skilled in the art may appreciate that there are many ways to separate the precipitate from the mixture. Preferably, the precipitate is separated by filtration. After separation, the precipitate may optionally be washed with an organic solvent such as diethyl ether to remove impurities.

The separated precipitate is then preferably dried, under either ambient or reduced pressure. In a preferred embodiment, the precipitate is dried under a vacuum. Preferably, the precipitate is heated to accelerate the drying process. More preferably, it is heated from about 40°C to about 80°C. Most preferably, it is heated to about 50°C-65°C for about 24 hours in a vacuum oven. One skilled in the art may appreciate that many ways exist for drying a compound, and that by manipulating the conditions, other temperatures, pressures and time periods would suffice.

Clopidogrel Form III may be obtained in yields of about 97%, which shows the high efficiency and effectiveness of this novel process.

In another aspect, the present invention provides novel amorphous clopidogrel hydrogensulfate. In accordance with the invention, amorphous clopidogrel hydrogensulfate is highly pure. More preferably, it is essentially free of crystalline clopidogrel hydrogensulfate. Most preferably, the amorphous clopidogrel hydrogensulfate is free of crystalline clopidogrel hydrogensulfate within the detection limits of a powder X-ray diffractometer comparable to the instrumentation described. The purity of clopidogrel hydrogensulfate can be assessed by a comparison of the PXRD pattern of an unknown sample with those of mixtures of authentic pure amorphous and authentic pure crystalline clopidogrel hydrogensulfate.

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⑤ Comprobante de pago No. _____

Fecha _____

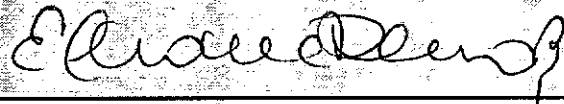
⑥ ANEXOS

- 92
- ☒ Comprobante de pago de la tasa.
 - ☒ Poderes, si fuere el caso.
 - ☒ Pruebas de los fundamentos de la oposición.
 - ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
 - ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____



C.C. 51.975.664

TP. 83823

Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 06106511
Asunto : Oposición a la solicitud de patente de Invención
titulada "SAL DE CLOPIDOGREL Y SUS FORMAS
POLIMORFAS"
Solicitante : SANOFLAVENTIS.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 583 del 18 de diciembre de 2007

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión

del registro de la Patente de Invención titulada "SAL DE CLOPIDOGREL Y SUS FORMAS POLIMORFAS", cuyo titular es SANOFI-AVENTIS, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular clopidogrel. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

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- 2.1. La solicitud objeto de la presente fue presentada el 20 de octubre de 2006, reivindicando prioridad bajo la solicitud US20040563795P del 2004-04-20; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 583 del 18 de diciembre de 2007, cuya publicación internacional corresponde a la WO2005103059 del 2005-11-03.
- 2.2. La solicitud colombiana 06106511 objeto de la presente oposición, se refiere a naftaleno-1,5-disulfonato de (+)-(S)-a-(2-clorofenil)-6,7-dihidrotieno[3,2-c]piridina-5(4H)-acetato de metilo, o una de sus formas polimorfas y/o uno de sus hidratos y/o uno de sus solvatos; donde la forma polimorfa A de naftaleno-1,5-disulfonato de (+)-(S)-a-(2-clorofenil)-6,7-dihidrotieno[3,2-c]piridina-5(4H)-acetato de metilo.1,4-dioxano; donde la forma polimorfa A de naftaleno-1,5-disulfonato de (+)-(S)-a-(2-clorofenil)-6,7-dihidrotieno[3,2-c]piridina-5(4H)-acetato de metilo.1,4-dioxano tiene un patrón de difracción de rayos X de polvo con un pico a aproximadamente 11,7 grados dos-theta; que tiene un patrón de difracción de rayos X de polvo con picos a aproximadamente 10,8, 11,7, y 13,0 grados dos-theta; que tiene un espectro de IR-TF con picos a aproximadamente 1249, 1452, 1760, 2848, 2955, 3090, y 3490 cm^{-1} ; que tiene un punto de fusión de aproximadamente 165°C; y, que tiene un patrón de difracción de rayos X de polvo sustancialmente como se ha representado en la figura 1A.
- 2.3. En primera instancia, se debe advertir que las reivindicaciones 41 y 42 se refieren al método de tratamiento y no sólo a la composición

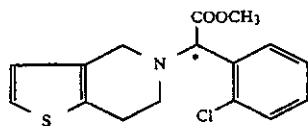
farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "Los Países Miembros [✓] otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)", los usos no están contemplados como patentables; y, Artículo 20.-[✓] "No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente [✓] refieren al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN que reza: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". Así las cosas, [las invenciones objeto de patente deben ser nuevas y tener nivel inventivo] Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

- D1: WO03051362 publicada el 26 de junio de 2003.
- D2: WO03066637 publicada el 14 de agosto de 2003.
- D3: US4847265 publicada el 11 de julio de 1989.

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2.5. Ahora bien, el documento D1) revela nuevas Formas cristalinas III, IV, la V y VI de clopidogrel hidrogensulfato y la forma amorfa del mismo, así como sus composiciones farmacéuticas y el método de tratamientos con tales composiciones. Particularmente tal documento anterior D1 en la descripción página 5 línea 21 a página 9 línea 14 define formas cristalinas de clopidogrel y procesos para la preparación de clopidogrel hidrogensulfato de Forma I, II, III, IV, V, VI y la forma amorfa. de formas III a VI. Por su parte, el documento D2) a partir de la página 4 línea 16 a página 7 línea 1, revela polimorfos de clopidogrel HCL con formas cristalinas I y II hidrocloreto metil-S-+2-clorofenil-2-6,7-dihidro-4h-tieno [3,2.c] piridina-5-yl-acetato de Fórmula I. De igual forma el documento D2, también hace referencia a un proceso para la preparación de dichas composiciones farmacéuticas que contienen el mismo, así como la nueva forma polimórfica. De igual forma, el documento D3) se relaciona con el enantiómero dextrógiro de Fórmula:



y sus sales farmacéuticamente aceptables con la agregación de plaquetas que inhiben la actividad. Igualmente dicho documento D3) define un proceso para la preparación de este compuesto y las composiciones farmacéuticas que lo contienen. Particularmente en el ejemplo 1 de D3 se define la preparación de las sales de clopidogrel con ácidos, alcanfor-10-sulfónico, HCL, H2SO4, HBr y ácido taurocólico. Así las cosas,

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Estos tres documentos evidencian la pre-existencia de una variedad de formas polimorfos de clopidogrel. Por lo tanto, a partir de dichos documentos D1, D2 y D3 en combinación, cualquier persona versada en la materia puede llegar de manera obvia a las formas cristalinas de clopidogrel reivindicadas en la presente solicitud objeto de oposición. De esta forma, es posible concluir que el presente documento objeto de oposición a la luz de la combinación de los documentos D1, D2 y D3 carece evidentemente de ALTURA INVENTIVA.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 06106511 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- "Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.". A la fecha de prioridad, 20 de abril de 2004, a partir de dichos documentos D1, D2 y D3 en combinación, cualquier persona versada en la materia puede llegar de manera

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obvia a las formas cristalinas de clopidogrel sobre el cual busca protección en el capítulo reivindicatorio.

2.7.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486

de la CAN consagra en su artículo 14 lo siguiente: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".

La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

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2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“SAL DE CLOPIDOGREL Y SUS FORMAS POLIMORFAS”**, cuyo titular es **SANOFLAVENTIS**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 583 del 18 de diciembre de 2007.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO03051362 publicada el 26 de junio de 2003.
- D2: WO03066637 publicada el 14 de agosto de 2003.
- D3: US4847265 publicada el 11 de julio de 1989.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

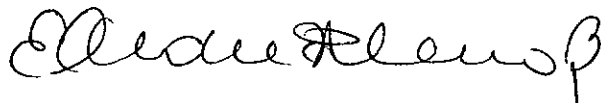
4.1. Numeral 1 del artículo 586 del Código de Comercio.

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6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

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PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **06,106511**, titulada "**SAL DE CLOPIDOGREL Y SUS FORMAS POLIMORFAS**", cuyo titular es **SANOFI-AVENTIS**, publicada en la gaceta No. 583 del 18 de Diciembre de 2007.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los ____ días del mes de Marzo de 2008.

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 22,137
FECHA : MARZO 13 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-106511- -00004-0000

Rev. 2008-03-13 14:22:38 Dep. 2020 NUECREACION
Lic. 13 PATENTUJIN Eve: 378 FASENACIONAL
Act. 400 OPOS/OBSERVTER Folios: 137

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	64054112	07/11/2007	1,536,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEMAS COMERCIALES	266,000.00
TOTAL :			\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE N°. _____



***** Pag. 1
 C A M A R A D E C O M E R C I O
 D E B A R R A N Q U I L L A
 03*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303911.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

***** C O N T I N U A *****



***** Pag. 2
 CAMARA DE COMERCIO
 DE BARRANQUILLA
 03*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o in-

***** C O N T I N U A *****



***** Pag. 3
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
03*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta

***** C O N T I N U A *****



***** Pag. 4

CAMARA DE COMERCIO
DE BARRANQUILLA

03*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.*****32,696,645

***** C O N T I N U A *****



***** Pag. 5
 CAMARA DE COMERCIO
 DE BARRANQUILLA
 03*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

MIL DOLARES, DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), -----
 liquidados a la tasa representativa del mercado vigente en el dia
 que se realice la respectiva transaccion. Grupo A. WALTER NANAKA
 TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO -----
 CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN -----
 VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA -----
 DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO -----
 CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME
 FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----
 amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA -----
 CC.No.8.715.941, y al señor ANTONIO VARELA DIAZ CC.No.72.004.699,
 para que en nombre y representacion de PROCAPS S.A., suscriban ----
 declaraciones cambiarias, aduaneras y tributarias a que este -----
 obligada la sociedad, en el giro normal de sus negocios y -----
 operaciones sociales, por tanto quedan facultados para firmarlas,
 como tambien los demas documentos relacionados con ellas, -----
 notificarse, aportar y solicitar las pruebas que sean necesarias.
 c.-Otorgar poder especial amplio y suficiente al señor MARLON ----
 TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
 CERRA CC.No.8.715.941, para que en nombre y representacion de ----
 PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
 documento relacionado con los tramites o registros de Comercio ----
 Exterior y o cualquier entidad del Estado que haga sus veces: d)
 Otorgar poder especial amplio y suficiente a la doctora CARMEN ----
 ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER
 TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y -----
 representacion de PROCAPS S.A.; endosen los titulos valores de la
 sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
 (1.000.000.000.00) M.L. CUARTO: EI representante legal de la -----
 sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta
 que la presente reforma fue aprobada por la Asamblea General -----
 Extraordinaria de Accionista de PROCAPS S.A., con observancia de
 las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores
 de documentos referentes a reforma, disolución, liquidación o
 nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 20 de Marzo de 2007.

La información sobre embargos de establecimiento se suministra en

***** C O N T I N U A *****

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ANEXO 1

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: POLYMORPHS OF CLOPIDOGREL HYDROGENSULFATE

(57) Abstract: Provided are new crystalline Forms III, IV, V and VI of clopidogrel hydrogensulfate and the amorphous form of clopidogrel hydrogensulfate, as well as their pharmaceutical compositions, and method of treatments with such compositions. Also provided are novel processes for preparation of clopidogrel hydrogensulfate Form I, Form II, Form III, Form IV, Form V, Form VI and amorphous form.

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POLYMORPHS OF CLOPIDOGREL HYDROGENSULFATE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of provisional applications Serial Numbers
5 60/342,440, filed December 18, 2001; 60/342,351, filed December 21, 2001; 60/348,182,
filed January 11, 2002; 10/074,409, filed February 12, 2002 and 60/359,157, filed February
21, 2002, all of which are incorporated herein by reference.

FIELD OF THE INVENTION

10 The present invention relates to the solid state chemistry of clopidogrel hydrogensulfate.

BACKGROUND OF THE INVENTION

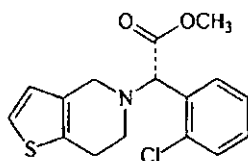
Atherosclerosis is the buildup of plaque in the wall of the arteries leading to a thickening
and a reduction in elasticity of the arteries. Atherosclerosis results from injury to the inside
15 layer of the artery. The injury is caused by common activities and diseases such as high
cholesterol, high blood pressure, smoking and infection.

Plaques form on the inner walls of the artery at these sites of injury. The plaques are
mainly composed of fatty tissue and smooth muscle cells. The formation of plaque often
20 leads to blood clotting due to platelet aggregation at the site of the injury. This clotting
may result in a reduction or elimination of blood flow to vital organs, causing heart attacks
or other serious conditions. The plaque may also rupture and send a blood clot through the
artery, referred to as an embolus, which if deposited in a smaller blood vessel may
completely block blood flow.

25 Antiplatelet activity is desirable in fighting the often fatal results of atherosclerosis.
Clopidogrel is an inhibitor of induced platelet aggregation which act by inhibiting the
binding of adenosine diphosphate to its receptor. Clopidogrel is metabolized by the liver
into active form. Its antiplatelet activity is extended in that it stops any platelet activity
30 even up to ten days after administration.

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The chemical name of clopidogrel is methyl (+)-(S)- α -(*o*-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate. It has the following structure:



5 Clopidogrel's platelet inhibiting activity makes it an effective drug for reducing the incidence of ischemic strokes, heart attacks or claudication due to vascular diseases such as atherosclerosis. By inhibiting platelet aggregation, clopidogrel reduces the chance of arterial blockage, thus preventing strokes and heart attacks. U.S. Pat. No. 5,576,328 describes a method of preventing the occurrence of a secondary ischemic event by
10 administration of clopidogrel, and is incorporated herein as a reference.

Recent studies have shown that clopidogrel is more effective in blocking platelet aggregation than aspirin and is much gentler on the gastrointestinal tract. Clopidogrel is more effective than aspirin even at much lower dosage. A dosage of 75 mg of base
15 equivalent has been shown to be more effective than a dosage of 325 mg of aspirin. In addition to being more effective, clopidogrel produces much less gastrointestinal bleeding than aspirin.

Clopidogrel is administered as its hydrogensulfate (*syn.* bisulfate) salt. Clopidogrel
20 hydrogensulfate has an empirical formula of $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$. It is currently being marketed as PLAVIX[®] tablets, which contain about 98 mg clopidogrel hydrogensulfate, which is the equivalent of 75 mg clopidogrel base. PLAVIX[®] is a white to off-white powder that is practically insoluble in water at neutral pH but highly soluble at acidic pH. It dissolves freely in methanol, somewhat in methylene chloride, and poorly in ethyl ether.

25 U.S. Patent Nos. 4,847,265; 5,132,435; 6,258,961; 6,215,005 and 6,180,793, which are hereby incorporated by reference in their entirety, disclose methods that can be used to

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prepare clopidogrel hydrogensulfate.

The present invention relates to the solid state physical properties of clopidogrel hydrogensulfate prepared by any of these or other methods. These properties can be
5 influenced by controlling the conditions under which clopidogrel is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each
10 other easily, a formulation specialist must take that fact into account when developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's
15 stomach fluid can have therapeutic consequences because it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

20 These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance. The polymorphic form may give rise to thermal behavior different from that of the amorphous material or another polymorphic form. Thermal behavior is measured in the
25 laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC), and can be used to distinguish some polymorphic forms from others. A particular polymorphic form may also give rise to distinct properties that may be detectable by powder X-ray diffraction, solid state ¹³C NMR spectrometry and infrared spectrometry.

30 The discovery of new crystalline forms of a pharmaceutically useful compound provides a

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new opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

5

U.S. Pat. No. 4,529,596 is directed to the composition of clopidogrel and methods of its use. The '596 patent teaches synthesis of clopidogrel, but fails to suggest or disclose the existence of polymorphs or the amorphous form of clopidogrel. U.S. Pat. No. 4,847,265 is directed to the enantiomer of clopidogrel, and also does not suggest or teach any polymorphs or the amorphous form of clopidogrel. These U.S. patents are incorporated herein by reference.

10

International Publication No. WO 99/65915 discloses two polymorphs of clopidogrel hydrogensulfate, referred to as Forms I and II, though Form I is originally disclosed in EP 281459.

15

According to the International Publication No. WO 99/65915, Form I has a PXRD pattern with peaks at 9.2, 10.9, 15.2, 17.9, 18.5, 20.6, 23.0, 23.2, 23.4 and 25.5 ± 0.2 degrees two theta. Form I also has an infrared spectrum with absorption bands at 2987, 1753, 1222, 1175 and 841 cm^{-1} .

20

WO 99/65915 also discloses clopidogrel hydrogensulfate Form II, according to which has a PXRD pattern with peaks at 12.9, 13.6, 15.6, 17.7, 19.5, 21.6, 23.0, 23.3 and 24.7 ± 0.2 degrees two theta. It has an infrared spectrum with absorption bands at 2551, 1753, 1497, 1189 and 1029 cm^{-1} .

25

According to Applicants' English translation, in Example 1B, Form I is prepared by dissolving clopidogrel camphorsulfonate in dichloromethane under a nitrogen atmosphere. A solution of potassium carbonate in water is then introduced. The organic phase is then removed, concentrated and added to acetone. The acetone solution is placed in a reactor under nitrogen and a 94% solution of concentrated sulfuric acid is added. The mixture is

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The amorphous character and purity of the material we have produced is confirmed by a powder X-ray diffraction pattern obtained from a sample thereof, which is provided as Fig. 4. The pattern is without intense focused reflections and is featureless except for a halo with a maximum centered at about 24 degrees two-theta.

5

The amorphous form has a FTIR spectrum (Fig. 5) with peaks at about 583, 723, 762, 846, 1040, 1167, 1223, 1438, 1478, 1638, 1752, 2585 and 2960 cm^{-1} .

10

The invention further provides a process for preparing amorphous form of clopidogrel hydrogensulfate comprising the steps of preparing a solution of clopidogrel hydrogensulfate in methanol or ethanol, and admixing the solution with an antisolvent to precipitate clopidogrel hydrogensulfate and separating the clopidogrel hydrogensulfate.

15

The alcoholic solution of clopidogrel hydrogensulfate may be heated to increase the solubility of clopidogrel hydrogensulfate in the alcohol. Preferably, the solution is heated from about room temperature to about reflux, with temperatures at or near reflux being most preferred. After dissolution, the solution may be cooled, preferably to room temperature.

20

The alcohol may optionally be removed from the solution to obtain a foam or an oily residue. Preferably, the alcohol is removed by evaporation. The alcohol may be evaporated under ambient or reduced pressure and optionally heated to accelerate the evaporation. The antisolvent in such a case is then added to the foam or the oily residue.

25

Alternatively, the solution of clopidogrel hydrogensulfate and alcohol may be added to the antisolvent to precipitate clopidogrel hydrogensulfate. Preferably, the solution is added slowly to the antisolvent. Preferably, the antisolvent is an ether. Each alkyl radical of the ether may be independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, 1-butyl, 2-butyl and tert-butyl. In one preferred embodiment, the ether is methyl t-butyl ether. In another preferred embodiment, the ether is diethyl ether.

30

A precipitate forms in the ether. The precipitate should be separated from the ether at an early stage, preferably within a few hours. Otherwise, the amorphous form will change to Form 1, resulting in a lower yield.

5 The precipitate may be separated by techniques well-known in the art. Preferably, the precipitate is separated by filtration. Optionally, vacuum filtration may be utilized.

The precipitate may be dried under ambient or reduced pressure. Preferably, the precipitate is heated in a vacuum oven for about 24 hours. More preferably, the precipitate is heated to
10 a temperature of about 40°C to about 70°C. Most preferably, it is heated to about 50°C for about 24 hours.

The present invention also provides a process for preparing amorphous clopidogrel hydrogensulfate comprising the steps of preparing a solution of clopidogrel
15 hydrogensulfate in methanol or ethanol, admixing the solution with an antisolvent; and removing the alcohol and the antisolvent. Preferably, the solution is added to the antisolvent.

In one preferred embodiment, the antisolvent is a one ring aromatic hydrocarbon, such as
20 toluene, benzene or xylene. Most preferably, the one ring aromatic hydrocarbon is toluene.

Clopidogrel hydrogensulfate is first dissolved in the alcohol to form a solution. After dissolving the clopidogrel hydrogensulfate in the alcohol, the solution is added to the antisolvent. In a less preferred embodiment, the solution is concentrated before addition to
25 the antisolvent. Preferably, the antisolvent is heated to a temperature of about room temperature to reflux so that the clopidogrel hydrogensulfate becomes more soluble in the antisolvent, with temperatures at or near reflux being preferred. Most preferably, the antisolvent is heated to reflux temperature. Besides heating the antisolvent, the mixture may be added to the antisolvent at a substantially slow rate to increase the total amount of
30 clopidogrel taken up by the antisolvent.

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After addition of the mixture to the antisolvent, the resulting mixture is preferably cooled to about room temperature, though one skilled in the art may appreciate that other temperatures may achieve the same result. To obtain the amorphous form, the antisolvent and the alcohol are removed, preferably by evaporation, to leave the amorphous form.

5 Evaporation may occur under ambient or reduced pressure, and the solution may be heated to accelerate the evaporation process.

The present invention provides a process for preparing the amorphous form of clopidogrel hydrogensulfate comprising the steps of preparing a solution of clopidogrel
10 hydrogensulfate in acetone and removing acetone to obtain the amorphous form. The mixture of clopidogrel hydrogensulfate and acetone is heated to form a solution. Preferably, the mixture is heated to a temperature where a homogeneous solution forms. Most preferably, the mixture is heated to about reflux for a few hours.

15 After heating, the solution is preferably cooled to about room temperature. The solution may be stirred. Preferably, the solution is stirred for a few hours. After stirring, the acetone is removed to obtain a powder, which is the amorphous form of clopidogrel hydrogensulfate. Preferably, the acetone is removed by evaporation. To accelerate the drying process, the pressure may be reduced and the temperature may be raised. One
20 skilled in the art would appreciate that preparation of the amorphous form may be possible under other conditions.

The present invention also provides a process for preparing clopidogrel hydrogensulfate Form I and mixtures of clopidogrel Form I and amorphous clopidogrel hydrogensulfate.

25 The amorphous form converts into Form I over time when contacted, preferably suspended, in an ether. Preferably, the ether is a C₂ to C₈ ether as described above, more preferably methyl t-butyl ether or diethyl ether. One skilled in the art may appreciate that the ratio of Form I to the amorphous form increases with time, and that, through routine experimentation, the ratio of the forms to each other may be determined for any specific
30 time.

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The examples illustrate that the amorphous form of clopidogrel hydrogensulfate undergoes a transformation to Form I in an ether, particularly in the time period from about 45 minutes to one hour. To obtain substantially Form I, clopidogrel hydrogensulfate is suspended in the ether for preferably one hour, with longer periods of time, such as four and eight hours, being most preferred. The transformation time may be longer if the starting material is clopidogrel free base rather than clopidogrel hydrogensulfate.

As the examples illustrate and one skilled in the art may appreciate, it is possible to obtain clopidogrel hydrogensulfate Form I from clopidogrel hydrogensulfate through the use of the amorphous form as an intermediate. First the amorphous form is obtained as illustrated, and then suspended in an ether to obtain Form I. The examples of the present invention obtain Form I through this mechanism.

The present invention also provides clopidogrel hydrogensulfate Form IV. Clopidogrel hydrogensulfate Form IV is characterized by powder X-Ray diffraction (PXRD), thermal analysis and FTIR spectroscopy. The clopidogrel hydrogensulfate Form IV of the present invention is characterized by a PXRD pattern (Fig. 6) with peaks at about 22.0, 25.9, 26.9, 27.4, 28.1, 28.6 and 28.9 ± 0.2 degrees two theta. More particularly, clopidogrel hydrogensulfate Form IV is characterized by a PXRD pattern with peaks at about 11.0, 12.5, 13.3, 14.0, 17.6, 18.2, 18.8, 20.5, 22.0, 22.9, 24.1, 25.9, 26.9, 27.4, 28.1, 28.6 and 28.9 ± 0.2 degrees two theta.

Clopidogrel hydrogensulfate Form IV is also characterized by DSC. The DSC thermogram of clopidogrel hydrogensulfate Form IV (Fig. 7) is characterized by an endothermic peak at about 160-170°C. Clopidogrel hydrogensulfate Form IV is also characterized by a FTIR spectrum (Fig. 8) with peaks at about 618, 769, 842, 893, 935, 974, 1038, 1116, 1370, 1384 cm^{-1} .

The present invention provides a process for preparing clopidogrel hydrogensulfate Form IV comprising the steps of preparing a solution of clopidogrel hydrogensulfate in isopropanol, precipitating clopidogrel hydrogensulfate and separating the clopidogrel

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hydrogensulfate.

Clopidogrel hydrogensulfate is dissolved in isopropanol to form a solution. Preferably, the isopropanol is heated to about reflux, before the addition of the clopidogrel

hydrogensulfate, to make the isopropanol substantially soluble for the clopidogrel hydrogensulfate. The resulting solution is then cooled to about room temperature. One skilled in the art appreciates that other conditions and temperatures may have the same result.

In one embodiment, the cooled solution is allowed to sit at room temperature until precipitation occurs. The solution may optionally be stirred. After stirring for a few hours, precipitation occurs, and is subsequently separated. The precipitate may be separated according to methods well known in the prior art, such as by filtering, decanting and centrifugation, filtering being the most preferred method.

After separating the precipitate, it may optionally be dried. To dry, the precipitate may be heated, or the pressure reduced to accelerate the drying process. Preferably, a vacuum oven is used to heat the precipitate for about 16 hours at a temperature of about 50°C. The result of this process is clopidogrel hydrogensulfate Form IV.

In another embodiment, after cooling the solution, the solvent is removed to leave a dry residue. The solvent is preferably removed by evaporation. The pressure may be reduced to accelerate the drying process. Analysis of the residue confirmed that it is clopidogrel hydrogensulfate Form IV. With this embodiment, a subsequent separation and drying step is not necessary since the obtained residue is already dry and separated from the solvent. The process for preparation of Form IV does not require an additional step of using an antisolvent.

The present invention also provides for clopidogrel hydrogensulfate Form V. Clopidogrel hydrogensulfate Form V is characterized by PXRD, thermal analysis and by FTIR spectroscopy.

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Preferably, the antisolvent is an ether. More preferably, each alkyl radical of the ether is independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, 1-butyl, 2-butyl and t-butyl. Most preferably, the ether is diethyl ether or methyl-t-butylether.

5

After addition of the antisolvent, a precipitate forms. The solution or the suspension is optionally stirred from about a few hours to about several days. The precipitate is then separated. The precipitate may be separated by methods well known in the art, such as filtering.

10

After separation, the precipitate may optionally be washed with an organic solvent, such as an ether. The precipitate may then be dried. The pressure may be reduced or the temperature raised to accelerate the drying process. Preferably, the precipitate is dried in a vacuum oven at a temperature of about 40°C to 70°C for about 24 hours.

15

The present invention also provides for clopidogrel hydrogensulfate Form VI. Clopidogrel hydrogensulfate is characterized by a PXRD pattern (Fig. 12) with peaks at about 8.3, 9.1, 23.2, 23.6±0.2 degrees two theta. More particularly, clopidogrel hydrogensulfate Form VI is characterized by a PXRD pattern with peaks at about 12.6, 13.2, 13.8, 14.7, 15.0, 15.4, 19.1, 20.0, 20.4, 21.5, 22.1, 22.5, 24.3, 24.7 and 25.1±0.2 degrees two theta.

20

Clopidogrel hydrogensulfate Form VI is also characterized by a DSC thermogram (Fig. 13) with an endothermic peak at about 136°C.

25

Clopidogrel hydrogensulfate Form VI is also characterized by a FTIR spectrum (Fig. 14) with peaks at about 959, 1061, 1430, 1751, 1757 and 3118 cm⁻¹.

30

The present invention also provides for a process for preparing clopidogrel hydrogensulfate Form VI comprising the steps of preparing a solution of clopidogrel hydrogensulfate in 1-propanol, removing the 1-propanol from the solution to obtain a residue, admixing an antisolvent with the residue to precipitate clopidogrel

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hydrogensulfate and separating the precipitate.

Clopidogrel hydrogensulfate is dissolved in 1-propanol to obtain a solution. The solution may be heated to substantially dissolve the clopidogrel hydrogensulfate in 1-propanol.

5 Preferably, the solution is heated to about reflux for a few hours.

After heating, the solution is preferably cooled to about room temperature and stirred. The solvent is then removed, preferably by evaporation. To accelerate the evaporation process, the pressure may be reduced. Preferably, the solvent is completely evaporated to obtain an
10 oily residue.

An antisolvent is then added to the residue. Preferably, the antisolvent is an ether. More preferably, each alkyl radical of the ether is independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, 1-butyl, 2-butyl and t-butyl. Most
15 preferably, the ether is methyl t-butylether.

The antisolvent is added to the residue, and the resulting mixture is preferably stirred for a day. A precipitate starts to form, which may be separated by methods well known in the art, such as filtration.

20 The precipitate is preferably dried. The precipitate may be heated or the pressure reduced to accelerate the drying process. Preferably the precipitate is heated from about 40°C to about 60°C, with about 50°C being the most preferred. A vacuum oven known in the art may be used for about one or two days to dry the precipitate.

25 The present invention further provides a process for preparing clopidogrel hydrogensulfate Form II comprising the steps of preparing a solution of clopidogrel hydrogensulfate in a solvent selected from the group consisting of chloroform, dichloromethane, 1,4-dioxane, toluene, ethyl acetate, methylethyl ketone and t-butylmethyl ether, precipitating clopidogrel
30 hydrogensulfate from the solution, and separating the clopidogrel hydrogensulfate.