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(54) Titre : FORME POLYMORPHIQUE DE 5 CHLORO N ({5S) 2 OXO 3 [4 (3 OXO 4 MORPHOLINYL)PHENYL] 1,3 OXAZOLIDIN 5 YL} METHYL) 2 THIOPHENECARBOXAMIDEL)-2-THIOPHENECARBOXAMIDE

(54) Title: POLYMORPHIC FORM OF 5-CHLORO-N-({5S)-2-OXO-3-[4-(3-OXO-4-MORPHOLINYL)-PHENYL]-1,3-OXAZOLIDIN-5-YL}-METHYL)-2-THIOPHENECARBOXAMIDE

(57) Abrégé/Abstract:
The present invention relates to a novel polymorphic form of 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl- methyl)-2-thiophenecarboxamide, processes for their preparation and medicaments comprising these forms.

30725-504

Abstract

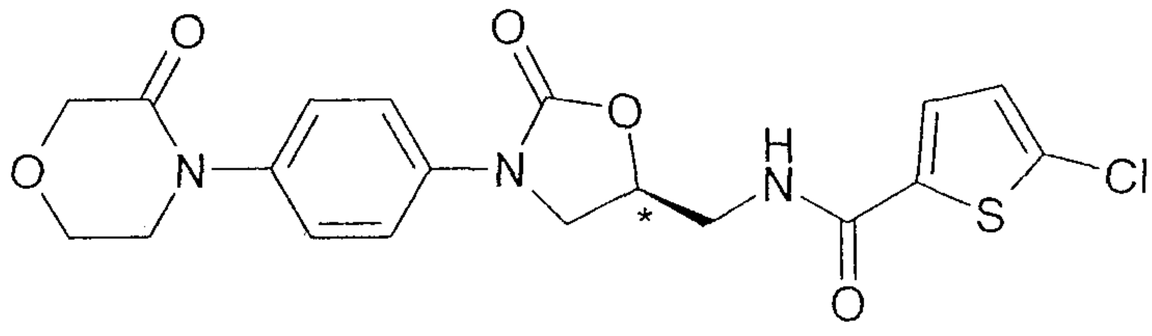
The present invention relates to a novel polymorphic form of 5-chloro-N-({(*5S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide, processes for their preparation and medicaments comprising these forms.

30725-504

POLYMORPHIC FORM OF 5-CHLORO-N-({(5*S*)-2-OXO-3-[4-(3-OXO-4-MORPHOLINYL)-PHENYL]-1,3-OXAZOLIDIN-5-YL}-METHYL)-2-THIOPHENECARBOXAMIDE

The present invention relates to a novel polymorphic form and the amorphous form of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophene-carboxamide, processes for their preparation and medicaments comprising these forms.

The compound 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide is known from WO 01/47949 and WO 2004/060887 and corresponds to the formula (I):



(*I*)

The compound of the formula (I) is a low molecular weight, orally administrable inhibitor of blood clotting factor Xa, which might therefore be employed for the prophylaxis, secondary prophylaxis and/or treatment of various thromboembolic diseases (for this see WO 01/47919), in particular of myocardial infarct, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, cerebral stroke, transitory ischemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep vein thromboses.

The compound of the formula (I) can be prepared as described in WO 01/47919 and WO 2004/060887. The compound of the formula (I) is obtained here in a crystal modification which is designated below as modification I. Modification I has a melting point of 230°C and a characteristic X-ray diffractogram, IR spectrum, Raman spectrum, FIR spectrum and NIR spectrum (Tab. 1-6, Fig. 1-6). It has now been found that modification I has a solubility lower by the factor 4 in comparison to the modification II.

Surprisingly, two further modifications, a hydrate, an NMP solvate and an inclusion compound with THF of the compound of the formula (I) have been found. The compound of the formula (I) in the modification II melts at approximately 203°C and has a transition point of approximately 195°C, the compound of the formula (I) in the modification III has a transition point of approximately 127°C. The hydrate contains approximately 4% of water, the NMP solvate contains 18.5% of N-methylpyrrolidone and the inclusion compound with THF approximately 5-7% of

tetrahydrofuran.

The present invention relates to the compound of the formula (I) in the modification II. By means of the use according to the invention of the compound of the formula (I) in the modification II, it is ensured that a higher solubility is achieved in comparison to the known modification.

Modification II of the compound of the formula (I), in comparison to modification I, modification III, the hydrate form, the NMP solvate and the inclusion compound with THF, has a clearly distinguishable X-ray diffractogram, IR spectrum, NIR spectrum, FIR spectrum and Raman spectrum (Fig. 2-6). The compound of the formula (I) in the modification II melts at 203°C and converts at approximately 195°C and is thus clearly distinguishable from modification I (melting point 230°C) and modification III (transition point approximately 127°C). In contrast to these solvent-free forms, the hydrate of the compound of the formula (I), the NMP solvate of the compound of the formula (I) and the inclusion compound with THF of the compound of the formula (I) show mass losses in thermogravimetric analysis (TGA) of 4%, 18.5% and 5-7% respectively (Fig. 1).

The compound of the formula (I) in the modification II shows peak maxima in the NIR spectra at 4086, 4228, 4418, 4457, 4634, 4905, 5846, 5911, 6026, 6081 and 6582 cm^{-1}.

It is generally known that crystalline polymorphic forms have a poorer water solubility than the amorphous form. This leads to a lower bioavailability in comparison to the amorphous form.

The present invention furthermore relates to the compound of the formula (I) in amorphous form. By means of the use according to the invention of the compound of the formula (I) in the amorphous form, it is ensured that maximum bioavailability is achieved.

The amorphous form of the compound of the formula (I) has a characteristic X-ray diffractogram, NIR spectrum, FIR spectrum and Raman spectrum (Fig. 8-12). The compound of the formula (I) in the amorphous form has a glass transition temperature of approximately 83°C (DSC, Fig. 7).

The compound of the formula (I) according to the invention in the modification II or in the amorphous form is employed in high purity in pharmaceutical formulations. For reasons of stability, a pharmaceutical formulation mainly contains the compound of the formula (I) in the modification II or in the amorphous form and no relatively large proportions of another form such as, for example, of another modification or of a solvate of the compound of the formula (I). Preferably, the medicament contains more than 90 percent by weight, particularly preferably more than 95 percent by weight of the compound of the formula (I) in the modification II or in the amorphous form based on the total amount of the compound of the formula (I) contained.

The compounds of the formula (I) in the modification II or in the amorphous form might be used for the treatment and/or prophylaxis of diseases, preferably of thromboembolic diseases and/or thromboembolic complications.

The "thromboembolic diseases" within the meaning of the present invention in particular include diseases such as myocardial infarct with ST segment elevation (STEMI) and without ST segment elevation (non-STEMI), stable angina pectoris, unstable angina pectoris, reocclusions and restenoses after coronary interventions such as angioplasty or aortocoronary bypass, peripheral arterial occlusive diseases, pulmonary embolisms, deep vein thromboses and renal vein thromboses, transitory ischemic attacks, and thrombotic and thromboembolic cerebral stroke.

The compound according to the invention might also be suitable for the prevention and treatment of cardiogenic thromboembolisms, such as, for example, cerebral ischemias, stroke and systemic thromboembolisms and ischemias in patients with acute, intermittent or persistent cardiac arrhythmias, such as, for example, atrial fibrillation, and those who are subject to cardioversion, furthermore in the case of patients with heart valve diseases or with artificial heart valves. Moreover, the compound according to the invention might be suitable for the treatment of disseminated intravasal clotting (DIC).

Thromboembolic complications furthermore occur in microangiopathic hemolytic anemias, extracorporeal blood circulations, such as hemodialysis, and heart valve prostheses.

Moreover, the compound according to the invention might also be suitable for the prophylaxis and/or treatment of atherosclerotic vascular diseases and inflammatory diseases such as rheumatic diseases of the locomotor system, moreover might also be useful for the prophylaxis and/or treatment of Alzheimer's disease. Moreover, the compound according to the invention might also be employed for the inhibition of tumor growth and of metastasis formation, in microangiopathies, age-related macular degeneration, diabetic retinopathy, diabetic nephropathy and other microvascular diseases, and for the prevention and treatment of thromboembolic complications, such as, for example, venous thromboembolisms, in tumor patients, in particular those who are subjected to relatively large surgical interventions or chemo- or radiotherapy.

The compound according to the invention might also moreover be employed for the prevention of coagulation *ex vivo*, e.g. for the preservation of blood and plasma products, for the cleaning/pretreatment of catheters and other medical aids and equipment, for the coating of artificial surfaces of medical aids and equipment employed *in vivo* or *ex vivo* or in biological samples which contain factor Xa.

The compound according to the invention might also be used for the treatment and/or prophylaxis of diseases, in particular of the aforementioned diseases.

The compound according to the invention might also be used for the production of a medicament for the treatment and/or prophylaxis of diseases, in particular of the

aforementioned diseases.

The present invention furthermore relates to medicaments comprising the compound according to the invention and one or more other active substances, which might be used for the treatment and/or prophylaxis of the aforementioned diseases. Suitable combination active substances which may be mentioned by way of example and preferably are:

- lipid-lowering agents, in particular HMG-CoA-(3-hydroxy-3-methylglutaryl-coenzyme A)-reductase inhibitors;

- coronary therapeutics/vasodilators, in particular ACE (angiotensin converting enzyme) inhibitors; AII (angiotensin II) receptor antagonists; β-adrenoceptor antagonists; alpha-1-adrenoceptor antagonists; diuretics; calcium channel blockers; substances which bring about an increase in cyclic guanosine monophosphate (cGMP), such as, for example, stimulators of soluble guanylate cyclase;

- plasminogen activators (thrombolytics/fibrinolytics) and thrombolysis/fibrinolysis-increasing compounds such as inhibitors of the plasminogen activator inhibitor (PAI inhibitors) or inhibitors of the thrombin-activated fibrinolysis inhibitor (TAFI inhibitors);

- substances having anticoagulatory activity (anticoagulants);

- substances inhibiting platelet aggregation (platelet aggregation inhibitors, thrombocyte aggregation inhibitors);

- and fibrinogen receptor antagonists (glycoprotein IIb/IIIa antagonists).

The present invention further relates to medicaments which contain the compound according to the invention, customarily together with one or more inert, nontoxic, pharmaceutically suitable excipients, and their possible use for the aforementioned purposes.

The compound according to the invention can act systemically and/or locally. For this purpose, they can be administered in a suitable manner, such as, for example, orally, parenterally, pulmonarily,

nasally, sublingually, lingually, buccally, rectally, dermally, transdermally, conjunctivally, otically or as an implant or stent.

For these administration routes, the compound according to the invention can be administered in suitable administration forms.

For oral administration, administration forms functioning according to the prior art, releasing the compound according to the invention rapidly and/or in modified form, which contain the compound of the formula (I) in the modification II or in the amorphous form, such as, for example, tablets (noncoated or coated tablets, for example with enteric coatings or coatings which dissolve with a delay or are insoluble, which control the release of the compound according to the invention), tablets disintegrating rapidly in the oral cavity or films/wafers, films/lyophilizates, capsules (for example hard or soft gelatin capsules), coated tablets, granules, pellets, powders, suspensions or aerosols are suitable.

Parenteral administration can take place with circumvention of an absorption step (e.g. intravenously, intraarterially, intracardially, intraspinally or intralumbarly) or with intervention of an absorption (e.g. intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). For parenteral administration, suitable administration forms are, inter alia, injection and infusion preparations in the form of suspensions, lyophilizates or sterile powders.

For the other administration routes, for example, inhalation pharmaceutical forms (inter alia powder inhalers, nebulizers), tablets to be administered lingually, sublingually or buccally, films/wafers or capsules, suppositories, ear or eye preparations, vaginal capsules, aqueous suspensions (lotions, shake mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (e.g. patches), milk, pastes, foams, dusting powders, implants or stents are suitable.

Oral or parenteral administration is preferred, in particular oral administration.

The compound according to the invention can be converted to the administration forms mentioned. This can take place in a manner known per se by mixing with inert, nontoxic, pharmaceutically suitable excipients. These excipients include, inter alia, vehicles (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersants or wetting agents (for example sodium dodecylsulfate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants such as, for example, ascorbic acid), colorants (e.g. inorganic pigments such as, for example, iron oxides) and taste and/or odor corrigents.

In general, it has proven advantageous in the case of parenteral administration to administer amounts of approximately 0.001 to 1 mg/kg, preferably approximately 0.01 to 0.5 mg/kg of body weight to

achieve effective results. In the case of oral administration, the dose is approximately 0.01 to 100 mg/kg, preferably approximately 0.01 to 20 mg/kg and very particularly preferably 0.1 to 10 mg/kg of body weight.

In spite of this, it may optionally be necessary to depart from the amounts mentioned, namely depending on body weight, route of administration, individual behavior toward the medicament, type of preparation and time or interval at which administration takes place. Thus in some cases it may be adequate to manage with less than the aforementioned minimum amount, whereas in other cases the upper limit mentioned must be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these into a number of individual doses over the course of the day.

The invention further relates to a process for the preparation of the compound of the formula (I) in the modification II, by dissolving the compound of the formula (I) in the modification I in an inert solvent and precipitating the active substance by addition of a precipitating agent at a temperature between 0°C and 80°C, preferably from 20 to 25°C. The precipitate is isolated and dried. The compound of the formula (I) is thus obtained in the modification II.

The invention likewise relates to a process for the preparation of the compound of the formula (I) in the modification II, by dissolving the compound of the formula (I) in the modification I in an inert solvent and storing it, preferably at elevated temperature, in particular at a temperature of 30°C up to the reflux temperature of the solvent, until the complete evaporation of the solvent and crystallization of the active substance. The compound of the formula (I) is thus obtained in the modification II.

The invention likewise relates to a process for the preparation of the compound of the formula (I) in the modification II, by suspending the compound of the formula (I) in the amorphous form in an anhydrous inert solvent and stirring or shaking it until achieving the desired degree of conversion, in particular until quantitative conversion, to the modification II. The crystallizate obtained is isolated and dried. The compound of the formula (I) is thus obtained in the modification II.

Suitable inert solvents are lower alcohols such as, for example, methanol, ethanol, n-propanol, iso-propanol, n-butanol, sec-butanol, isobutanol, 1-pentanol, or ketones such as acetone, or alkanes such as n-pentane, cyclopentane, n-hexane, cyclohexane, or tetrahydrofuran, or acetonitrile, or toluene, or ethyl acetate, or 1,4-dioxane, or mixtures of the solvents mentioned, or mixtures of the solvents mentioned with water. Acetone, tetrahydrofuran, 1-pentanol or mixtures of the solvents mentioned are preferred. Suitable precipitating agents are inert, anhydrous solvents, in which the active substance is poorly soluble, such as, for example, n-heptane, cyclohexane or toluene. n-Heptane is preferred.

Preferably, the compound of the formula (I) is prepared in the modification II, by dissolving the compound of the formula (I) in the modification I in acetone or tetrahydrofuran and precipitating the active substance by addition of n-heptane at a temperature between 0 and 80°C, preferably at a temperature from 20 to 25°C. The precipitate is isolated and dried. The compound of the formula (I) is thus obtained in the modification II.

Likewise preferably, the compound of the formula (I) is prepared in the modification II, by dissolving the compound of the formula (I) in the modification I in 1,4-dioxane and storing at elevated temperature, in particular at a temperature from 30°C up to the reflux temperature of the solvent, for example 50°C, until the complete evaporation of the solvent and crystallization of the active substance. The compound of the formula (I) is thus obtained in the modification II.

Likewise preferably, the compound of the formula (I) is prepared in the modification II, by suspending the compound of the formula (I) in the amorphous form in an inert anhydrous solvent and stirring or shaking at a temperature of 20 to 25°C until achieving the desired degree of conversion to the modification II. The crystallizate obtained is isolated and dried. The compound of the formula (I) is thus obtained in the modification II.

The invention further relates to a process for the preparation of the compound of the formula (I) in the amorphous form, in which the compound of the formula (I) in a crystalline form is fused and subsequently rapidly cooled. The compound of the formula (I) is thus obtained in the amorphous form.

Preferably, the compound of the formula (I) is prepared in the amorphous form, by fusing the compound of the formula (I) in a crystalline form at a temperature of at least 230°C, in particular at a temperature of 240 to 250°C, and subsequently rapidly cooling it. The compound of the formula (I) is thus obtained in the amorphous form.

Of the crystalline forms modification I, II and III, preferably modification I or II, are employed here, in particular modification I.

By means of rapid cooling, the temperature of the compound (I) is preferably brought to or close to room temperature, for example to a temperature of approximately 15 to 30°C, in particular of approximately 20 to 25°C. The rapid cooling is preferably carried out in the course of a few seconds, for example in the course of approximately 5 seconds. Shock cooling is preferably employed for rapid cooling.

The compound of the formula (I) in the modification III can be prepared by dissolving the compound of the formula (I) in the modification I in an inert solvent, for example acetone. The

solution is treated with water and allowed to stand at room temperature until the solvent has completely evaporated. The compound of the formula (I) is thus obtained in the modification III.

The hydrate of the compound of the formula (I) can be prepared by dissolving the compound of the formula (I) in the modification I in ethanol:water (1:1). The solution is a stored at a temperature of approximately –20°C until the solvent has evaporated. The hydrate of the compound of the formula (I) is thus obtained.

The NMP solvate of the compound of the formula (I) can be prepared by suspending the compound of the formula (I) in the modification I in 1-methyl-2-pyrrolidone and stirring at room temperature. After 2 days, the suspension is filtered and the product is dried. The NMP solvate of the compound of the formula (I) with an NMP content of 18.5 percent by weight is thus obtained.

The inclusion compound with THF of the compound of the formula (I) can be prepared by dissolving the compound of the formula (I) in the modification I in tetrahydrofuran. The solution is stored at room temperature until the solvent has evaporated. The inclusion compound with THF of the compound of the formula (I) is thus obtained.

The percentages in the following tests and examples, if not stated otherwise, are percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and concentration data of liquid/liquid solutions in each case relate to the volume.

Working examples

The thermograms were obtained using a DSC 7 or Pyris-1 differential scanning calorimeter and TGA 7 thermogravimetric analyzer from Perkin-Elmer. The X-ray diffractograms were recorded in a Stoe transmission diffractometer. The IR, FIR, NIR and Raman spectra were recorded using IFS 66v Fourier IR (IR, FIR), IFS 28/N (NIR) and RFS 100 (Raman) spectrometers from Bruker.

Example 1: 5-Chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I

The preparation of the modification I of the title compound is described in WO 01/47949 and WO 2004/060887.

Example 2: Preparation of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification II

Example 2.1

208 g of chlorothiophenecarboxylic acid were suspended in 1100 ml of toluene and heated to 75 to 80°C. 112 ml of thionyl chloride were added dropwise at this temperature in the course of 2 h. The resulting reaction solution was stirred for a further 2 h until the end of evolution of gas. In the course of this, the internal temperature was increased to 100-110°C in 5° steps. The mixture was cooled and the solution of the acid chloride was concentrated on a rotary evaporator.

350 g of oxamine hydrochloride were suspended in 2450 ml of NMP, treated with 385 ml of triethylamine and stirred for 15 min. The mixture was cooled to 10°C, treated with the solution of the acid chloride and 70 ml of toluene and stirred. 350 ml of tap water were added to the suspension and it was heated to 82°C. After filtration, the active substance was precipitated using 3.5 l of water and the mixture was subsequently stirred for 2 h. Drying at 70°C in vacuo.

Example 2.2

About 200 mg of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I were dissolved hot in about 80 ml of tetrahydrofuran. The solution was filtered and divided in half. One half was treated at room temperature with n-heptane until the active substance precipitated. The residue was filtered off and dried at room temperature. It was investigated by X-ray diffractometry and corresponded to the title compound in the modification II.

Example 2.3

About 200 mg of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I were dissolved hot in about 40 ml of 1-pentanol. The solution was filtered and divided in half. One half was treated with n-heptane until the active substance precipitated. The residue was filtered off and dried at room temperature. It was investigated by X-ray diffractometry and corresponded to the title compound in the modification II.

Example 2.4

About 200 mg of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I were dissolved hot in about 40 ml of 1,4-dioxane. The solution was filtered and divided in half. One half was stored at 50°C in a drying oven until the solvent had evaporated. The residue was investigated by X-ray diffractometry and corresponded to the title compound in the modification II.

Example 2.5

About 50 mg of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the amorphous form, prepared by fusing on a Kofler heating bench at about 240°C and subsequent shock cooling to room temperature, were suspended in about 2 ml of ethanol and stirred at 25°C for 0.5 h. The crystallizate was isolated and dried. The residue was investigated by X-ray diffractometry and corresponded to the title compound in the modification II.

Example 2.6

About 100 mg of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I were dissolved hot in about 50 ml of acetone. The solution was filtered and treated with n-heptane in an ice bath until the active substance precipitated. The residue was filtered off and dried at room temperature. It was investigated by X-ray diffractometry and corresponded to the title compound in the modification II.

Example 3: Preparation of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification III

About 120 mg of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I were dissolved hot in about 50 ml of acetone. The solution was filtered, treated with about 50 ml of water and allowed to stand at room temperature until the solvent had evaporated. The residue was investigated thermoanalytically and

corresponded to the title compound in the modification III.

Example 4: Preparation of the hydrate of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

About 400 mg of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I were dissolved hot in about 60 ml of ethanol:water (1:1) and filtered. A part of the solution was stored in a freezer at a temperature of approximately –20°C until the solvent had evaporated. The residue corresponded to the hydrate of the title compound.

Example 5: Preparation of the NMP solvate of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

About 3.5 g of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I were suspended in 10 ml of 1-methyl-2-pyrrolidone and stirred at room temperature. After a few hours, about 20 ml of NMP were additionally added. After two days, the suspension was filtered off with suction and the residue was dried at room temperature. The residue was investigated thermoanalytically and corresponded to the NMP solvate of the title compound having an NMP content of 18.5 percent by weight.

Example 6: Preparation of the inclusion compound with THF of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

About 400 mg of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I were dissolved hot in about 50 ml of tetrahydrofuran and filtered. A part of the solution was stored at room temperature until the solvent had evaporated. The residue was investigated thermoanalytically and corresponded to the inclusion compound with THF of the title compound.

Tab. 1: Differential scanning calorimetry and thermogravimetry

	Modifi-cation I	Modifi-cation II	Modifi-cation III	Hydrate	NMP solvate	ESV toluene
Melting point [°C]	230	203	-	-	-	-
Transition point [°C]	-	ca. 192	ca. 127	-	-	-
Mass loss [% by wt.]	0.1	0.1	<0.5	ca. 4	18.5	5-7

Tab. 2: X-ray diffractometry

Reflections					
Modifi-cation I [2 theta]	Modifi-cation II [2 theta]	Modifi-cation III [2 theta]	Hydrate [2 theta]	NMP solvate [2 theta]	ESV with THF [2 theta]
8.9	12.8	11.7	3.6	4.8	9.0
12.0	17.7	16.5	14.3	5.8	12.0
14.3	18.1	17.5	16.4	7.3	14.3
16.5	18.4	19.1	16.6	10.9	14.7
17.4	19.0	19.6	17.5	14.5	16.5
18.1	19.9	19.8	19.3	15.2	16.8
19.5	20.8	23.1	19.6	15.7	17.5
19.9	21.6	23.2	19.9	16.0	19.6
21.7	22.1	23.8	20.2	17.6	19.9
22.5	22.9	24.3	21.7	17.9	21.7
23.4	24.1	28.1	22.5	20.0	22.5
24.1	26.1	28.2	24.2	20.6	23.4
24.5	26.4	31.2	25.6	21.3	24.5
24.7	26.6		25.8	21.8	24.7
25.6	27.2		28.8	22.3	25.2
26.4	27.5		29.5	22.7	25.6
26.7	28.8		31.8	23.1	26.4
30.0	29.8		32.7	23.3	26.7
30.1	31.0			23.5	28.7
31.8	31.6			24.0	30.1
	32.9			24.7	31.0
				24.9	31.8
				25.2	
				26.0	
				26.5	
				26.9	
				28.0	
				28.8	
				29.2	
				29.5	
				29.8	

Tab. 3: IR spectroscopy

Peak maxima				
Modification II [cm^{-1}]	Modification II [cm^{-1}]	Modification III [cm^{-1}]	Hydrate [cm^{-1}]	NMP solvate [cm^{-1}]
564	552	515	708	497
686	598	546	755	547
708	692	596	776	562
746	713	611	820	708
757	725	644	920	749
830	756	688	992	819
846	809	709	1054	838
920	825	748	1089	921
991	833	755	1120	987
1011	924	776	1146	1065
1056	994	812	1221	1088
1077	1067	816	1289	1123
1120	1085	842	1312	1143
1146	1097	864	1324	1162
1163	1121	921	1340	1225
1219	1146	992	1349	1242
1286	1232	1016	1413	1260
1307	1285	1054	1429	1292
1323	1310	1089	1469	1302
1341	1328	1121	1485	1315
1374	1345	1148	1518	1330
1411	1415	1161	1555	1354
1429	1431	1224	1630	1387
1470	1473	1261	1668	1414
1486	1523	1288	1738	1421
1517	1554	1313	2873	1430
1546	1631	1325	3341	1471
1605	1648	1348		1517
1646	1663	1380		1566
1669	1723	1412		1636

Peak maxima				
Modification II [cm^{-1}]	Modification II [cm^{-1}]	Modification III [cm^{-1}]	Hydrate [cm^{-1}]	NMP solvate [cm^{-1}]
1737	1745	1429		1665
2867	3341	1473		1755
2895		1518		2887
2936		1553		2928
2976		1629		2948
3354		1668		2983
		1741		3045
		2878		3085
		3080		3247
		3340		

Tab. 4: Raman spectroscopy

Peak maxima				
Modifi-cation I [cm^{-1}]	Modifi-cation II [cm^{-1}]	Modifi-cation III [cm^{-1}]	Hydrate [cm^{-1}]	NMP solvate [cm^{-1}]
84	86	85	85	85
111	184	112	111	105
642	276	165	132	119
672	345	671	642	485
687	485	712	672	671
745	643	743	711	710
779	672	778	744	743
792	716	793	778	776
1083	742	996	793	800
1099	778	1093	922	1193
1232	800	1288	1073	1229
1280	864	1322	1083	1233
1307	925	1428	1097	1242

Peak maxima				
Modifi-cation I [cm^{-1}]	Modifi-cation II [cm^{-1}]	Modifi-cation III [cm^{-1}]	Hydrate [cm^{-1}]	NMP solvate [cm^{-1}]
1325	995	1442	1231	1259
1343	1086	1475	1301	1282
1428	1119	1555	1325	1313
1473	1149	1610	1428	1319
1485	1196	1626	1473	1328
1548	1227	1663	1485	1412
1605	1248	1669	1548	1433
1638	1282	1723	1605	1473
1664	1310	2881	1638	1608
1722	1330	2992	1722	1629
2899	1432	3020	2885	1660
2944	1474	3098	2898	1763
2983	1556		2944	2844
3074	1608		2983	2889
	1631		3074	2931
	1648			2946
	1722			2984
	2885			3075
	2938			3096
	2989			
	3077			
	3091			

Tab. 5: FIR spectroscopy

Peak maxima			
Modification I [cm^{-1}]	Modification II [cm^{-1}]	Hydrate [cm^{-1}]	NMP solvate [cm^{-1}]
82	83	83	84
97	96	96	126
138	126	126	137
169	146	134	169
179	159	138	190
210	190	156	209
226	213	168	237
247	244	179	282
272	279	226	297
283	293	247	308
298	304	271	317
303	344	298	344
350	363	304	353
394	401	349	400
417	416	394	413
438	437	408	417
458	456	417	432
475	484	438	459
484		455	471
		472	485
		484	498

Tab. 6: NIR spectroscopy

Peak maxima				
Modification I [cm^{-1}]	Modification I [cm^{-1}]	Modification I [cm^{-1}]	Hydrate [cm^{-1}]	NMP solvate [cm^{-1}]
4082	4086	4080	4083	4040
4142	4228	4218	4228	4084
4170	4418	4329	4305	4213
4228	4457	4398	4384	4382
4299	4634	4606	4631	4552
4376	4905	4891	4905	4638
4429	5846	5066	5145	4830
4479	5911	6022	5760	5815
4633	6026	6072	5833	6091
4791	6081		5889	7213
4877	6582		6023	8527
4907			6076	
5081			6555	
5760			6868	
5885				
6002				
6441				
6564				
8473				
8833				

Example 7: Preparation of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in amorphous form

Example 7.1

About 50 mg of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I were fused on a Kofler heating bench at about 240°C and subsequently brought to room temperature by shock cooling. The active substance was investigated by X-ray diffractometry and was present in the amorphous form.

Example 7.2

About 3 g of 5-chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide in the modification I were fused in a drying oven at about 250°C and subsequently brought to room temperature by shock cooling. The active compound was investigated by X-ray diffractometry and was present in the amorphous form.

Tab. 7: Differential scanning calorimetry and thermogravimetry (amorphous form)

Glass transition temperature:	about 83°C

Tab. 8: Spectroscopy (amorphous form)

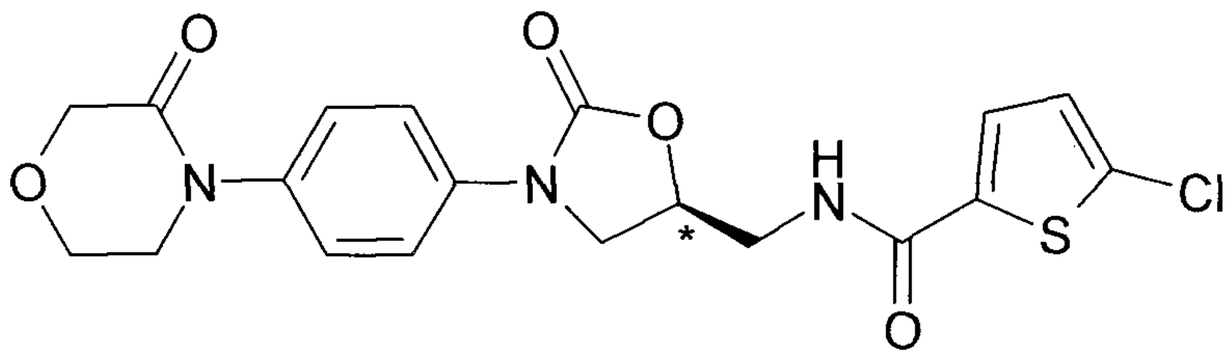
Peak maxima			
IR [cm^{-1}]	Raman [cm^{-1}]	FIR [cm^{-1}]	NIR [cm^{-1}]
467	486	91	4006
512	642	97	4081
550	673	137	4224
595	711	169	4307
613	742	246	4403
643	781	272	4634
689	923	297	4875
709	965	248	5193
725	1016	393	5865
750	1078	416	6017
810	1126	438	6073
834	1224	456	6696
864	1243	474	7028
921	1290	474	8452
995	1326		8873
1015	1428		
1026	1479		
1058	1548		
1083	1607		
1126	1642		
1161	2158		
1222	2975		

Peak maxima			
IR [cm^{-1}]	Raman [cm^{-1}]	FIR [cm^{-1}]	NIR [cm^{-1}]
1288	3090		
1312			
1325			
1380			
1407			
1428			
1480			
1516			
1549			
1607			
1647			
1753			
2126			
2869			
2933			
2967			
3084			
3317			

30725-504

CLAIMS:

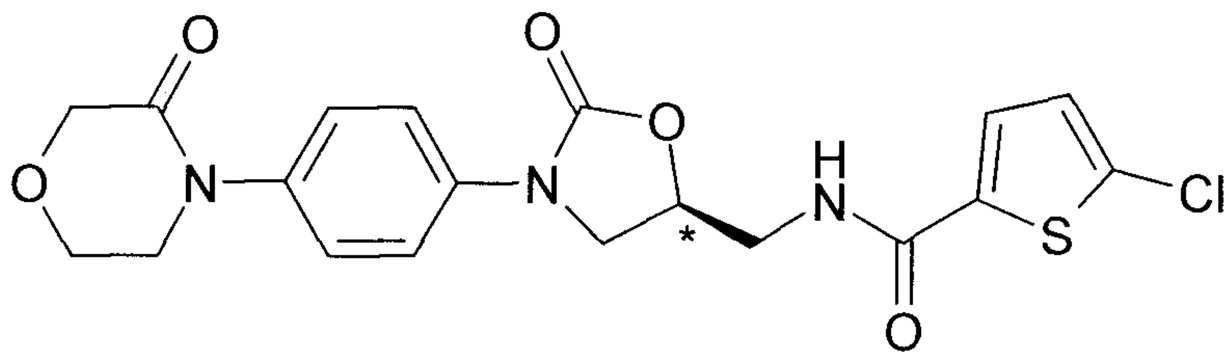
1. A compound of the formula (I)



(I)

in the modification II form.

2. A compound of the formula (I)

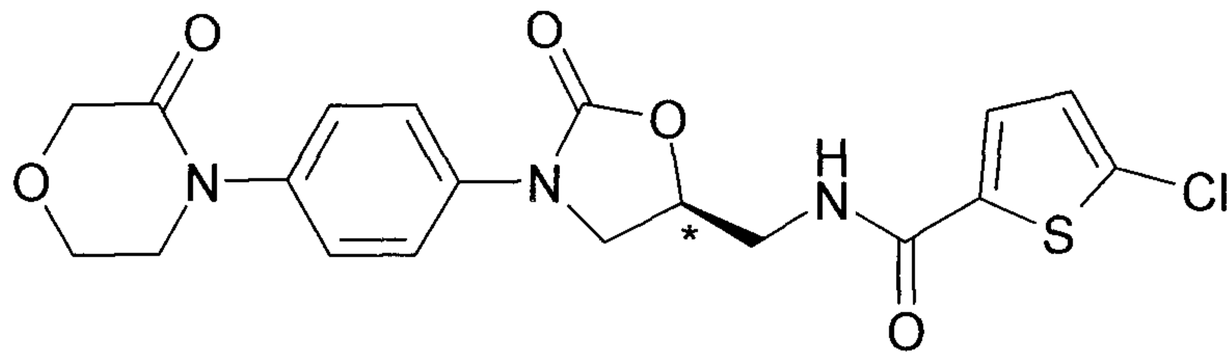


(I)

in the modification II, wherein the compound of the formula (I) in the modification II shows peak maxima in the NIR spectra at 4086, 4228, 4418, 4457, 4634, 4905, 5846, 5911, 6026, 6081 and 6582 cm^{-1}.

3. A medicament comprising the compound of claim 1 or 2, an inert, nontoxic, pharmaceutically suitable excipient.

4. Process for the preparation of a compound of the formula (I)



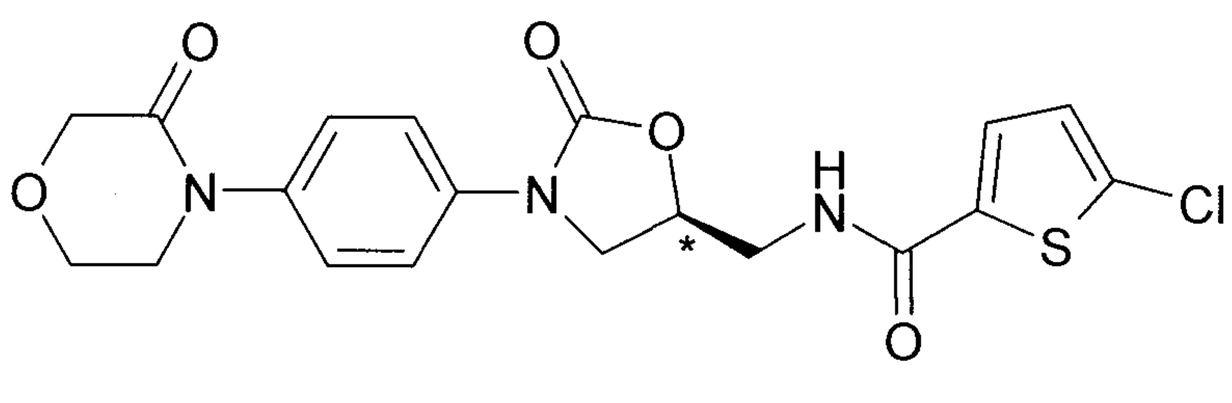
(I)

in the modification II which in the NIR spectrogram has peak maxima at 4086, 4228, 4418, 4457, 4634, 4905, 5846, 5911, 6026, 6081 and 6582, comprising:

dissolving the compound of formula (I) in the modification I which in the NIR spectrogram has peak maxima at 4082, 4142, 4170, 4228, 4299, 4376, 4429, 4479, 4633, 4791, 4877, 4907, 5081, 5760, 5885, 6002, 6441, 6564, 8473 and 8833, in methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, 1-pentanol, acetone, n-pentane, cyclopentane, n-hexane, tetrahydrofuran, acetonitrile, ethyl acetate, or 1,4-dioxane, or a mixture thereof, or a mixture thereof with water at a temperature between 0°C and 80°C, and

precipitating the compound by addition of n-heptane, cyclohexane or toluene.

5. Process for preparation of a compound of formula (I)



(I)

in the modification II which in the NIR spectrogram has peak maxima at 4086, 4228, 4418, 4457, 4634, 4905, 5846, 5911, 6026, 6081 and 6582, the compound of the formula (I) in the amorphous form comprising:

suspending in n-heptane, cyclohexane or toluene, and

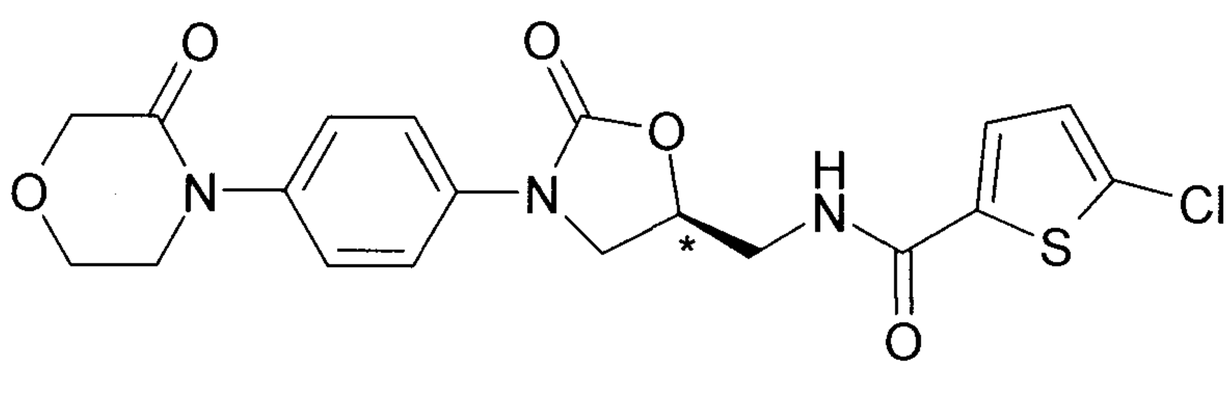
stirring or shaking the suspension until quantitative conversion to the modification II.

in the modification II which in the NIR spectrogram has peak maxima at 4086, 4228, 4418, 4457, 4634, 4905, 5846, 5911, 6026, 6081 and 6582, comprising:

dissolving the compound of formula (I) in the modification I which in the NIR spectrogram has peak maxima at 4082, 4142, 4170, 4228, 4299, 4376, 4429, 4479, 4633, 4791, 4877, 4907, 5081, 5760, 5885, 6002, 6441, 6564, 8473 and 8833, in methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, 1-pentanol, acetone, n-pentane, cyclopentane, n-hexane, tetrahydrofuran, acetonitrile, ethyl acetate, or 1,4-dioxane, or a mixture thereof, or a mixture thereof with water at a temperature between 0°C and 80°C, and

precipitating the compound by addition of n-heptane, cyclohexane or toluene.

5. Process for preparation of a compound of formula (I)



(I)

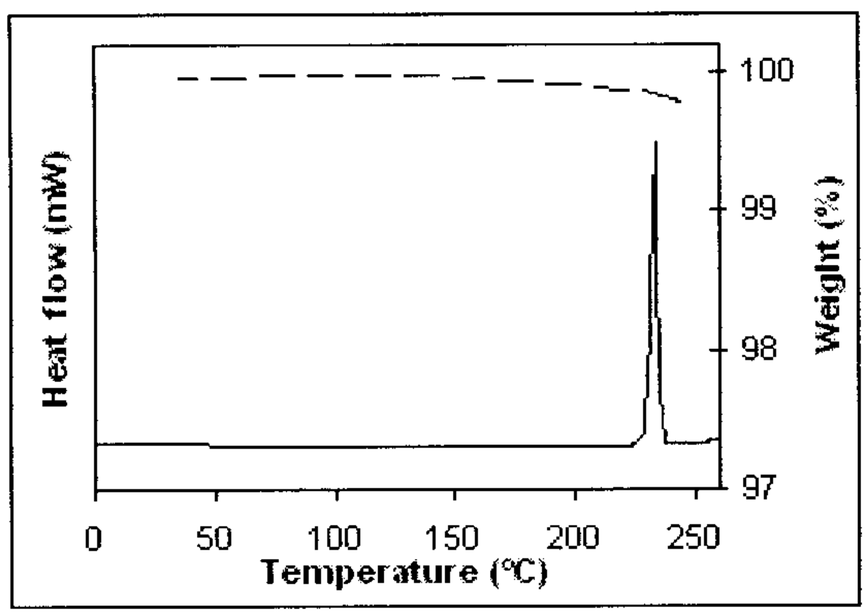
in the modification II which in the NIR spectrogram has peak maxima at 4086, 4228, 4418, 4457, 4634, 4905, 5846, 5911, 6026, 6081 and 6582, the compound of the formula (I) in the amorphous form comprising:

suspending in n-heptane, cyclohexane or toluene, and

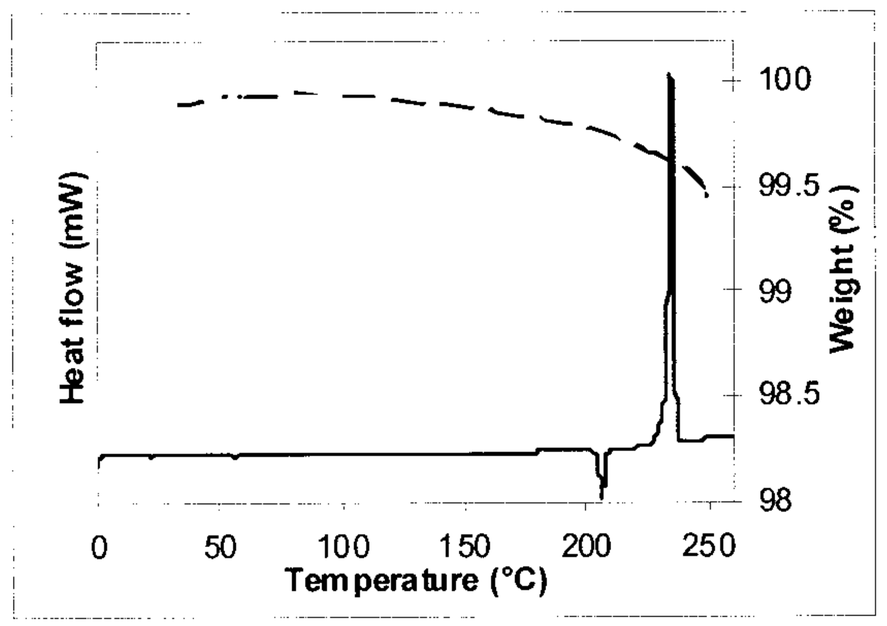
stirring or shaking the suspension until quantitative conversion to the modification II.

Fig. 1

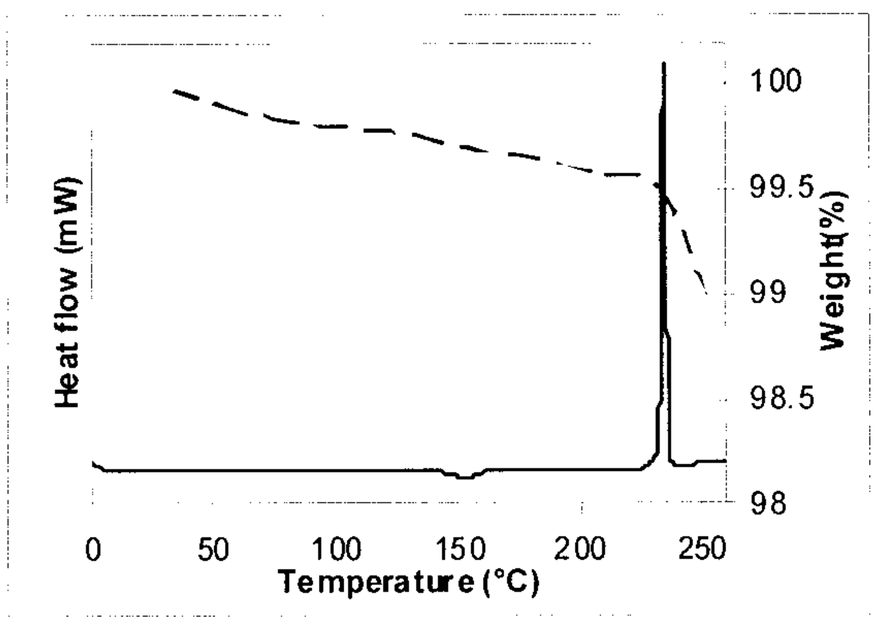
DSC (solid line) and TGA thermograms (dashed line)



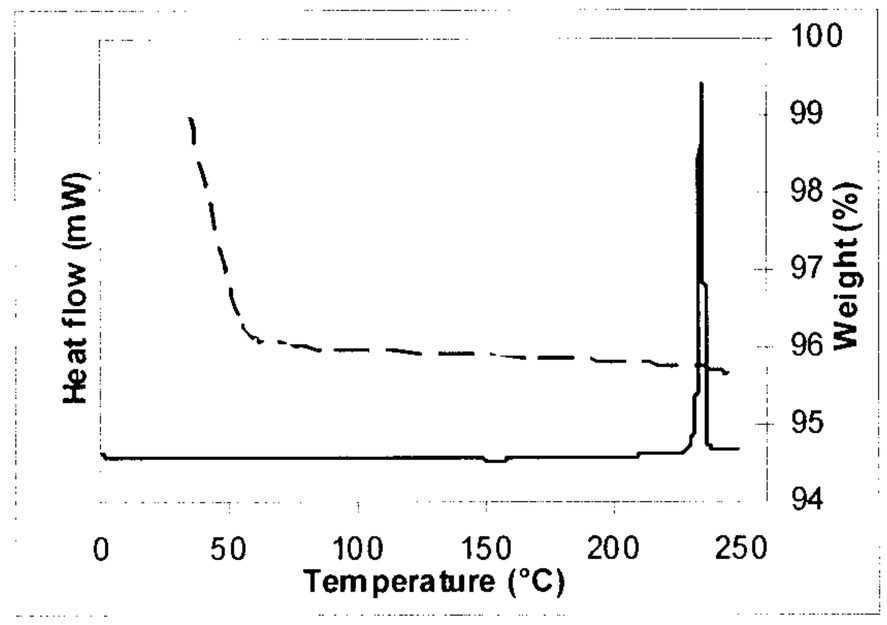
Modification I



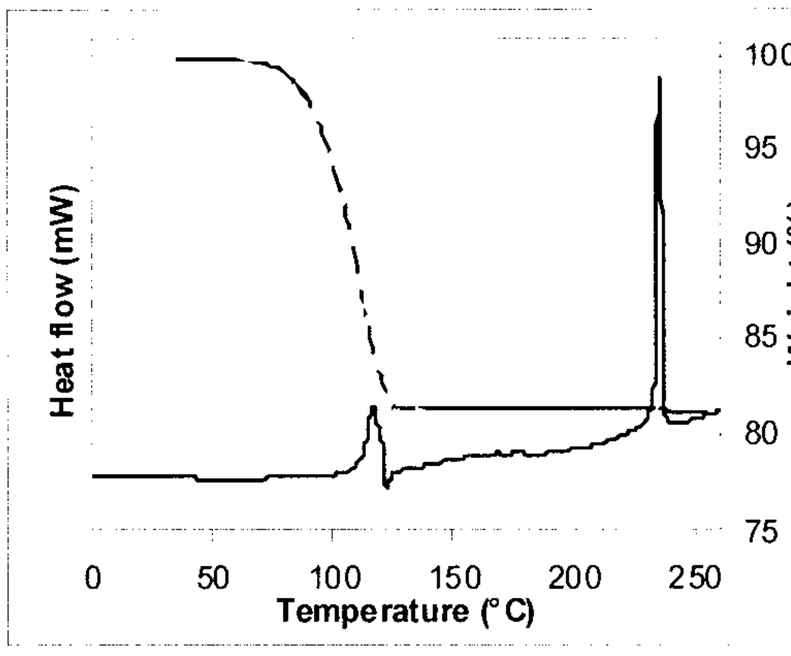
Modification II



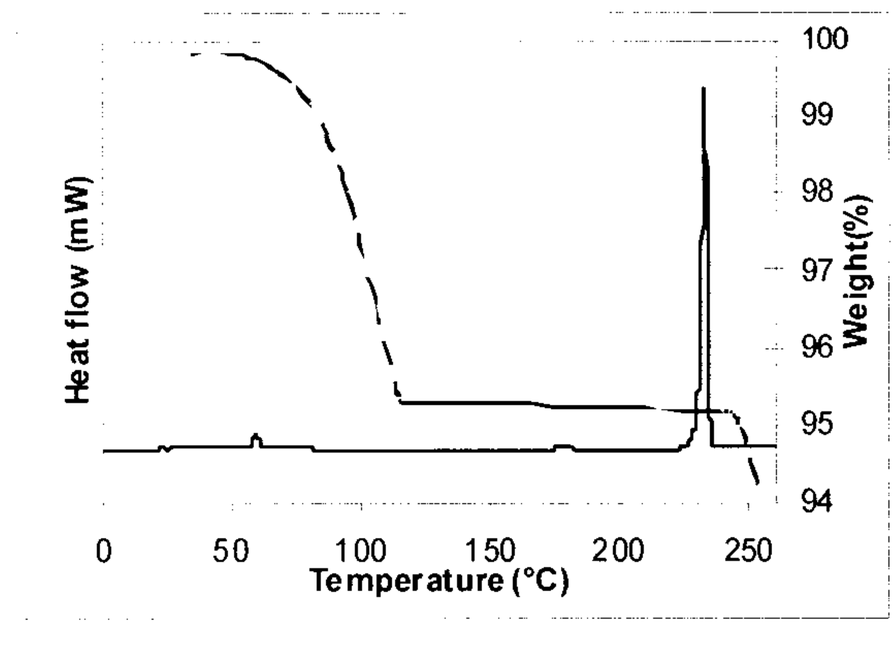
Modification III



Hydrate



NMP solvate



Inclusion compound with THF

Fig. 2

X-ray diffractograms

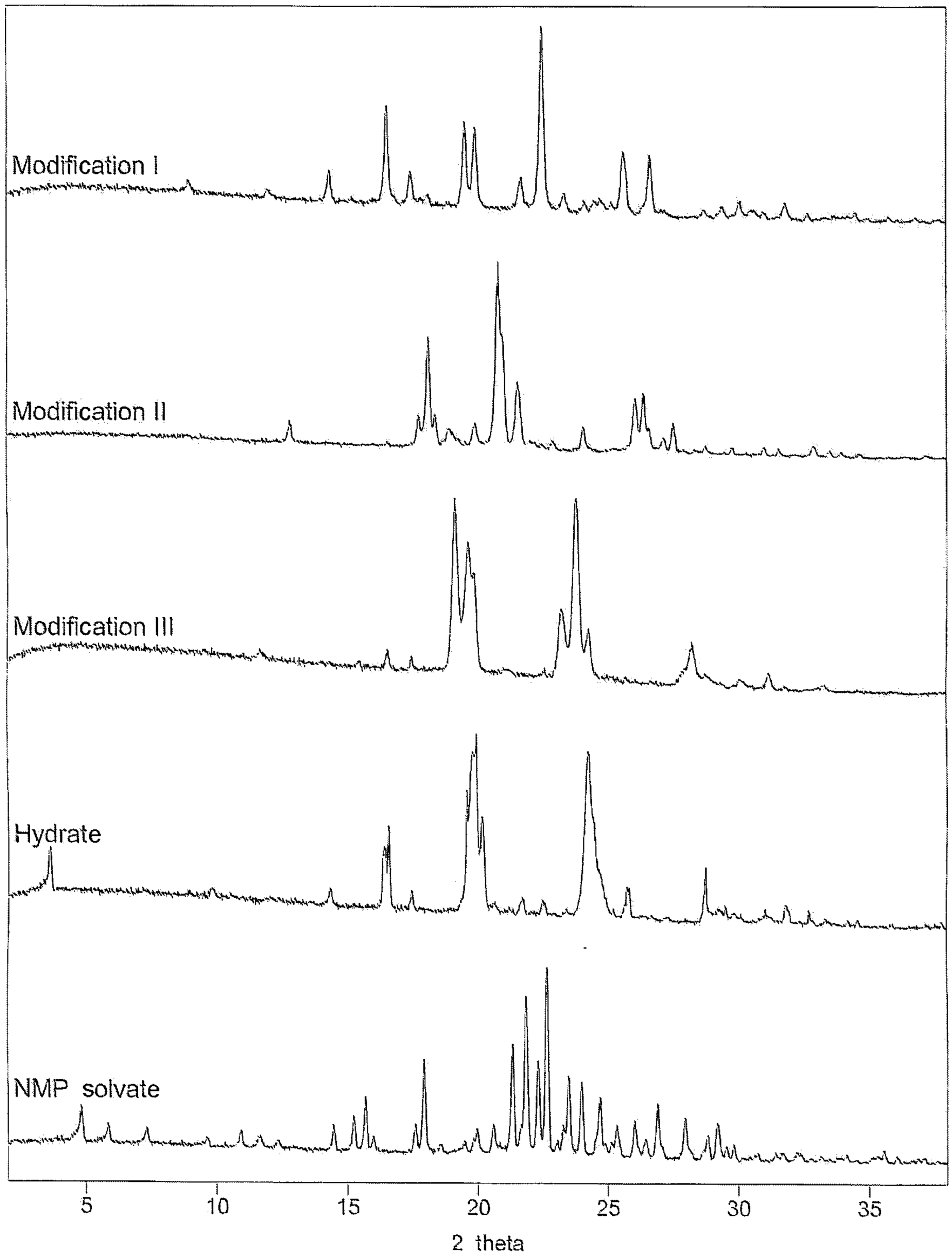


Fig. 3: IR spectra

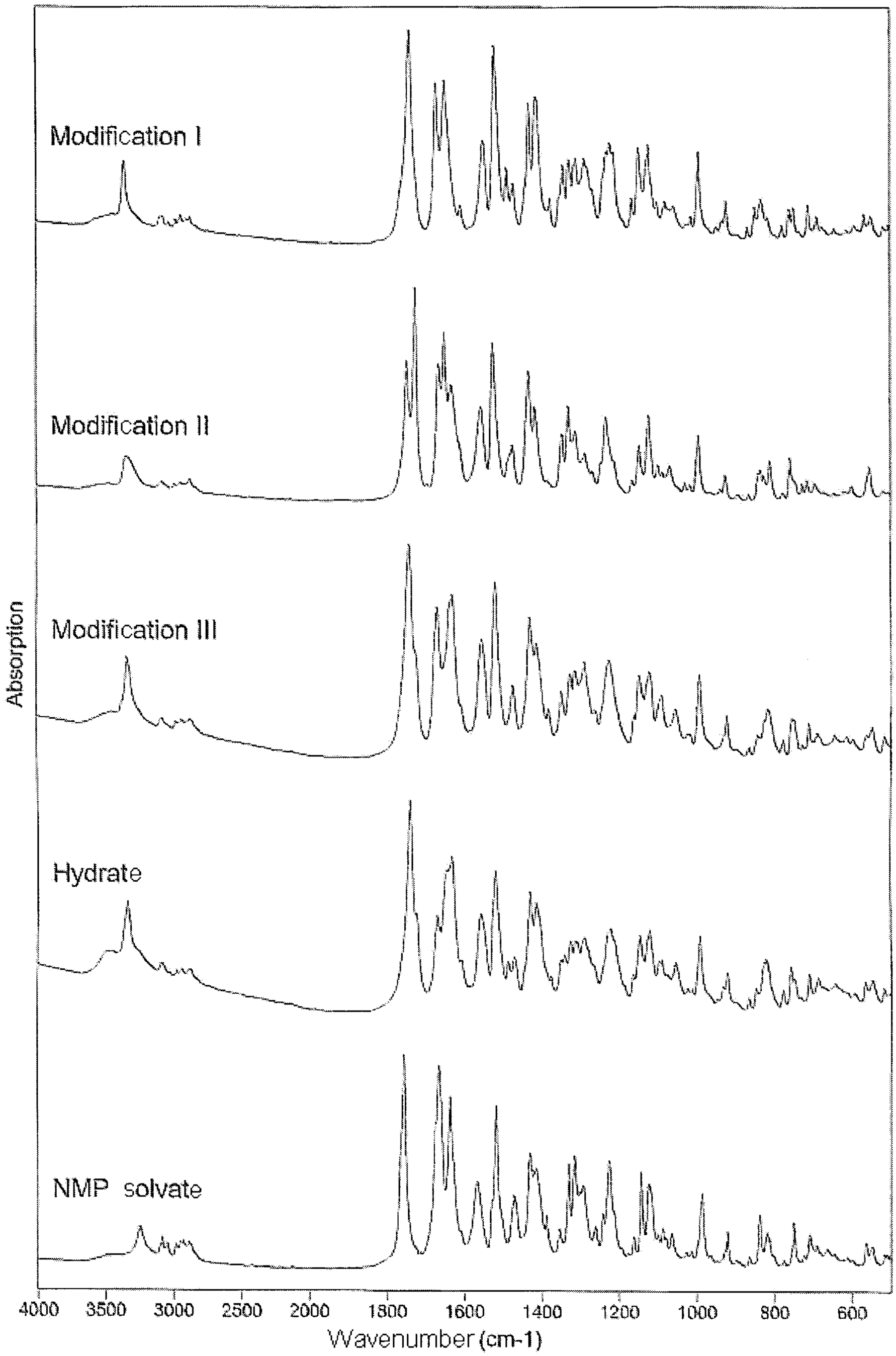


Fig. 4

Raman spectra

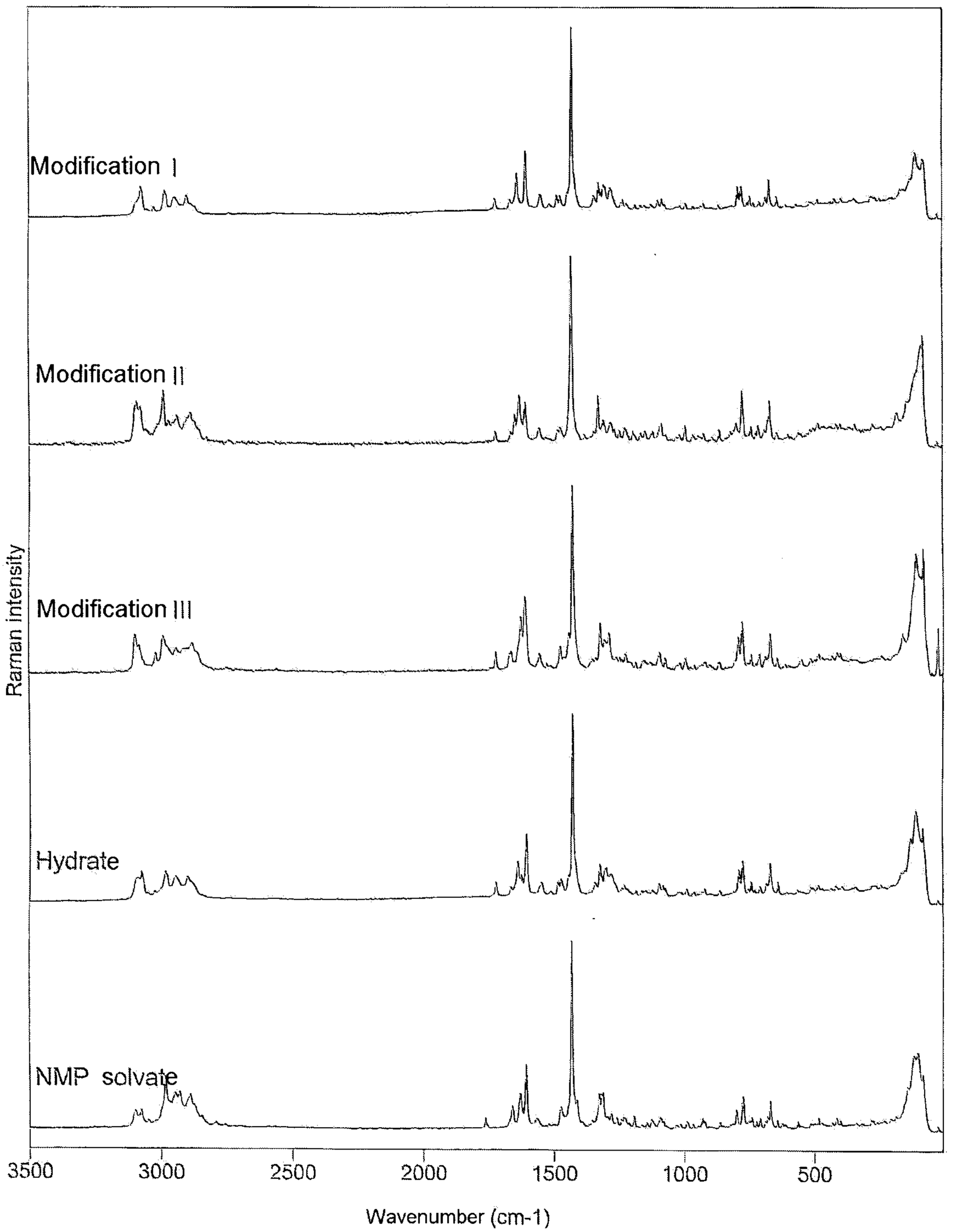


Fig. 5

FIR spectra

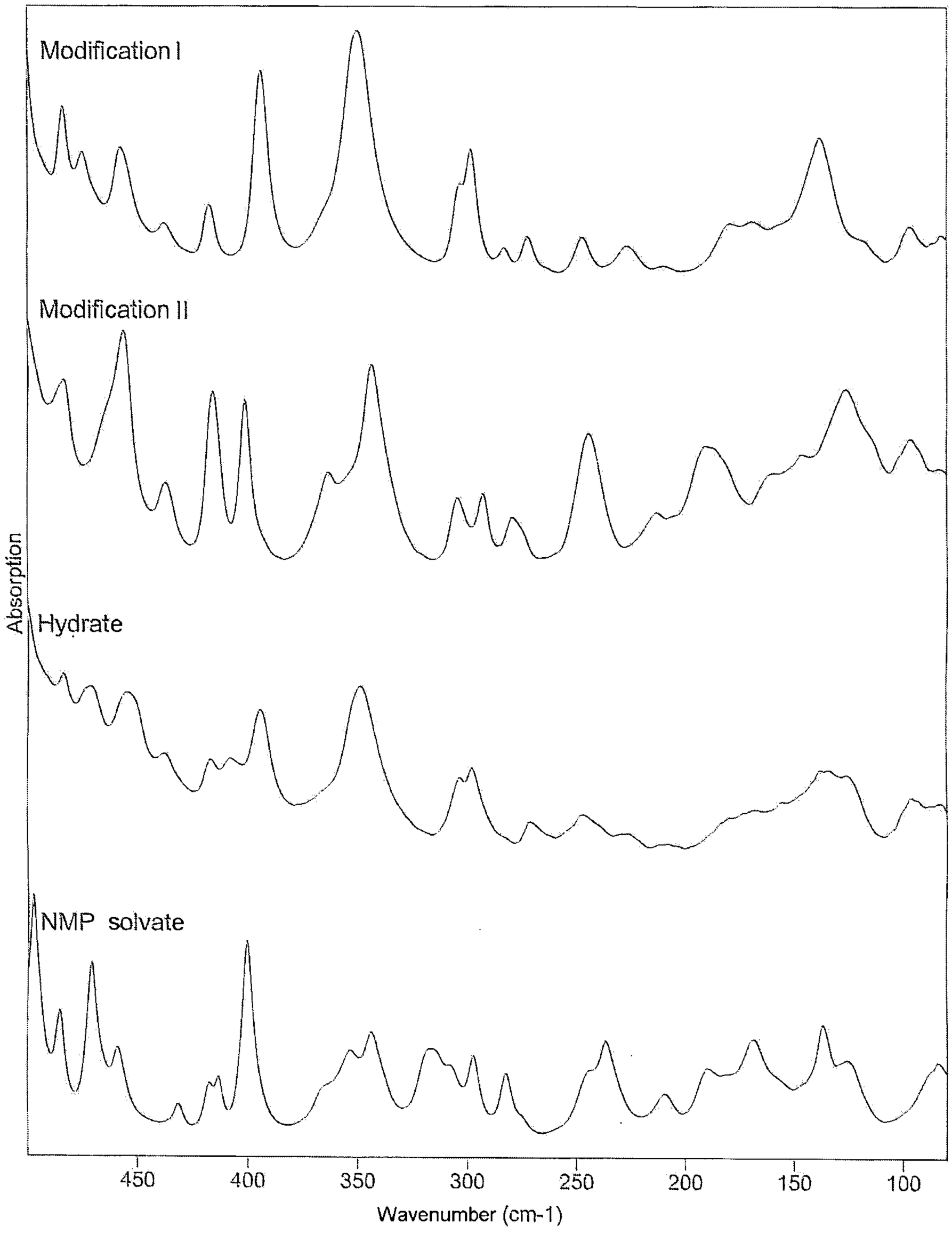


Fig. 6

NIR spectra

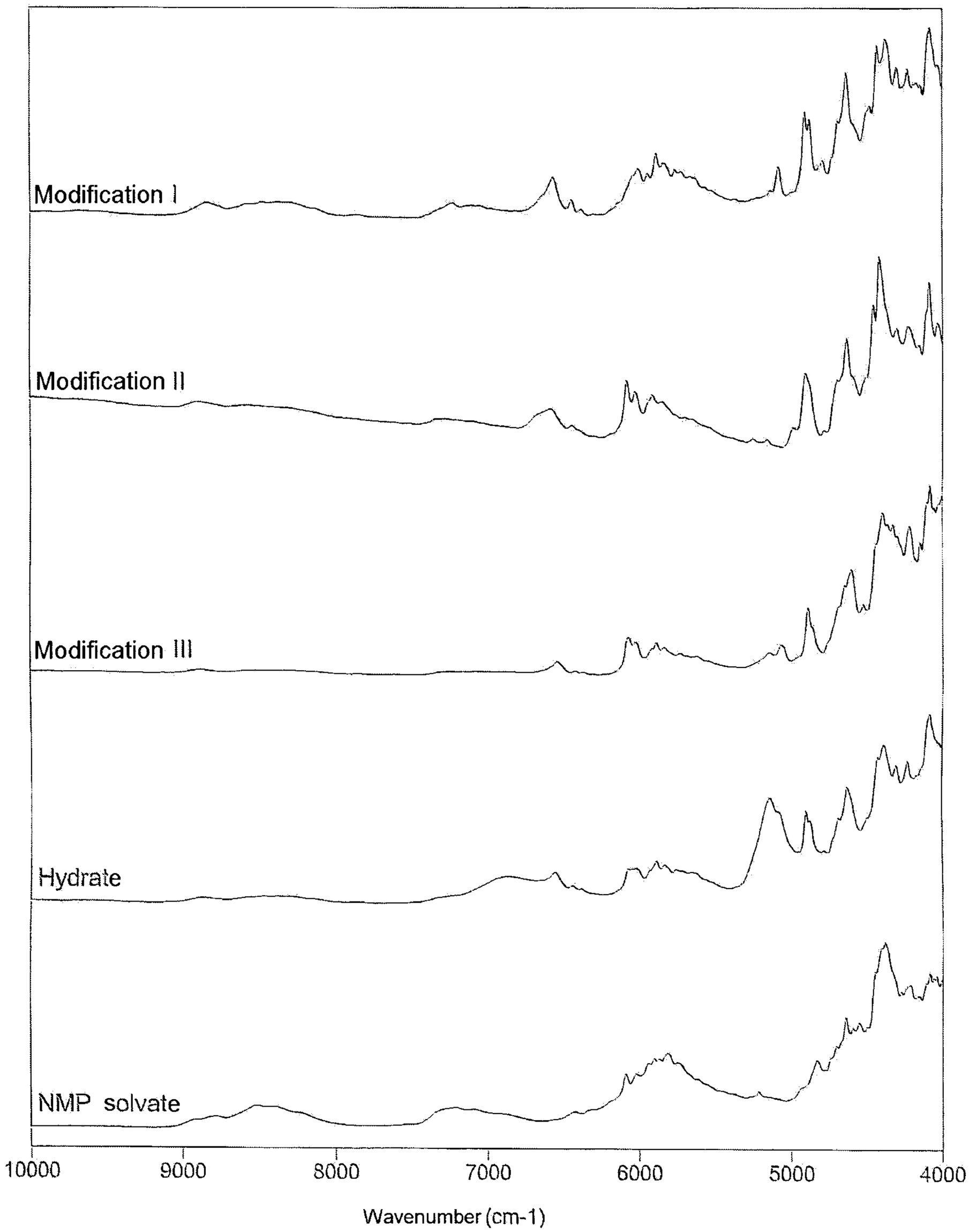


Fig. 7: DSC thermogram (amorphous form)

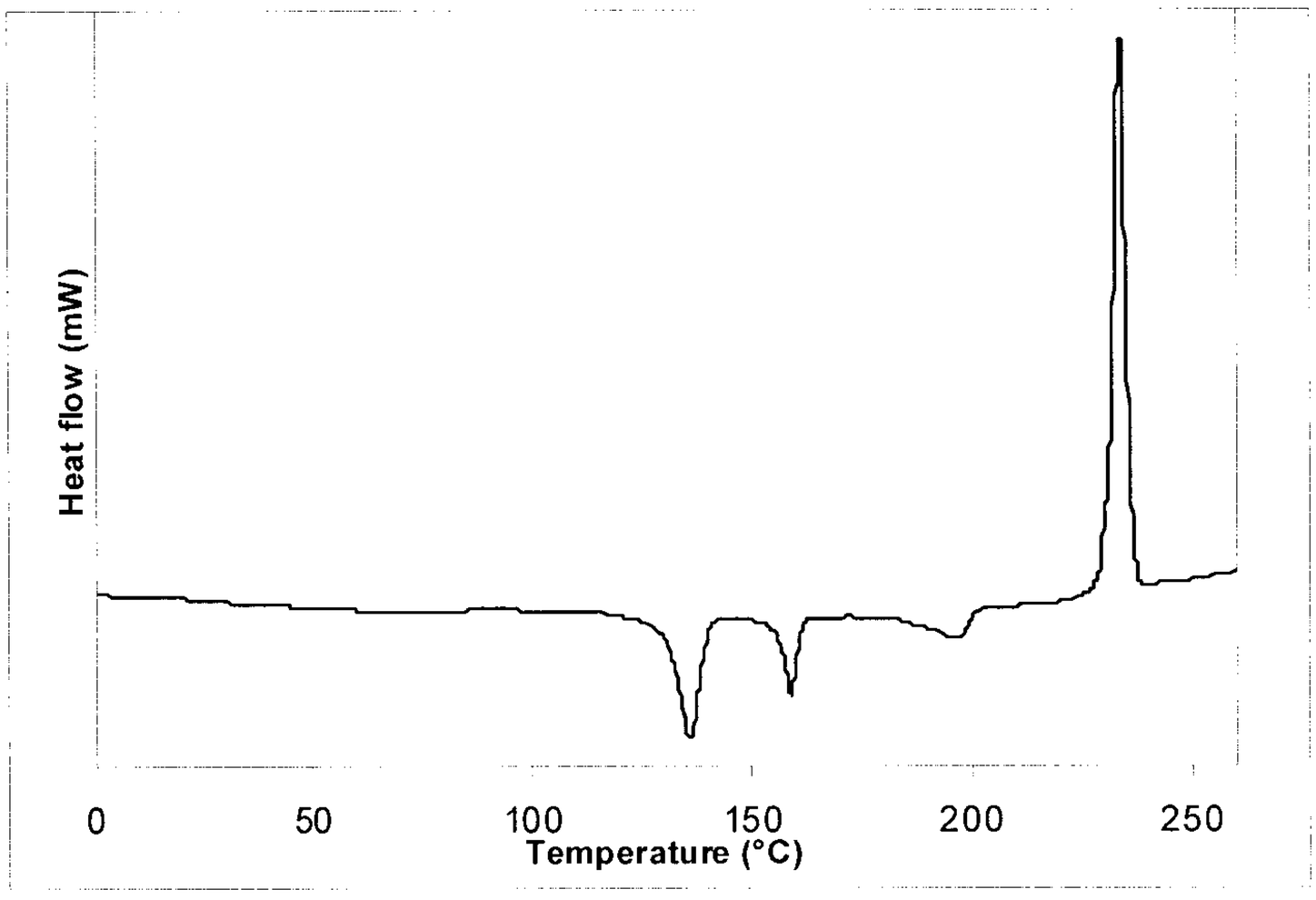


Fig. 8: X-ray diffractogram (amorphous form)

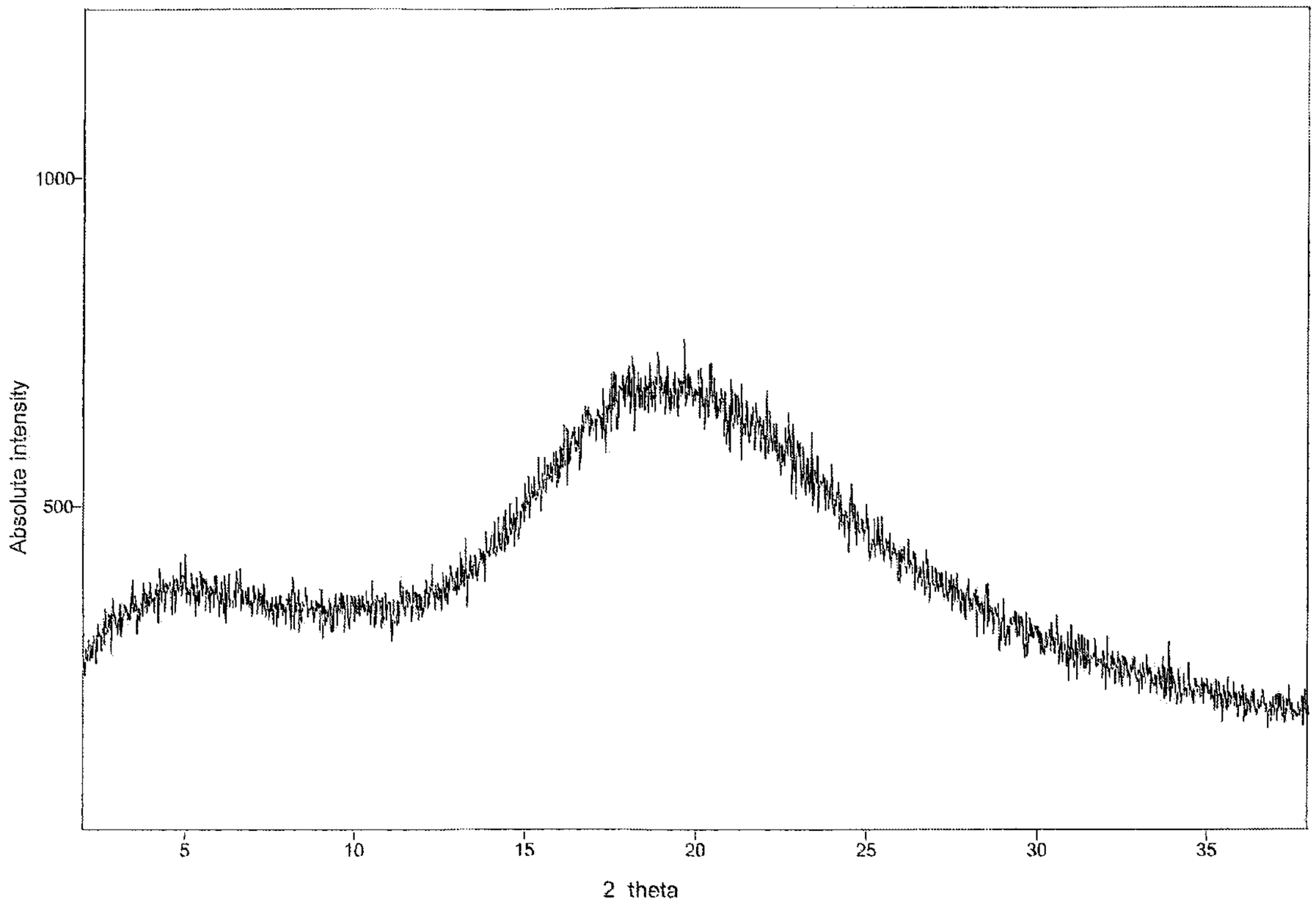


Fig. 9: IR spectrum (amorphous form)

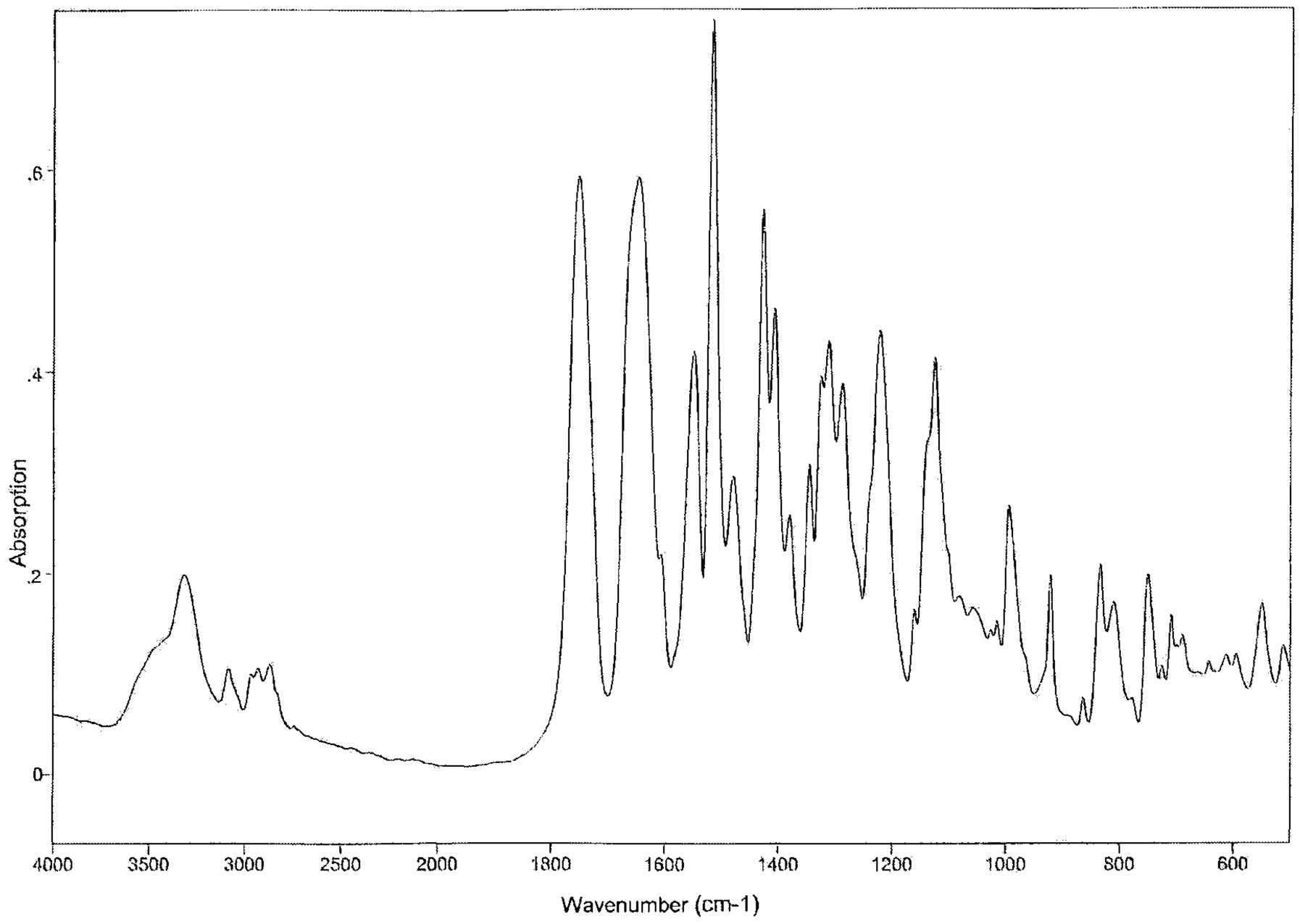


Fig. 10: Raman spectrum (amorphous form)

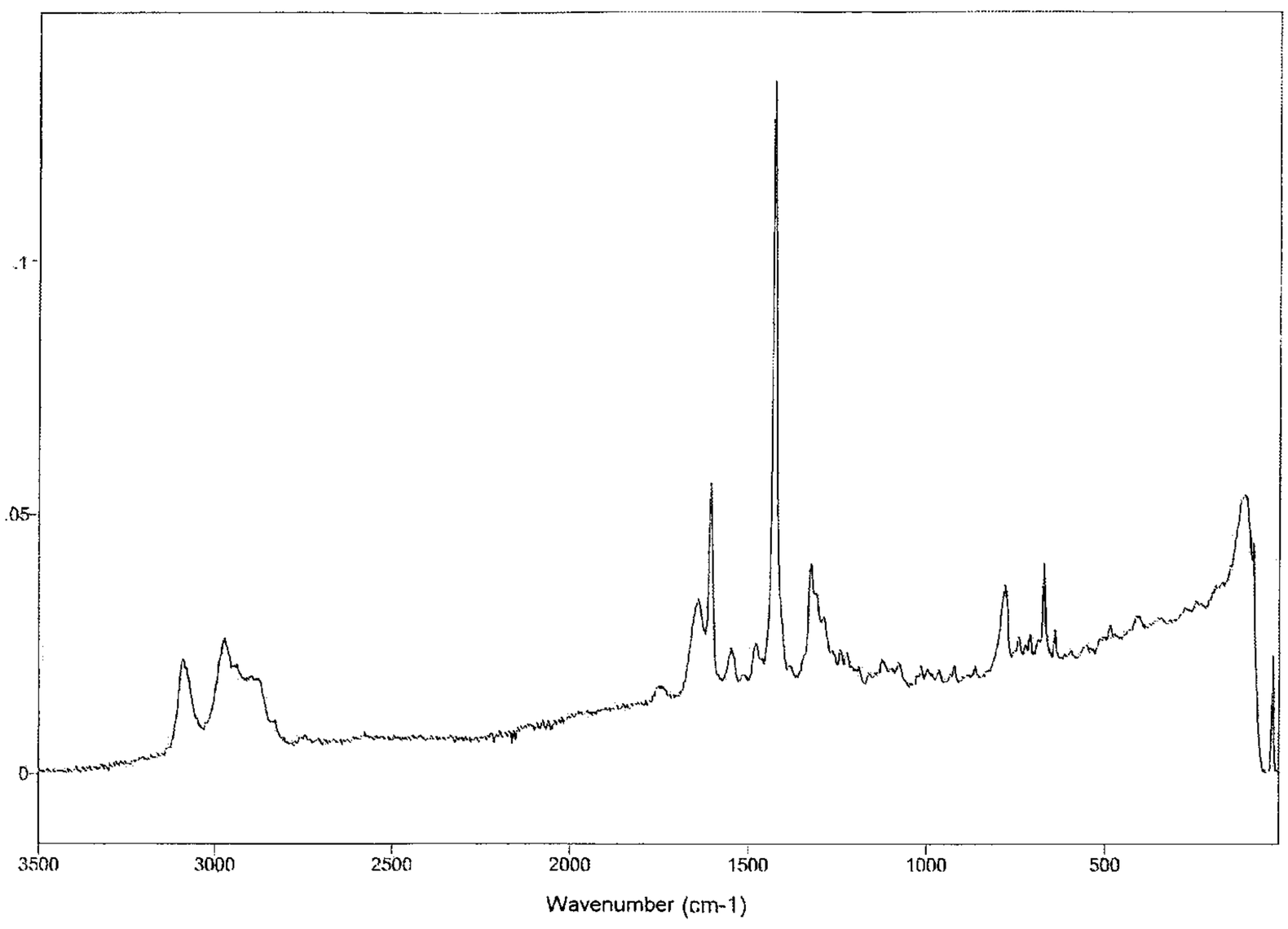


Fig. 11: FIR spectrum (amorphous form)

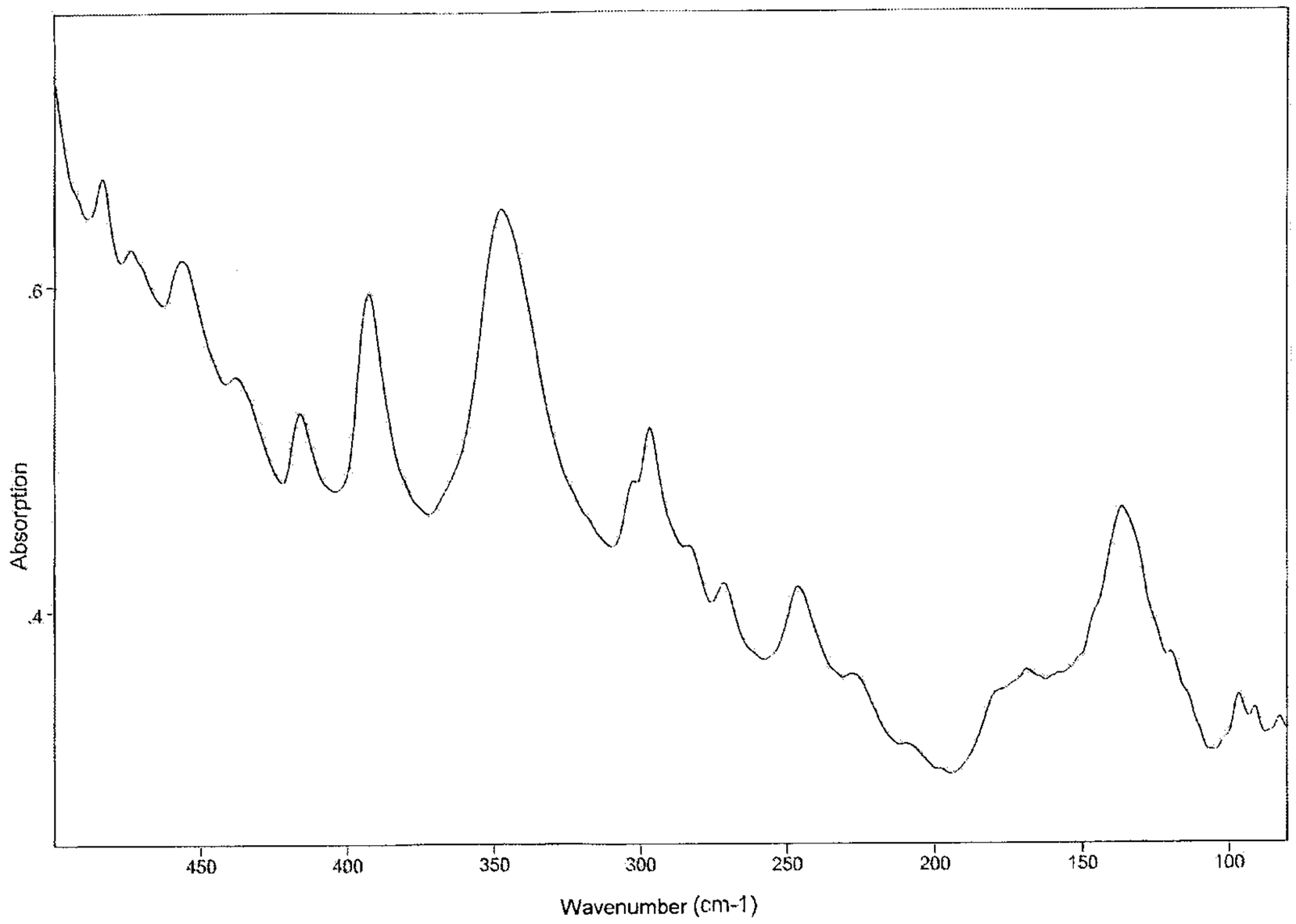


Fig. 12: NIR spectrum (amorphous form)