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(71) Demandeur/Applicant:
RECORDATI IRELAND LIMITED, IE

(72) Inventeurs/Inventors:
LEONARDI, AMEDEO, IT;
MOTTA, GIANNI, IT;
VON RAUMER, MARKUS, CH

(74) Agent: MACRAE & CO.

(54) Titre : SELS DE LERCANIDIPINE
(54) Title: LERCANIDIPINE SALTS

(57) Abrégé/Abstract:
The invention relates to new addition salts comprising lercanidipine and an acid counterion selected from the group consisting of: (i) inorganic acids, (ii) sulphonic acids, (iii) monocarboxylic acids, (iv) dicarboxylic acids, (v) tricarboxylic acids, and (vi) aromatic sulphonimides, with the proviso that said acid counterion is not hydrochloric acid. In particular, both amorphous and crystalline salts of lercanidipine with benzenesulphonic and naphthalene- 1,5-disulphonic acids are disclosed, as are amorphous salts of lercanidipine with several other acid counterions.

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(71) Applicant (*for all designated States except IT, US*): **RECORDATI IRELAND LIMITED** [IE/IE]; Raheens East, Ringsaskiddy, Co. Cork (IE).

(71) Applicant (*for IT only*): **RECORDATI INDUSTRIA CHIMICA E FARMACEUTICA S.p.A.** [IT/IT]; Via Matteo Civitali, 1, I-20148 Milano (IT).

(72) Inventors: **LEONARDI, Amadeo**; Via Poliziano, 16, I-20154 Milano (IT). **MOTTA, Gianni**; Via Ungaretti, 10, I-20030 Barlassina (IT). **VON RAUMER, Markus**; WKL 127.502, Klybeckstrasse 191, CH-4002 Basel (CH).

(74) Agent: **SERJEANTS**; 25 The Crescent, King Street, Leicester LE1 6RX (GB).

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(54) Title: LERCANIDIPINE SALTS

(57) Abstract: The invention relates to new addition salts comprising lercanidipine and an acid counterion selected from the group consisting of: (i) inorganic acids, (ii) sulphonic acids, (iii) monocarboxylic acids, (iv) dicarboxylic acids, (v) tricarboxylic acids, and (vi) aromatic sulphonimides, with the proviso that said acid counterion is not hydrochloric acid. In particular, both amorphous and crystalline salts of lercanidipine with benzenesulphonic and naphthalene- 1,5-disulphonic acids are disclosed, as are amorphous salts of lercanidipine with several other acid counterions.

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TITLE

Lercanidipine Salts

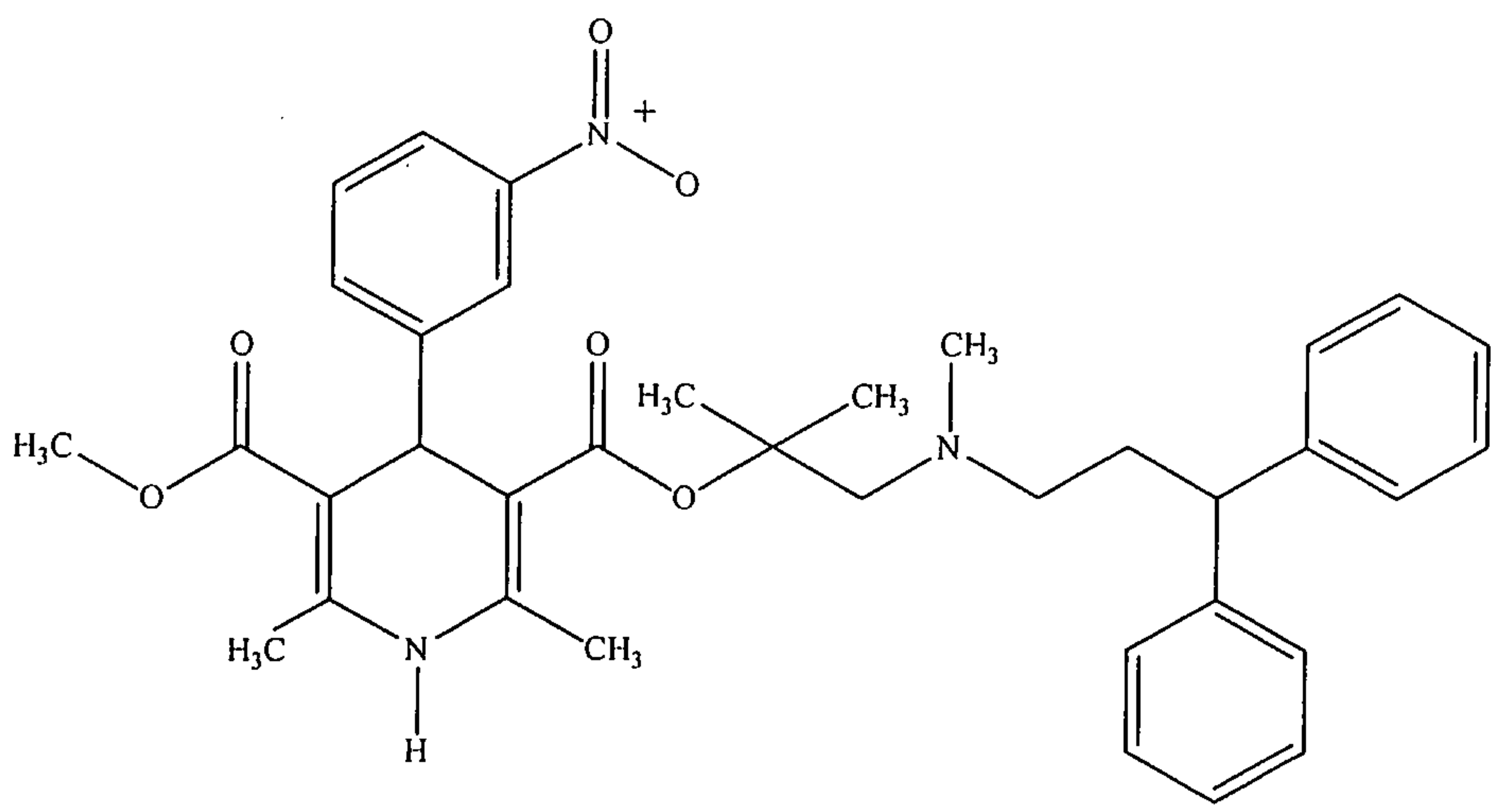
DESCRIPTION

Field of the Invention

[01] The invention relates to novel acid salts of lercanidipine, particularly amorphous and crystalline lercanidipine salts and processes for making the same. The invention also relates to novel amorphous and crystalline lercanidipine salts in hydrated and solvated forms. Additionally, the invention relates to pharmaceutical compositions containing the novel lercanidipine salts disclosed herein.

Background of the Invention

[02] Methyl 1,1,N-trimethyl-N-(3,3-diphenylpropyl)-2-aminoethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate (INN: Lercanidipine), depicted below, is a highly lipophilic dihydropyridine calcium antagonist with long duration of action and high vascular selectivity.



[03] The hydrochloride salt of lercanidipine is commercially available from Recordati S.p.A. (Milan, Italy). Methods of making both lercanidipine free base and its hydrochloride salt have been described previously along with methods of resolving lercanidipine into individual enantiomers in US 4705797, US 5767136, US 4968832, US 5912351 and US 5696139.

[04] A major disadvantage of the process of preparing lercanidipine, as described in US 4705797, is that the disclosed cyclization reaction generates several by-products, which results in a lower yield for the desired product. US 5912351 describes a simpler process for the preparation of lercanidipine hydrochloride. The process yields lercanidipine hydrochloride in an anhydrous non-hygroscopic crystalline form, and avoids the formation of unwanted by-products and the subsequent purification on chromatography columns.

[05] However, the isolation of lercanidipine hydrochloride in crystalline form is again quite complex. Additionally, the lercanidipine hydrochloride may exist as any one of at least four distinct polymorphs, each of which have distinct physical properties (see U.S. Patent Application No. 2003/0069285 and No. 2003/0083355). Therefore, there is a need in the art for a more simplified process of producing lercanidipine salts, especially crystalline lercanidipine salts. There is also a need for lercanidipine salts that have solubility and/or other physical properties that are distinct from, and preferably more desirable than, the previously isolated forms of lercanidipine hydrochloride, including, but not limited to, reduced inter-patient variability, reduced food effect, and little or no polymorphism.

Definitions and Abbreviations used in this Specification

[06] "DSC": Differential Scanning Calorimetry

[07] "amorphous" is used to describe compounds having no substantial crystal lattice structure, which is characteristic of the solid state. Such compounds present DSC plots with characteristic broad endothermic transitions, defined as glass transition, in place of the sharper exothermic peaks characteristic of crystalline compounds.

[08] "crystalline" is used to describe compounds having a melting point and x-ray spectra characteristic of crystalline forms. Such compounds present DSC plots with characteristic sharp exothermic peaks.

[09] "lercanidipine besylate": an acid salt of lercanidipine and the benzenesulphonic acid counterion in 1 to 1 molar ratio.

[10] "lercanidipine napadisylate": an acid salt of lercanidipine and the naphthalene-1,5-disulphonic acid counterion in a 2 to 1 molar ratio.

[11] "polymorphic" or "polymorphism": a property of a compound to exist in two or more forms with distinct structures. The different crystalline forms can be detected directly by crystallographic techniques or indirectly by assessment of differences in physical and/or chemical properties associated with each particular polymorph.

The Invention

[12] In one aspect, the invention provides acid addition salts of lercanidipine, wherein the acid counterion is selected from the group consisting of

(i) inorganic acids, other than hydrochloric acid, such as hydrobromic acid, phosphoric acid and sulphuric acid;

(ii) sulphonic acids, such as methanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid, and napthalene-1,5,-disulphonic acid.,

(iii) monocarboxylic acids, such as acetic acid, (+)-L-lactic acid, DL-lactic acid, DL-mandelic acid, gluconic acid, cinnamic acid, salicylic acid, and gentisic acid,

(iv) dicarboxylic acids, such as oxalic acid, 2-oxo-glutaric acid, malonic acid, (-)-L-malic acid, mucic acid, (+)-L-tartaric acid, fumaric acid, maleic acid, and terephthalic acid,

(v) tricarboxylic acids, such as citric acid, and

(vi) aromatic sulphonimides such as saccharin.

[13] Preferred lercanidipine salts according to the invention are the L-lactate, cinnamate, salicylate, maleate and saccharinate salts. Most preferred lercanidipine salts according to the invention are lercanidipine besylate and lercanidipine napadisylate. These preferred and most preferred salts can all be prepared in amorphous form; lercanidipine besylate and lercanidipine napadisylate can also be prepared in crystalline form.

[14] Crystalline lercanidipine salts of the invention may be present as polymorphs.

[15] The lercanidipine salts of the invention may be present in solvated and hydrated forms. Such solvated or hydrated forms may be present as either mono- or di- solvates or hydrates. Solvates and hydrates may be formed as a result of solvents used during the formation of the lercanidipine salts becoming imbedded in the solid lattice structure. Because formation of the solvates and hydrates occurs during the preparation of a lercanidipine salt, formation of a particular solvated or hydrated form depends greatly on the conditions and method used to prepare the salt. Solvents should be pharmaceutically acceptable.

[16] Crystalline lercanidipine besylate has a pale yellow colour and exhibits good stability. Its solubility in 0.1 M HCl at 22° C is from about 25 to about 35 mg/l and more specifically about 30 mg/l. This compares to the solubility of crystalline lercanidipine hydrochloride in the same media of about 10 mg/l. The melting point (DSC Peak) of crystalline lercanidipine besylate is within the range of about 170°C to about 175°C, more

specifically, about 172°C. In the Examples hereinbelow, crystalline lercanidipine besylate has not been obtained as either a hydrated or a solvated form but such forms are within the invention and can be obtained by recrystallization from polar solvents containing variable amounts of water. As prepared in the Examples hereinbelow, crystals of lercanidipine besylate are formed slowly, with the production of high yields of crystals only after the addition of seeding crystals, and do not exhibit polymorphism.

[17] Crystalline lercanidipine napadisylate also has a pale yellow colour and exhibits good stability. The crystal size is larger than that of crystalline lercanidipine besylate. Crystalline lercanidipine napadisylate has a solubility in 0.1 M HCl of from about 3 mg/l to about 4 mg/l and more specifically about 3.5 mg/l. This is less than the solubility of crystalline lercanidipine hydrochloride or crystalline lercanidipine besylate. The melting point (DSC peak) of crystalline lercanidipine napadisylate is within the range of about 145°C to about 155°C, more specifically about 150°C. Crystalline lercanidipine napadisylate may be prepared as a solvated hydrate, particularly as a dimethanolate hydrate or as an anhydrous form. As prepared in the Examples hereinbelow, crystals of lercanidipine napadisylate are formed spontaneously.

[18] The crystalline lercanidipine salts of the invention may be prepared in substantially pure form with little residual solvent. Particularly, crystalline lercanidipine besylate may be prepared such that residual solvent content is from about 0.1 to about 0.5 % (w/w) mass and more particularly less than about 0.2 % mass. Crystalline lercanidipine napadisylate may be prepared such that residual solvent content is from about 2.5 to about 5% (w/w) mass and more particularly less than about 4% mass. These crystalline lercanidipine salts forms can be isolated with a purity as high as 99.5% and a residual solvents content of <3000 ppm, but less pure (and/or with higher solvent or water content) forms can also be obtained by methods well known in the art. Pharmaceutically acceptable levels for each impurity are generally <0.1%; for organic solvents they range from 5000 ppm to 2 ppm depending on toxicity of each solvent. The lercanidipine salts of the invention can be purified by crystallization from different solvents and the solvent content can be reduced by drying under controlled conditions or azeotropic removal.

[19] The properties of the amorphous lercanidipine salts of the invention are distinct from those of the crystalline forms including the besylate, napadisylate and hydrochloride. The amorphous lercanidipine salts are characterized by the absence of crystalline material, even after repeated crystallization attempts using a variety of solvents and crystallization

conditions. The absence of crystalline material was confirmed by polarized microscopy, FT-Raman spectroscopy and DSC. A sample having no birefringency under cross polarizers, a broad FT-Raman spectrum, or a DSC curve having a glass transition temperature and no distinct melting peak was characterized as amorphous. The limits of detecting crystalline material using FT-Raman spectroscopy are generally from about 5 to about 10% (w/w of the sample) and the limit of detection using DSC is generally about 5 to about 10% (w/w of the sample).

[20] Compared to crystalline forms of lercanidipine salts, amorphous lercanidipine salts have a higher solubility in 0.1 M HCl and have glass transition temperatures (e.g., broad DSC curves) rather than distinct phase transitions. The amorphous lercanidipine salts of the present invention also have FT-Raman spectra which are distinct from both the novel crystalline salts of the invention and from those of crystalline lercanidipine hydrochloride.

[21] The invention also provides a method for the preparation of the novel lercanidipine acid salts of the invention by addition of a solution of the acid counterion dissolved in a suitable solvent to a solution of lercanidipine free base dissolved in a suitable solvent, followed by removal of the solvent(s). Crystalline salts of lercanidipine may be prepared by:

(a) reacting lercanidipine with an acid counterion in an organic solvent to form a lercanidipine salt, wherein said acid counterion cannot be hydrochloric acid;

(b) removing said organic solvent, thereby isolating the resultant lercanidipine salt; and

(c) recrystallizing the isolated lercanidipine salt in at least one of two successive steps, regardless of sequence, from a solution of the lercanidipine salt in

    (i) an aprotic solvent; and

    (ii) a protic solvent;

thereby isolating lercanidipine as its substantially pure crystalline salt. Further purification steps may include washing at different temperatures with different solvents or again recrystallization from different or mixed solvents.

Pharmaceutical Compositions

[22] The invention further provides a pharmaceutical composition comprising an acid addition salt according to the invention in admixture with a pharmaceutically acceptable excipient and/or carrier. Excipients may include diluents, flavourings agents, sweeteners, preservatives, dyes, binders, suspending agents, dispersing agents, colouring agents,

disintegrants, film forming agents, lubricants, plasticisers, edible oils or any combination of two or more of the foregoing.

[23] Pharmaceutical compositions according to the invention may further include lercanidipine hydrochloride, preferably crystalline lercanidipine hydrochloride. They may also or alternatively further include other active ingredients or such as angiotensin II receptor blockers and/or angiotensin converting enzyme inhibitors and/or diuretics.

[24] Both crystalline and amorphous salts of lercanidipine can undergo micronization, using any method known in the art. In one embodiment micronization may be carried out by a jet-mill process using a Micronette M300 (commercailly available from Nuova Guseo, Villanova sull'Arda -PC- Italy). Parameters are as follows: Injection pressure, 5 Kg/cmq; micronization pressure, 9 Kg/cmq; and cyclone pressure, 2.5 Kg/cmq. Capacity of micronization is 16 Kg/h. Particle size is determined by laser light scattering using a Galai Cis 1 laser instrument (Galai, Haifa, Israel). Micronization is performed to obtain an average particle size of D(90%)<15 μm, preferably, D(90%)<15 μm, (50%)2-8 μm.

[25] Suitable pharmaceutically acceptable carriers or diluents include ethanol; water; glycerol; propylene glycol, aloe vera gel; allantoin; glycerin; vitamin A and E oils; mineral oil; PPG2 myristyl propionate; magnesium carbonate; potassium phosphate; vegetable oil; animal oil; and solketal.

[26] Suitable binders include starch; gelatin; natural sugars, such as glucose, sucrose and lactose; corn sweeteners; natural and synthetic gums, such as acacia, tragacanth, vegetable gum, and sodium alginate; carboxymethylcellulose; hydroxypropylmethylcellulose; polyethylene glycol; povidone; waxes; and the like. Preferred binders are lactose, hydroxypropylmethylcellulose and povidone.

[27] Suitable disintegrants include starch (e.g., corn starch or modified starch) methyl cellulose, agar, bentonite, xanthan gum, sodium starch glycolate, crosspovidone and the like. A preferred disintegrant is sodium starch glycolate.

[28] Suitable lubricants include sodium oleate, sodium stearate, sodium stearyl fumarate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A preferred lubricant is magnesium stearate.

[29] Suitable suspending agents include bentonite, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, agar-agar and tragacanth, or mixtures of two or more of these substances, and the like. A preferred suspending agent is microcrystalline cellulose.

[30] Suitable dispersing and suspending agents include synthetic and natural gums, such as vegetable gum, tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone and gelatin.

[31] Suitable film forming agents include hydroxypropylmethylcellulose, ethylcellulose and polymethacrylates.

[32] Suitable plasticizers include polyethylene glycols of different molecular weights (e.g., 200-8000 Da) and propylene glycol. Preferred is polyethylene glycol 6000.

[33] Suitable colorants include ferric oxide(s), titanium dioxide and natural and synthetic lacquers. Preferred are ferric oxides and titanium dioxide.

[34] Suitable edible oils include cottonseed oil, sesame oil, coconut oil and peanut oil.

[35] Examples of additional additives include sorbitol, talc, stearic acid, dicalcium phosphate and polydextrose.

[36] The pharmaceutical composition may be formulated as unit dosage forms, such as tablets, pills, capsules, caplets, boluses, powders, granules, sterile parenteral solutions, sterile parenteral suspensions, sterile parenteral emulsions, elixirs, tinctures, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories. Unit dosage forms may be used for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation, transdermal patches, and a lyophilized composition. In general, any delivery of active ingredients that results in systemic availability of them can be used. Preferably the unit dosage form is an oral dosage form, most preferably a solid oral dosage form, therefore the preferred dosage forms are tablets, pills, caplets and capsules. However, parenteral preparations also are preferred, especially under circumstances wherein oral administration is cumbersome or impossible.

[37] Solid unit dosage forms may be prepared by mixing the active agents of the present invention with a pharmaceutically acceptable carrier and any other desired additives as described above. The mixture is typically mixed until a homogeneous mixture of the active agents of the present invention and the carrier and any other desired additives is formed, i.e., until the active agents are dispersed evenly throughout the composition. In this case, the compositions can be formed as dry or moist granules.

[38] Tablets or pills can be coated or otherwise compounded to form a unit dosage form which has preferably, a modified release profile. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of a layer or envelope over the former. The two components can be separated by a release modifying

layer which serves to permit dissolution of the active ingredient from the core component over a prolonged period of time. Alternatively, the lease modifying agent is a slowly disintegrating matrix. Additional modified release formulations will be apparent to those skilled in the art.

[39] Biodegradable polymers for controlling the release of the active agents, include, but are not limited to, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

[40] For liquid dosage forms, the active substances or their physiologically acceptable salts are brought into solution, suspension or emulsion, optionally with the usually employed substances such as solubilizers, emulsifiers or other auxiliaries. Solvents for the active combinations and the corresponding physiologically acceptable salts, can include water, physiological salt solutions or alcohols, e.g. ethanol, propane-diol or glycerol. Additionally, sugar solutions such as glucose or mannitol solutions may be used. A mixture of the various solvents mentioned may further be used in the present invention.

[41] A transdermal dosage form also is contemplated by the present invention. Transdermal forms may be a diffusion-driven transdermal system (transdermal patch) using either a fluid reservoir or a drug-in-adhesive matrix system. Other transdermal dosage forms include, but are not limited to, topical gels, lotions, ointments, transmucosal systems and devices, and iontohoretic (electrical diffusion) delivery system. Transdermal dosage forms may be used for timed release and sustained release of the active agents of the present invention.

[42] Pharmaceutical compositions and unit dosage forms of the present invention for administration parenterally, and in particular by injection, typically include a pharmaceutically acceptable carrier, as described above. A preferred liquid carrier is vegetable oil. Injection may be, for example, intravenous, intrathecal, intramuscular, intraruminal, intratracheal, or subcutaneous.

[43] The active agent also can be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

[44] The crystalline compounds of the present invention also may be coupled with soluble polymers as targetable drug carriers. Such polymers include, but are not limited to,

polyvinyl-pyrrolidone, pyran copolymer, polyhydroxypropylmethacryl-amidephenol, polyhydroxy-ethylaspartamidephenol, and polyethyl-eneoxideopolylysine substituted with palmitoyl residues.

Examples

[45] The invention is illustrated by the following Examples and by the accompanying drawings, of which:

[46] Figure 1 is a differential scanning calorimetry profile for crystalline lercanidipine napadisylate;

[47] Figure 2 is a differential scanning calorimetry profile for crystalline lercanidipine besylate;

[48] Figure 3 depicts FT-Raman pattern of crystalline lercanidipine besylate;

[49] Figure 4 depicts X-Ray diffraction pattern of crystalline lercanidipine besylate;

[50] Figure 5 depicts FT-Raman pattern crystalline lercanidipine napadisylate;

[51] Figure 6 depicts X-Ray diffraction pattern of crystalline lercanidipine napadisylate;

[52] Figure 7 depicts FT-Raman pattern of comparing amorphous lercanidipine besylate to an equimolar solid state mixture of lercanidipine free base and benzenesulphonic acid; and

[53] Figure 8 depicts FT-Raman pattern of comparing amorphous and crystalline lercanidipine besylate.

EXAMPLE 1: Preparation of amorphous lercanidipine besylate

[54] A stock solution of lercanidipine free base was prepared by dissolving 181.7 mg of lercanidipine free base (Recordati S.p.A., Milan, Italy) in 0.2 ml tetrahydrofuran (THF). An acid stock solution was prepared by dissolving 65.3 mg benzenesulphonic acid in 0.1 ml THF. An equimolar mixture of the lercanidipine stock solution (0.2 ml) and the acid stock solution (0.072 ml) was prepared. All of the solvent was removed under vacuum. Upon removal of the solvent a glassy film, characteristic of amorphous material, was observed. The amorphous material was dissolved in methanol (MeOH) and seeded with crystalline solid, resulting in a pale yellow crystalline material.

[55] Several initial attempts, using various solvent combinations, were made to crystallize the amorphous lercanidipine besylate. None of these attempts were successful at forming crystalline lercanidipine besylate (the only two successful crystallizations of lercanidipine besylate are the ones described below in Example 2, the second of which employs seeding using the product of the first method). The general experimental scheme for attempting to crystallize amorphous lercanidipine besylate involved: (1) dissolving about 35 mg amorphous lercanidipine besylate (prepared as described above) in about 0.5 ml of an organic solvent selected from MeOH, acetonitrile (MeCN), ethanol (EtOH), or dichloromethane (CH_2Cl_2), (2) slowly evaporating the solvent under ambient conditions for at least 20 days, (3) drying the sample completely under vacuum, (4) dissolving the sample in about 0.025 ml EtOH, and (5) storing the sample closed at -18°C for 5 days.

EXAMPLE 2: Preparation of crystalline lercanidipine besylate

[56] A stock solution of lercanidipine free base was prepared by dissolving 212.3 mg of lercanidipine free base (Recordati S.p.A.) in 1 ml tetrahydrofuran (THF). An acid stock solution was prepared by dissolving 21.7 mg benzenesulphonic acid in 0.1 ml THF. A mixture of the lercanidipine stock solution (0.236 ml) and the acid stock solution (0.06 ml) was prepared and stored closed at 25°C for 24 hours. The mixture was then stored at -18°C for 24 hours and at 25°C for an additional 24 hours. No precipitate was observed at this point.

[57] The solvent was allowed to evaporate under ambient conditions. After 4 days a glassy film was observed. The glassy film was dissolved in 0.15 ml ethyl acetate (EtAc). After 8 days no precipitate was observed. Again the solvent was evaporated and a glassy film developed. The glassy film was dissolved in 0.05 ml tert-butyl methyl ether (TBME) and the sample was allowed to stand closed at room temperature for 6 days. No precipitate was observed at this point.

[58] An additional 0.05 ml TBME were added and the sample was subjected to temperature cycling (20-40-20°C, 5 cycles, 2 hours rise time and 2 hours fall time, 10 minutes isotherm periods at 20 and 40°C). No precipitate was observed and the solvent was evaporated under a gentle nitrogen flow.

[59] Following evaporation of the solvent, a sticky sample was obtained. The sample was stored under vacuum for 24 hours. The sample was suspended in 0.05 ml methanol (MeOH) and the sample was stored closed at 20°C. The sample produced a viscous liquid

containing several solid particles. The sample was stored for an additional three days at 20°C after which time the sample was completely solid and demonstrated a birefringency under crossed polarizers, confirming the presence of crystalline material.

[60] The crystalline material was used as seeding material in a second experiment to obtain greater yields of crystalline lercanidipine besylate. Again stock solutions of lercanidipine free base (1.10 g free base dissolved in 2.2 ml MeOH) and acid (0.2844 g benzenesulphonic acid dissolved in 0.5 ml MeOH) were prepared and mixed together. Solvent was removed from the solution under a gentle nitrogen flow. When the solution volume had been reduced to 2 ml, crystalline lercanidipine besylate obtained as described above, was added to the solution. Again the solvent was removed under a gentle nitrogen flow, until the solution volume had been reduced to 1 ml. The sample was allowed to stand closed at room temperature for 7 days. The sample was filtered on a glass filter and dried under vacuum.

[61] A final yield of 1.21 g, pale yellow, crystalline lercanidipine besylate was obtained. Elemental analysis revealed that the crystalline salt had a composition of $C_{42}H_{47}N_2O_9S$ (MW 755.9, non-solvated) which corresponds to an acid to free base ratio of 1:1 (mol/mol). The salt was non-solvated and non-hygroscopic and displayed a mass loss of 0.1% as determined by TG-FTIR.

[62] A larger scale production has been performed as follows. A solution of 48 g of lercanidipine free base in 96 ml of methanol was added with 12.7 g of benzenesulphonic acid in 22 ml of methanol at room temperature. The resulting suspension was filtered and evaporated at 55°C to a final volume of 50 ml. The solution was then seeded with crystalline lercanidipine besylate, and allowed to stand at room temperature for 24 hours, followed by storage at 5 C for 6 days. The resulting compact mass of crystals was collected by suction, washed with 2x40 ml of methanol and dried under vacuum in the presence of P_2O_5. 51.1 g of lercanidipine besylate was obtained.

EXAMPLE 3: Preparation of crystalline (and amorphous) lercanidipine napadisylate

[63] A stock solution of lercanidipine free base was prepared by dissolving 169.6 mg of lercanidipine free base (Recordati S.p.A.) in 0.82 ml methanol (MeOH). A solution was prepared by mixing 0.2 ml of the lercanidipine free base stock solution and 0.195 ml of aqueous naphthalene-1,5-disulphonic acid (50 mg/ml). Upon mixing, a precipitate was observed. The precipitate was dissolved by the addition of 1.0 ml MeOH. The sample was

stored at -18°C for 4 days, with daily warming to room temperature for observation. The sample was then stored open at room temperature for seven days in order to allow the solvent to evaporate. Crystals were observed upon evaporation of the solvent. The crystals were suspended in 0.25 ml H_2O and 0.01 ml MeOH. Following suspension, the crystals were collected by filter centrifugation (10,000 RPM, 0.22 μm filter) and dried under vacuum.

[64] The crystalline material was used as seeding material in a second experiment in order to obtain even higher yields of crystalline lercanidipine napadisylate. A solution of lercanidipine free base was prepared by dissolving 1.1 g of lercanidipine free base in 4.4 ml MeOH. To the free base solution, 5.184 ml of aqueous naphthalenedisulphonic acid (50 mg/ml) was added and a precipitate immediately formed. The precipitate was dissolved upon the addition of 23 ml MeOH. The solution was seed with crystalline material obtained above and the solution was stored at 4°C for four days, followed by an additional three days at -18°C. Crystals were collected by filter centrifugation and dried under vacuum.

[65] A final yield of 0.905 g, pale yellow, crystalline lercanidipine napadisylate was obtained. Elemental analysis revealed that the crystalline salt had a composition of $C_{82}H_{90}N_6O_{18}S_2$ (MW 1511.76, non-solvated) which corresponds to an acid to free base ratio of 1:2 (mol/mol). The salt occurred as a hydrated dimethanolate and displayed a total mass loss of 4.1% (0.4% H_2O loss and 3.7% MeOH loss) as determined by TG-FTIR.

[66] Amorphous lercanidipine napadisylate is produced by rapid evaporation in vacuo of the solution obtained in this Example 3.

EXAMPLE 4: Preparation of amorphous salts and attempts to form additional crystalline lercanidipine salts

[67] A salt screening was performed using a number of counterions and lercanidipine free base in order to determine which, if any, counterions were capable of producing crystalline lercanidipine salts. The screening experiments involved the investigation of eleven counterions; acetate, cinnamate, fumarate, L-lactate, DL-lactate, L-malate, maleate, DL-mandelate, mesylate, sulphate, and tosylate. Several crystallization attempts were made with each of the counterions. None of the counterions were capable of producing crystalline lercanidipine, even after several attempts. The general experimental scheme used in the screening of each of the eleven counterions is discussed in detail below. The choice of crystallization techniques was influenced by the known difficulty in obtaining crystalline lercanidipine and therefore, sufficient storage times and slow processes were chosen.

[68] The final lercanidipine salts obtained from each of the salt screening experiments was dried completely and subjected to chemical and physical analysis. The chemical composition of each of the salt was determined by elemental analysis, thermogravimetric analysis coupled to infra-red spectroscopy, and water content analysis. The salts also underwent physical testing using FT-Raman spectroscopy and were subjected to solubility testing.

Example 4a. Counterion Dissolved in Tetrahydrofuran

[69] Separate stock solutions of lercanidipine free base and acid were prepared by dissolving lercanidipine free base (Recordati S.p.A.) in tetrahydrofuran (THF) and the respective acid in THF, as follows:

Stock Solution	Solute	Solvent
Lercanidipine	212.3 mg lercanidipine free base	1 ml THF
Cinnamate	21.5 mg cinnamic acid	0.1 ml THF
Maleate	31.6 mg maleic acid	0.2 ml THF

[70] Aliquots of lercanidipine free base and acid stock solution were mixed, accounting for the stereochemistry of the acids, as well as the molar ratios of acid to base. No precipitate was observed upon mixing of the stock solutions. Samples were stored closed for 24 hours at 25°C, followed by additional storage for 24 hours at 4°C and 24 hours at -18°C. No solid was observed after storage.

[71] Solvent was removed from the samples by evaporation under ambient conditions. After four days, a glassy film was observed. The glassy film was dissolved in acetone and allowed to stand at room temperature for two days. No precipitate was observed. Samples were allowed to stand for an additional six days and again no precipitate was observed.

[72] Solvent was evaporated under a gentle nitrogen flow and a glassy film formed. The glassy film was dissolved in tert-butyl methyl ether (TBME) and the sample was allowed to stand at room temperature for six days. Additional TBME was added to the sample and the sample was subjected to temperature cycling (20-40-20°C, 5 cycles, 2 hours rise time and 2 hours fall time, 10 minutes isotherm periods at 20 and 40°C). No solid was observed and again solvent was evaporated under a gentle nitrogen flow.

[73] Following evaporation of the solvent, a sticky sample was obtained. The sample was stored under vacuum for 24 hours. The sample was suspended in methanol (MeOH) and stored closed at 20°C. The sample produced a sticky mass, however no crystalline particles were observed. The sample was stored for an additional 24 hours under vacuum to remove the solvent. No crystalline material was observed following removal of the solvent.

[74] The present example yielded two amorphous salts of lercanidipine; lercanidipine cinnamate and lercanidipine maleate. The chemical composition of each salt of the present example was determined by elemental analysis, thermogravimetric analysis coupled to infra-red spectroscopy, and water content analysis. Each amorphous salt also underwent physical testing using FT-Raman spectroscopy and was subjected to solubility testing. The results are described below:

Salt form	**Proposed formula**	**Elemental Analysis**	**TG-FTIR (mass loss)**	**FT Raman spectrum**	**Solubility in 0.1 N HCl**
Cinnamate	$C_{36}H_{41}N_3O_6.C_9H_8O_2$ 0.2 H_2O (0.47% H_2O)	Calcd % : C 70.8, H 6.3, N 5.5 Found % : C 70.7, H 6.4, N 5.5	0.3% (H_2O)	agrees with proposed structure	89 mg/l
Maleate	$C_{36}H_{41}N_3O_6.C_4H_4O_4$ 0.25 MeOH	Calcd % : C 65.7, H 6.3, N 5.7 Found % : C 65.7, H 6.3, N 5.6	1.9% (MeOH)	agrees with proposed structure	71 mg/l

Example 4b. Counterion Dissolved in Methanol

[75] Additional salt screening experiments were carried out by preparing separate stock solutions of lercanidipine free base and acid. Stock solutions were prepared by dissolving lercanidipine free base (Recordati S.p.A.) in TBME and the respective acid in MeOH, as follows:

Stock Solution	**Solute**	**Solvent**
Lercanidipine	223.7 mg lercanidipine free base	0.8 ml TBME
L-lactate	14.6 L-lactic acid	0.2 ml THF

[76] Aliquots of lercanidipine free base and acid stock solution were mixed, accounting for the stereochemistry of the acids, as well as the molar ratios of acid to base. No precipitate was observed upon mixing of the stock solutions. Samples were stored closed for 24 hours at 25°C, followed by additional storage for 8 hours at 60°C and six days at 4°C. No solid was observed after storage.

[77] Water was added to the sample, followed by evaporation of the solvent under ambient conditions. After four days, a glassy film was observed. The sample was stored under vacuum for 24 hours. The glassy film was dissolved in MeOH and stored closed for 24 hours at 20°C. After 24 hours a sticky mass was observed, but no solid particles were observed. The sample was stored for an additional two days and again, no solid particles were observed. Solvent was removed from the sample by storage under vacuum for 24 hours. No crystalline material was observed following removal of the solvent.

[78] The present example yielded lercanidipine L-lactate. The chemical composition of the salt of the present example was determined by elemental analysis, thermogravimetric analysis coupled to infra-red spectroscopy, and water absorption analysis. The amorphous salt also underwent physical testing using FT-Raman spectroscopy and was subjected to solubility testing. The results of physical testing are summarized below.

Salt form	Proposed formula	Elemental Analysis	TG-FTIR (mass loss)	FT Raman spectrum	Solubility in 0.1 N HCl
L-Lactate	$C_{36}H_{41}N_3O_6.C_3H_6O_3$ 0.2 MeOH	Calcd % : C 66.5, H 6.8, N 5.9 Found % : C 66.5, H 6.6, N 5.9	1% (MeOH)	agrees with proposed structure	85 mg/l

EXAMPLE 5: Preparation of amorphous salts and attempts to form crystalline lercanidipine salts

[79] In addition to the salt screening experiments described in Example 4, single attempts to form crystalline lercanidipine salts were carried out for an additional twelve counterions: citrate, mucate, gentisate, gluconate, 2-oxo-glutarate, phosphate, saccharinate, salicylate, L-tartrate, terephtalate, malonate, and oxalate. A single attempt to form crystalline lercanidipine salts was made using each of the twelve counterions. None of the twelve counterions were capable of producing crystalline lercanidipine salts, and few of them produced characterized amorphous salts. The general experimental scheme used in screening

each of the counterions is discussed in detail below. The choice of crystallization techniques was influenced by the known difficulty in obtaining crystalline lercanidipine and therefore, sufficient storage times and slow processes were chosen.

[80] The final lercanidipine salts obtained from each of the salt screening experiments was dried completely and subjected to chemical and physical analysis. The chemical composition of each of the salt was determined using elemental analysis, thermogravimetric analysis coupled to infra-red spectroscopy, and water absorption analysis. The salts were also subjected to physical testing using FT-Raman spectroscopy and underwent solubility testing.

[81] A stock solution of lercanidipine was prepared by dissolving 530 mg lercanidipine free base (Recordati S.p.A.) in 2.67 ml methanol (MeOH). To screen for crystal formation aliquots (0.1 ml) of lercanidipine stock solution were mixed with an acid as described below.

Sample No.	Lercanidipine Stock Solution:	Counterion:	Solvent:
1	0.1 ml	0.1258 ml aqueous citric acid (50 mg/ml)	1 ml MeOH
2	0.1 ml	6.9 mg mucic acid	0.1 ml H_2O / 2 ml MeOH
3	0.1 ml	5 mg gentisic acid	0.1 ml H_2O / 2 ml MeOH
4	0.1 ml	0.2570 ml aqueous gluconic acid (50 mg/ml)	1.2 ml MeOH
5	0.1 ml	0.0955 ml aqueous 2-oxo-glutaric acid (50 mg/ml)	0.0045 ml H_2O / 1 ml MeOH
6	0.1 ml	0.0754 ml aqueous phosphoric acid (50 mg/ml)	0.0246 ml H_2O / 1 ml MeOH
7	0.1 ml	6 mg saccharin	1.016 ml H_2O / 1.2 ml MeOH
8	0.1 ml	0.1254 ml aqueous salicylic acid (50 mg/ml)	1 ml MeOH
9	0.1 ml	0.0981 ml aqueous L-tartaric acid (50 mg/ml)	0.0981 ml H_2O / 1 ml MeOH
10	0.1 ml	5.5 mg terephtalic acid	0.01 ml H_2O / 1.4 ml MeOH
11	0.1 ml	0.0680 ml aqueous malonic acid (50 mg/ml)	0.032 ml H_2O / 1 ml MeOH
12	0.1 ml	0.0589 ml aqueous oxalic acid (50 mg/ml)	0.0411 ml H_2O / 1 ml MeOH

[82] Each of the samples of the present example were handled identically. After combining the lercanidipine free base and the corresponding counterion, the sample was allowed to stand closed at -18°C for two days. After two days no precipitate was visible in any of the samples. The samples were then allowed to stand open under ambient conditions for 8 hours followed by storage at -18°C for an additional 5 days. Again no precipitate was observed at the end of the storage period. The samples were then stored open under ambient conditions for 15 hours followed by an additional 2 days at -18°C. No precipitate was observed in any of the samples after storage. The solvent was removed from each of the samples under vacuum and the remaining solid was stored closed.

[83] All of the attempts to form crystalline lercanidipine salts from lercanidipine free base and the counterions of the present example failed to produce any crystalline material. The present example, as well as experiments described in Example 4, demonstrate the difficulty and unpredictability of forming crystalline salts of lercanidipine.

[84] The present example yielded two amorphous salts of lercanidipine; saccharinate and salicylate. The chemical composition of each salt of the present example was determined by elemental analysis, thermogravimetric analysis coupled to infra-red spectroscopy. Each amorphous salt also underwent physical testing using FT-Raman spectroscopy and was subjected to solubility testing. The results of physical testing is summarized below.

Salt form	**Proposed formula**	**Elemental Analysis**	**TG-FTIR (mass loss)**	**FT Raman spectrum**	**Solubility in 0.1 N HCl**
Saccharin	$C_{36}H_{41}N_3O_6.C_7H_5SO_3$ 0.5 MeOH	Calcd % : C 64.4, H 6.0, N 6.9, S 3.9 Found % : C 64.1, H 5.9, N 6.8, S 3.8	1.8% (MeOH)	agrees with proposed structure	72 mg/l
Salicylate	$C_{36}H_{41}N_3O_6.C_7H_6O_3$ 0.6 MeOH	Calcd % : C 68.1, H 6.5, N 5.5 Found % : C 68.1, H 6.4, N 5.7	2.5% (MeOH)	agrees with proposed structure	

EXAMPLE 6: Chemical composition of amorphous and crystalline lercanidipine salts

[85] The elemental composition of both amorphous and crystalline lercanidipine salts was determined using dry combustion / thermal conductivity and non dispersive IR detection. Results of the elemental analysis are summarized in Table 1.

[86] The residual solvent content of both amorphous and crystalline lercanidipine salts was determined using gravimetric analysis coupled with an infra-red (IR) spectrometer. A Netzsch Thermobalance TG-209 (Selb, Germany, Selb) in combination with a spectrometer FTIR Bruker Vector 22 (Fällanden, Switzerland) was used to for the analysis. The analysis were carried out according to the following conditions: 2-5 mg of sample heated in aluminum crucibles under nitrogen atmosphere at a heating rate of 10°C/minute from 25°C to 250°C. Results of the gravimetric analysis are shown in Table 1.

[87] The hygroscopicity of both amorphous and crystalline lercanidipine salts was determined by DVS analysis using a water absorption analyzer (Surface Measurement System Ltd., Marion, Buckinghamshire, UK). The analysis were carried out according to the following conditions: 10-15 mg of sample were placed on a quartz or platinum holder, the holder was placed in-turn on a microbalance, and the sample underwent humidity cycling between 0 and 95% relative humidity (RH) at 25°C (50-95-0-95-0-50% at a rate of 5%RH/hr). The results of the hygroscopicity analysis are summarized in Table 1 below.

TABLE 1

Chemical Composition of amorphous and crystalline lercanidipine salts

Salt	Elemental Composition	Residual Solvent	Hygroscopicity
Amorphous besylate	$C_{42}H_{47}N_3O_9S$	2.8% (MeOH)	non-hygroscopic
Crystalline besylate	$C_{42}H_{47}N_3O_9S$	0.2%	non-hygroscopic
Crystalline napadisylate	$C_{82}H_{90}N_6O_{18}S_2$	3.7% (MeOH)	hygroscopic 0:4 % H2O

EXAMPLE 7: Solubility of crystalline and amorphous salts of lercanidipine

[88] The solubility of crystalline lercanidipine besylate, napadisylate and hydrochloride and amorphous lercanidipine besylate was evaluated by UV-Visible spectroscopy in aqueous 0.1 M HCl (pH 1) at 22°C. Suspensions of approximately 0.3 mg/ml of the respective compounds were prepared in an aqueous 0.1 M HCl and equilibrated by shaking for 24 hours.

Following equilibration, the samples were filtered (0.1 μm filter) and the concentration was determined photometrically using Perkin Elmer Lambda 16 (Überlingen, Germany). Reference measurements were performed with 20% acetonitrile as a co-solvent.

TABLE 2

Solubility in 0.1 M HCl at 22°C

Salt	Solubility [mg/ml]	pH of solution
Crystalline hydrochloride	10.0	1
Crystalline besylate	30.0	1
Amorphous besylate	155	1
Crystalline napadisylate	3.5	1

[89] It can be seen from Table 2 that both crystalline besylate and crystalline napadisylate have lower solubilities than the amorphous salt. It can also be seen from Table 2 that the solubility of the crystalline salts varies greatly and that crystalline besylate is substantially more soluble than either crystalline hydrochloride or napadisylate.

EXAMPLE 8: Raman spectra of novel lercanidipine salts

[90] The novel lercanidipine salts were analyzed using FT-Raman spectroscopy. A Bruker FT-Raman RFS100 Spectrophotometer was utilized under the following typical conditions: about 10 mg sample (without any previous treatment), 64 scans 2 cm^{-1} resolution, 100 mW laser power, Ge-detector.

[91] The following Tables 3, 4 and 5 show the most significant peaks of Raman spectra for crystalline lercanidipine besylate and napadisylate, respectively, as well as amorphous lercanidipine besylate.

TABLE 3

Raman spectrum of crystalline lercanidipine besylate

Wave number (cm^{-1})	Peak intensity *
86.1	vs
177.4	m
227.3	m
318.3	m
812.1	m
1002.3	vs
1035.5	s
1126.6	m
1162.0	m
1178.9	m
1197.5	m
1351.8	vs
1438.2	m
1448.4	m
1485.7	s
1533.9	m
1583.6	s
1609.9	s
1647.8	s
1683.0	s
2925.7	s
2956.0	s
2972.9	m
2991.1	m
3000.0	m
3023.3	m
3042.1	m
3064.0	s
3075.4	s

* m= moderate; s= strong, vs =very strong

TABLE 4

Raman spectrum of crystalline lercanidipine napadisylate

Wave number (cm^{-1})	Peak intensity *
79.2	vs
96.4	vs
151.7	s
203.4	m
272.9	m
293.7	m
330.4	m
479.4	m
511.6	m
530.5	m
618.2	m
654.4	m
737.4	m
747.7	m
819.9	s
854.5	m
965.2	m
1001.4	vs
1033.4	m
1065.4	m
1089.0	m
1157.1	m
1173.3	m
1196.3	s
1248.4	m
1345.6	vs
1384.4	m
1400.8	s
1450.7	m
1462.5	m
1477.7	s
1519.8	m
1528.0	m
1572.0	s
1581.4	s
1603.1	m
1613.9	m
1648.6	s
1669.4	vs
2951.9	s
2985.2	s
2997.0	s
3025.5	m
3062.4	s

* m= moderate; s= strong, vs =very strong

TABLE 5

Raman spectrum of amorphous lercanidipine besylate

Wave number (cm^{-1})	Peak intensity *
84.1	vs
146.6	s
269.0	m
314.4	m
617.4	m
727.4	m
816.1	m
827.9	m
997.7	vs
1001.5	vs
1017.2	m
1034.0	m
1124.3	m
1156.5	m
1185.8	m
1191.2	m
1196.4	m
1227.2	m
1348.4	vs
1384.6	m
1453.5	m
1492.0	m
1527.5	m
1580.3	s
1588.4	m
1603.9	m
1646.4	s
1673.9	m
1700.5	m
2932.2	m
2950.2	m
2980.8	m
3002.6	m
3052.4	m
3063.6	s

* m= moderate; s= strong, vs =very strong

EXAMPLE 9: X-Ray Diffraction patterns of novel crystalline lercanidipine salts

[92] The X-ray diffraction patterns of crystalline lercanidipine besylate and napadisylate were obtained using a Philips X-pert PW 3040 or Philips PW 1710 powder difractometer (Eindhoven, Holland) under the following typical conditions: about 5-70 mg sample (without any previous treatment) with application of a slight pressure to obtain a flat sample, ambient air atmosphere and Copper Kα radiation, 0.02 °2θ, step size, 2 seconds per step, 2-50 °2θ. The obtained spectra are shown in Figures 4 (besylate) and 6 (napadisylate), and the corresponding main peaks are described in Tables 6 (napadisylate) and 7 (besylate). One skilled in the art will recognize that the 2θ values will generally be reproducible to within a range from about ±0.10 to about ±0.20 degrees, while the relative intensity of individuals peaks may vary from sample to sample. *See e.g,* United States Pharmacopiea XXV (2002), pages 2088-2089.

TABLE 6

XRD of crystalline lercanidipine napadisylate

D(Å)	Relative Intensity (I/Io)	2 θ angle
21.3	2	4.15
11.9	19	7.44
10.6	29	8.35
9.3	14	9.52
8.7	21	10.12
7.9	17	11.14
7.5	16	11.81
7.2	3	12.34
7.0	4	12.66
6.5	4	13.67
6.2	15	14.29
5.90	8	15.02
5.68	23	15.60
5.53	4	16.02
5.44	6	16.30
5.29	37	16.75
5.12	10	17.32
5.04	6	17.60
4.77	4	18.62
4.67	7	18.99
4.55	5	19.51
4.46	5	19.90
4.40	10	20.20
4.23	100	20.98
4.16	21	21.34
4.11	97	21.62
3.96	64	22.44
3.83	14	23.21
3.79	6	23.49
3.68	16	24.19
3.61	9	24.64
3.56	8	25.01
3.44	3	25.90
3.29	3	27.07
3.15	13	28.34
3.10	38	28.82
3.06	9	29.14
3.03	16	29.52
2.86	3	31.30
2.44	2	36.82
2.35	2	38.29

TABLE 7

XRD of crystalline lercanidipine besylate

D(Å)	Relative Intensity (I/Io)	2 θ angle
14.0	100	6.31
10.4	7	8.54
9.7	2	9.13
8.1	24	10.92
7.2	21	12.31
6.9	34	12.77
6.6	39	13.50
6.5	17	13.73
6.2	22	14.23
5.71	77	15.52
5.41	36	16.40
5.18	19	17.12
4.95	34	17.92
4.85	40	18.30
4.78	43	18.55
4.67	93	19.00
4.49	17	19.78
4.42	23	20.08
4.36	29	20.35
4.18	16	21.24
4.03	31	22.07
3.96	72	22.47
3.83	53	23.22
3.79	29	23.45
3.70	19	24.05
3.53	10	25.24
3.45	10	25.81
3.42	11	26.04
3.26	7	27.36
3.23	6	27.62
3.11	16	28.73
3.00	7	29.77
2.95	4	30.32
2.91	4	30.74
2.84	8	31.52
2.74	3	32.70
2.71	6	33.09
2.54	6	35.32

EXAMPLE 10: DSC analysis of crystalline lercanidipine besylate and napadisylate

[93] The melting points of the lercanidipine salts of the invention and of crystalline lercanidipine hydrochloride were analyzed using differential scanning calorimetry (DSC). DSC analysis measures changes that occur in a given sample with heating, wherein the changes identify transition phases. Enthalpy variations taking place in a transition phase are calculated on the basis of the area under the curve. The most common transition phases are melting and sublimation. The temperature at which transition starts, onset T, is given by the point in which the curve starts to deviate from the base line (flex point).

[94] DSC of crystalline lercanidipine besylate: 4.040 mg of crystalline lercanidipine besylate was placed in a golden pan of the apparatus Perkin Elmer DSC7. The heating speed during the test was 10°C/min.

[95] DSC crystalline lercanidipine napadisylate: 3.697 mg of crystalline lercanidipine napadisylate was placed in a golden pan of the apparatus Perkin Elmer DSC7. The heating speed during the test was 10°C/min.

[96] The data are shown in Figures 1 (napadisylate) and 2 (besylate) and the characteristic points of the figures are briefly summarized in Table 8.

TABLE 8

Melting point analysis by DSC

Salt	Melting T (Tpeak) [°C]	Onset T [°C]
Crystalline Lercanidipine Besylate	172.6	148
Crystalline Lercanidipine Napadisylate	149.8	98
Crystalline Lercanidipine Hydrochloride Form (I)	198.7	179.8
Crystalline Lercanidipine Hydrochloride Form (II)	209.3	169.0

CLAIMS

1. An acid addition salt of:
   (a) lercanidipine, and
   (b) an acid counterion selected from the group consisting of: (i) inorganic acids, (ii) sulphonic acids, (iii) monocarboxylic acids, (iv) dicarboxylic acids, (v) tricarboxylic acids, and (vi) aromatic sulphonimides,

   with the proviso that the acid counterion is not hydrochloric acid.

2. An acid addition salt according to claim 1, which salt is an amorphous L-lactate, cinnamate, salicylate, maleate or saccharinate of lercanidipine.

3. An acid addition salt according to claim 1, which salt is an amorphous benzenesulphonate of lercanidipine in 1:1 molar ratio (also named lercanidipine besylate).

4. An acid addition salt according to claim 1, which salt is a crystalline benzenesulphonate of lercanidipine in 1:1 molar ratio (also named lercanidipine besylate).

5. An acid addition salt according to claim 1, which salt is an amorphous naphthalene-1,5-disulphonate of lercanidipine in 1:2 molar ratio (also named lercanidipine napadisylate).

6. An acid addition salt according to claim 1, which salt is a crystalline naphthalene-1,5-disulphonate of lercanidipine in 1:2 molar ratio (also named lercanidipine napadisylate).

7. An acid addition salt according to any one of the preceding claims, which salt is hydrated or solvated.

8. A pharmaceutical composition comprising an acid addition salt according to any one of the preceding claims in admixture with a pharmaceutically acceptable excipient and/or carrier.

9. A pharmaceutical composition according to claim 8, further comprising lercanidipine hydrochloride.

10. A method for the preparation of a crystalline salt of lercanidipine, the method comprising the steps of:

(a) reacting lercanidipine with an acid counterion (other than hydrochloric acid) in an organic solvent to form a lercanidipine salt;

(b) removing the organic solvent, thereby isolating the resultant lercanidipine salt; and

(c) recrystallizing the isolated lercanidipine salt in at least one of two successive steps, regardless of sequence, from a solution of the lercanidipine salt in

(i) an aprotic solvent; and

(ii) a protic solvent;

thereby isolating lercanidipine as its substantially pure crystalline salt.

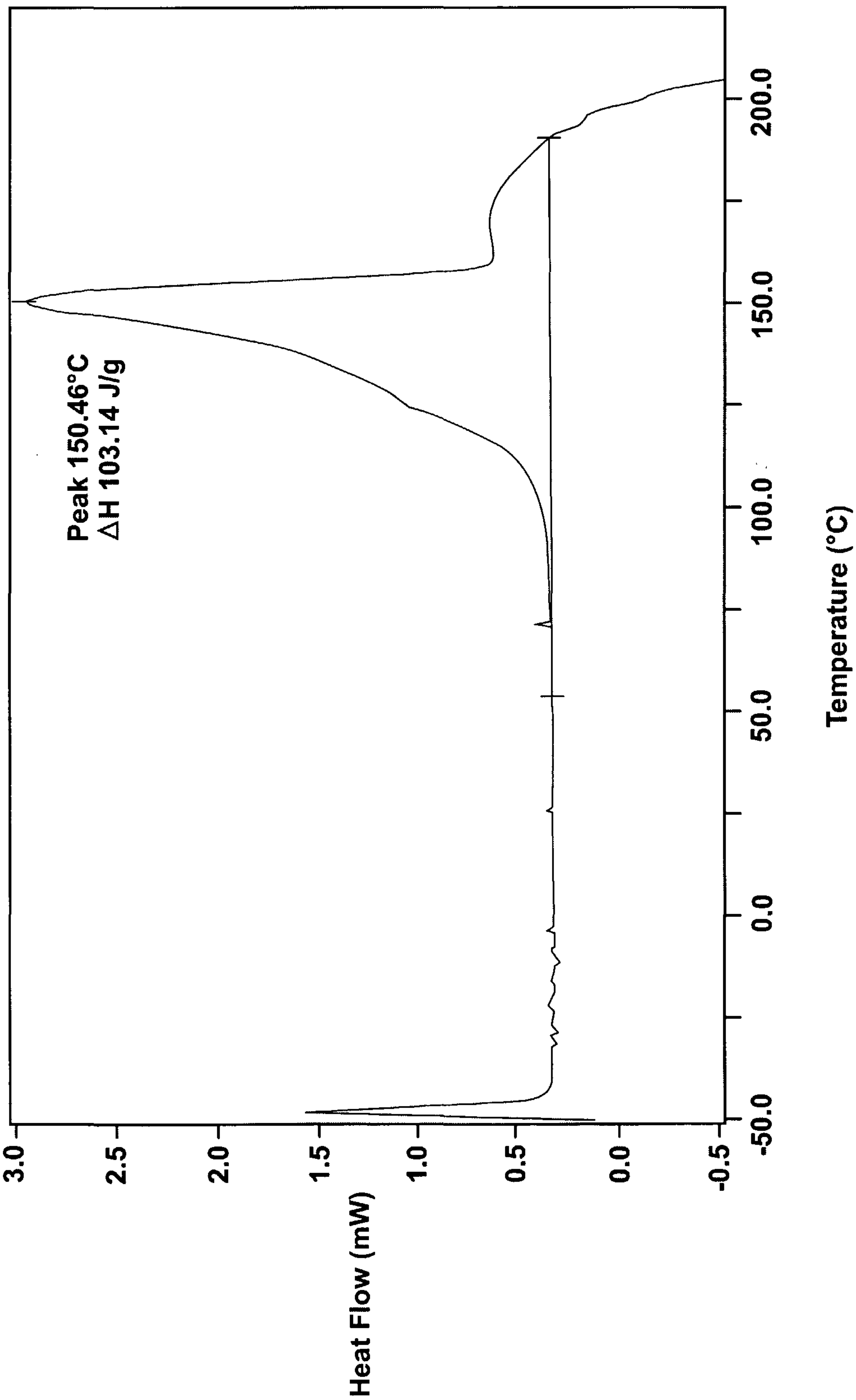

Peak 150.46°C
ΔH 103.14 J/g
Heat Flow (mW)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
Temperature (°C)
-50.0
0.0
50.0
100.0
150.0
200.0

Figure 1

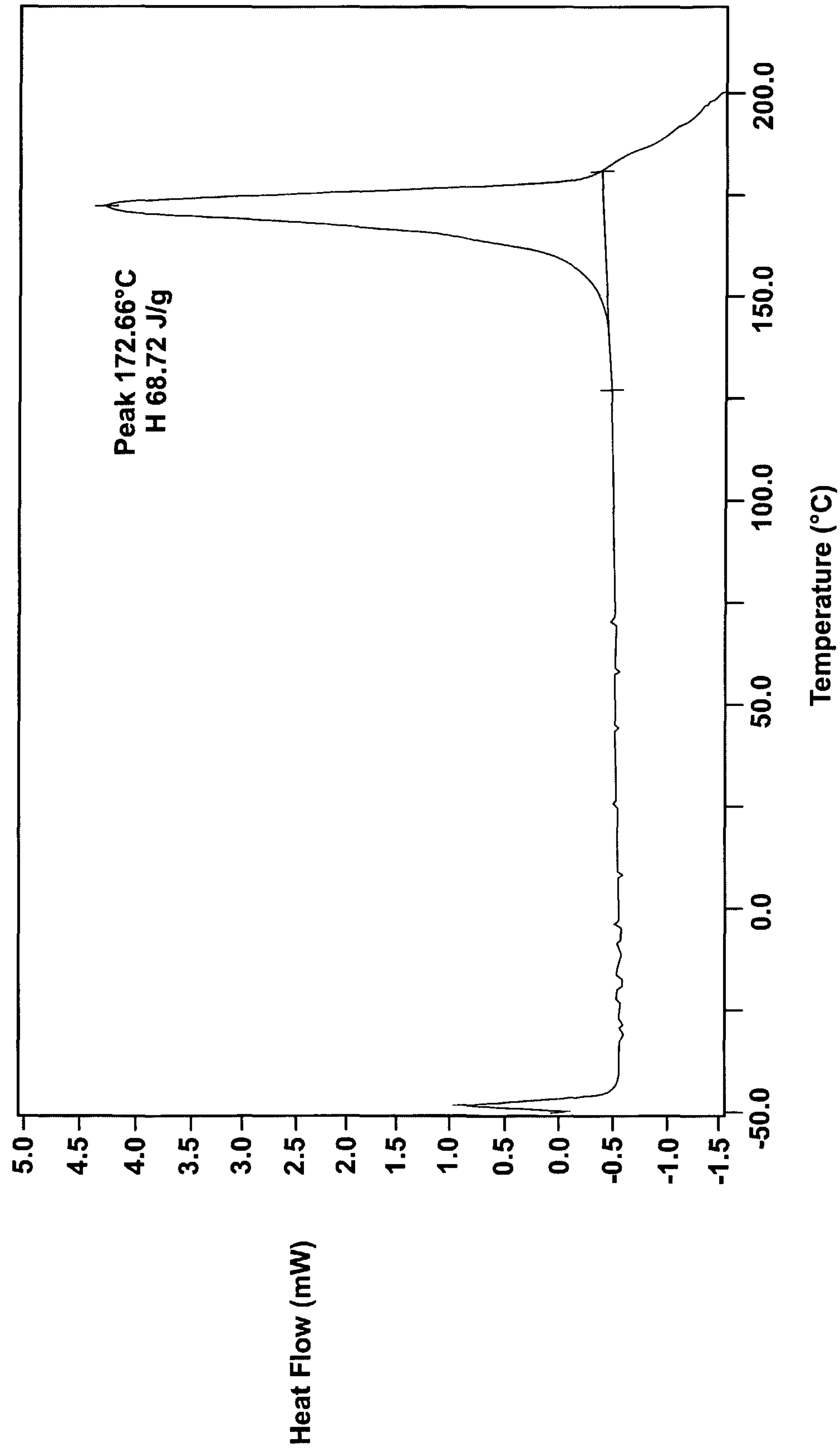

Peak 172.66°C
H 68.72 J/g
Heat Flow (mW)
Temperature (°C)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-50.0
0.0
50.0
100.0
150.0
200.0

Figure 2

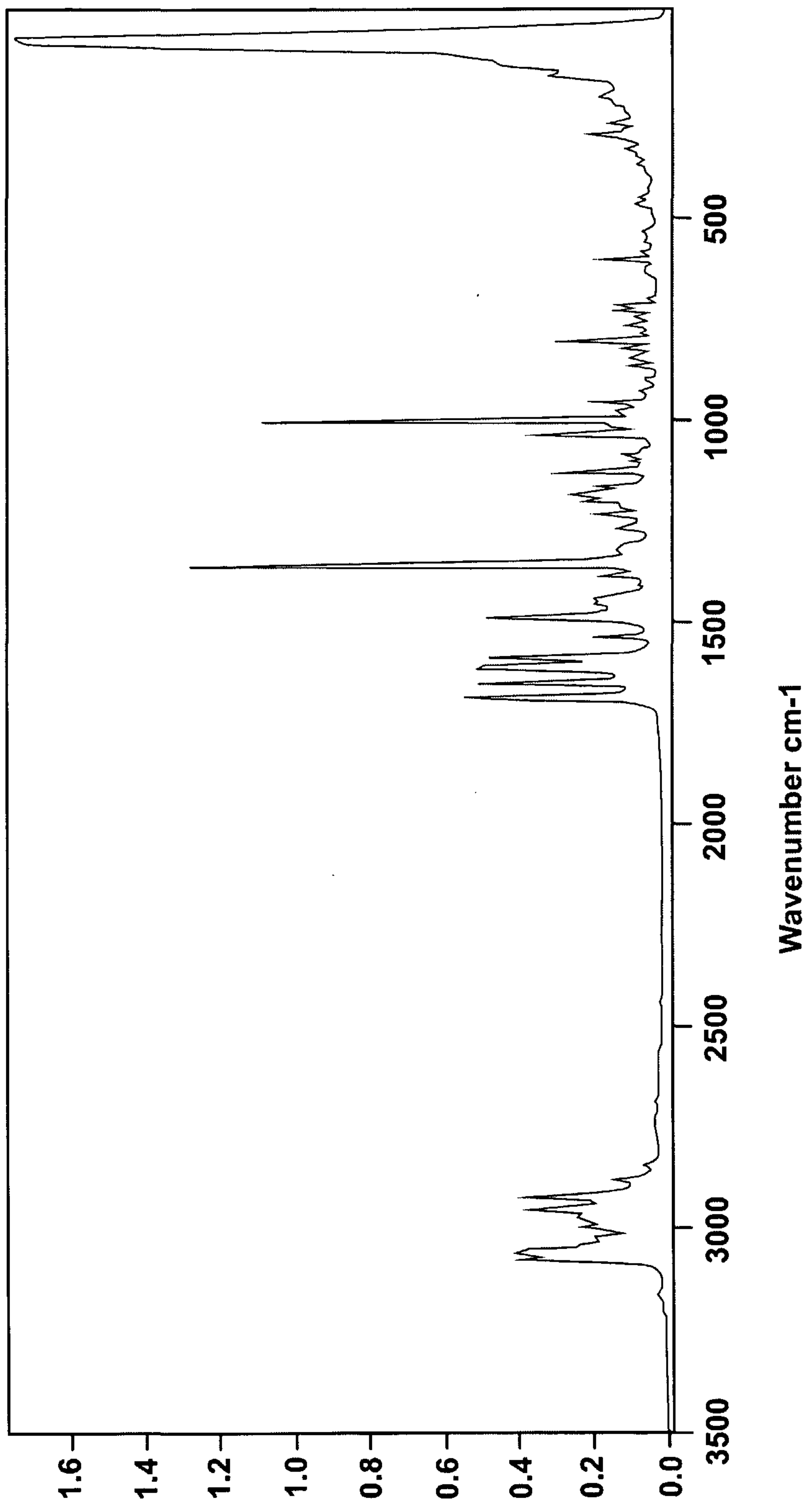

Wavenumber cm-1
500
1000
1500
2000
2500
3000
3500
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6

Figure 3

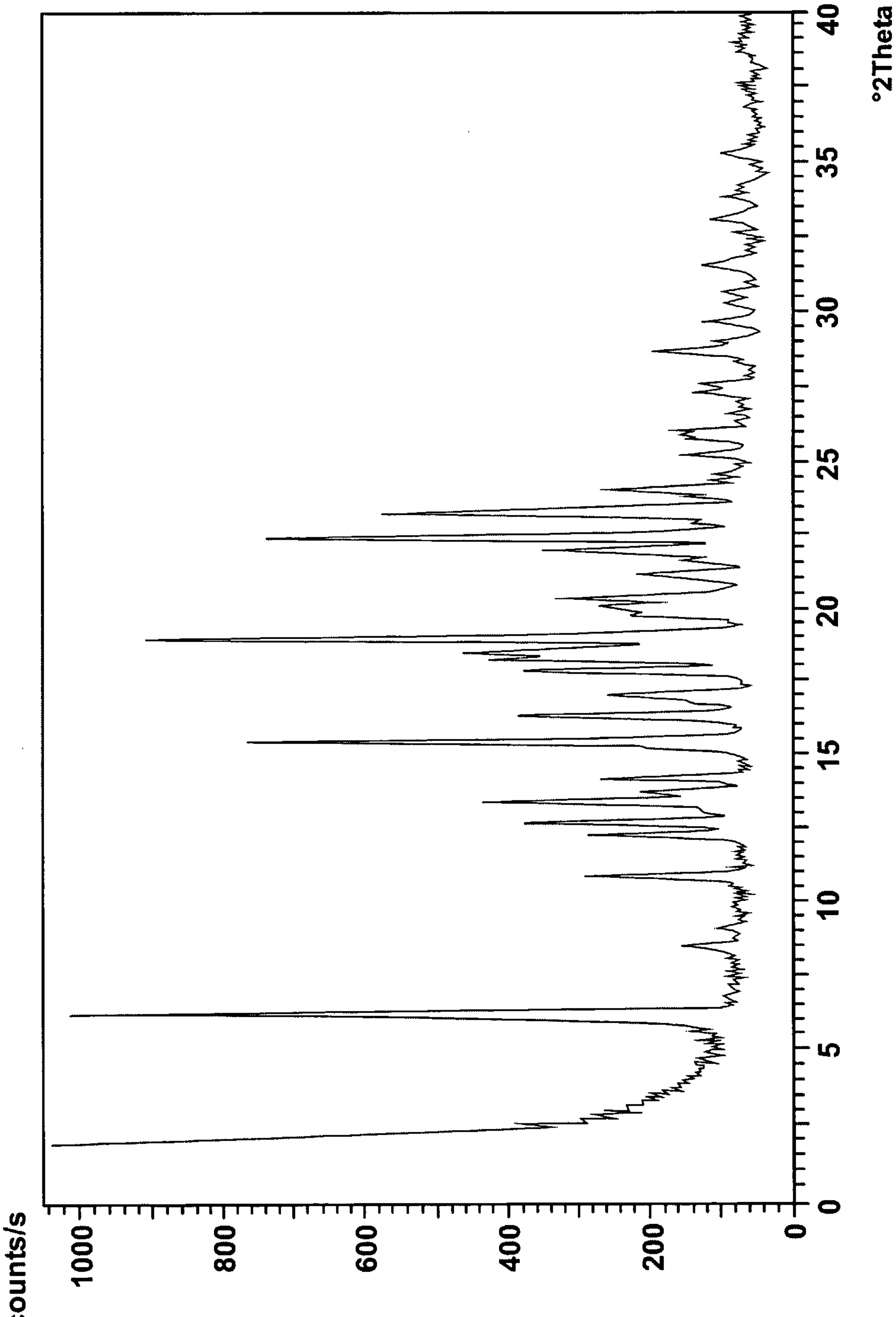


Figure 4

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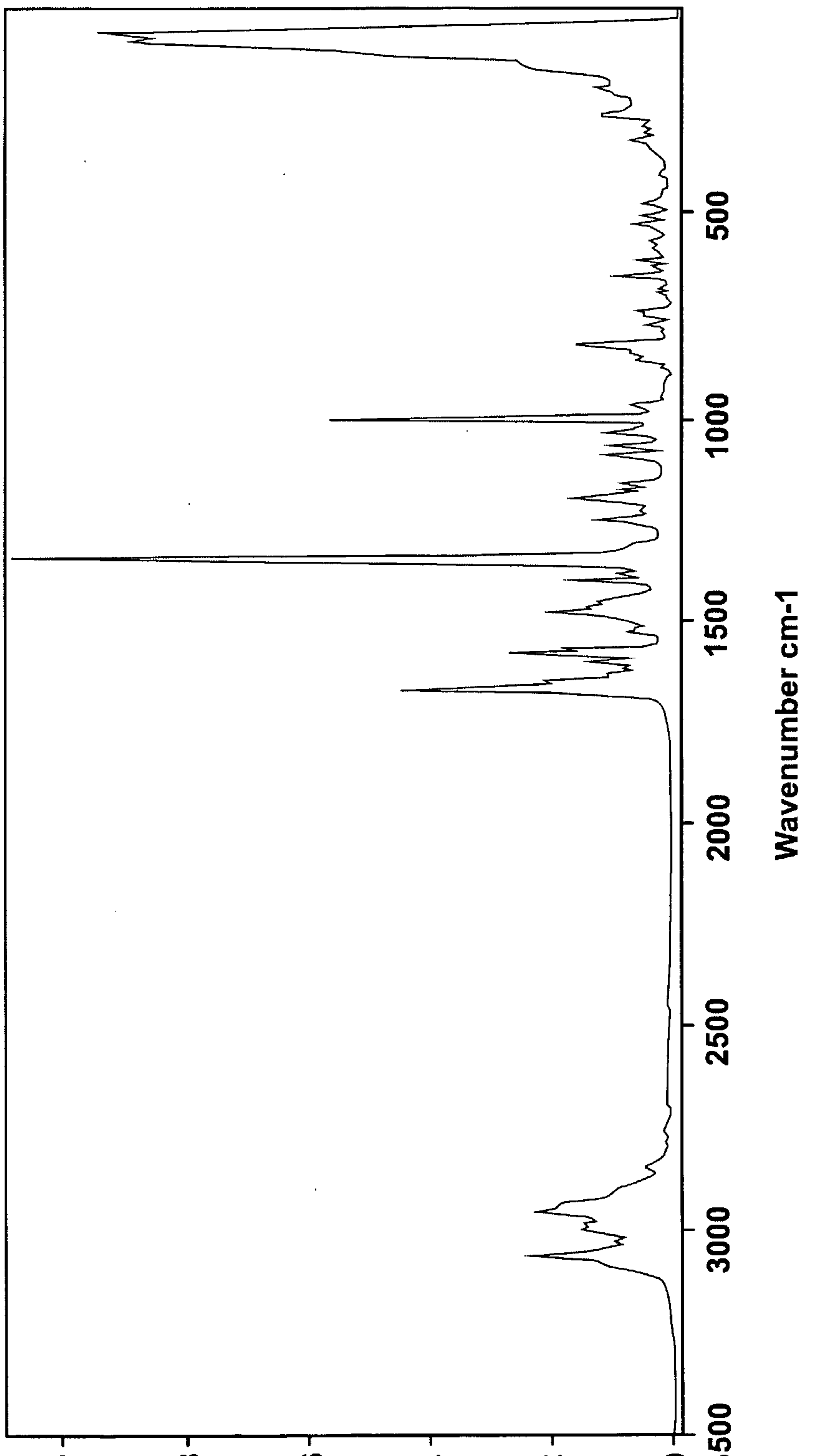
1.0
0.8
0.6
0.4
0.2
0.0
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

Figure 5

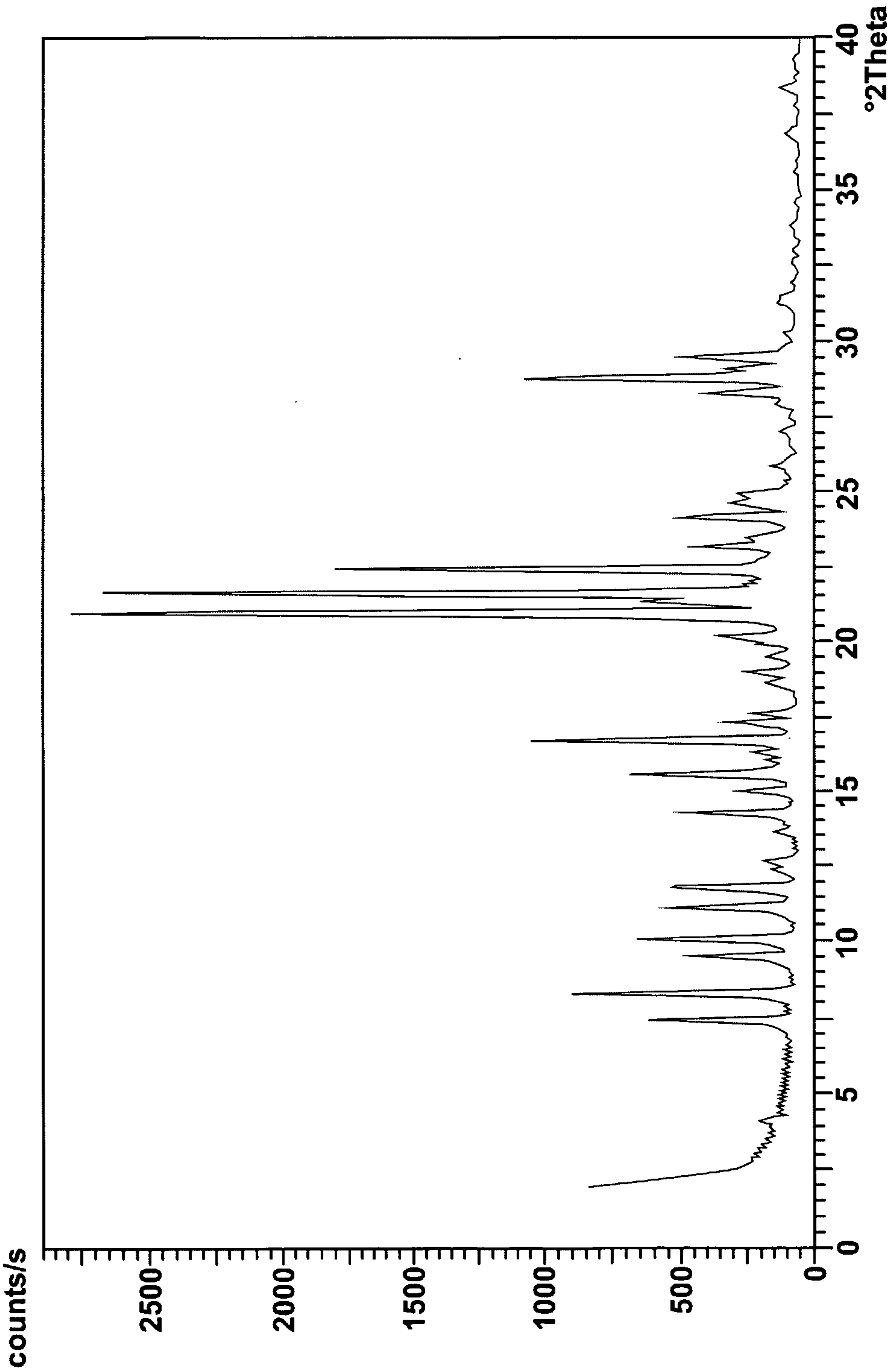

Figure 6

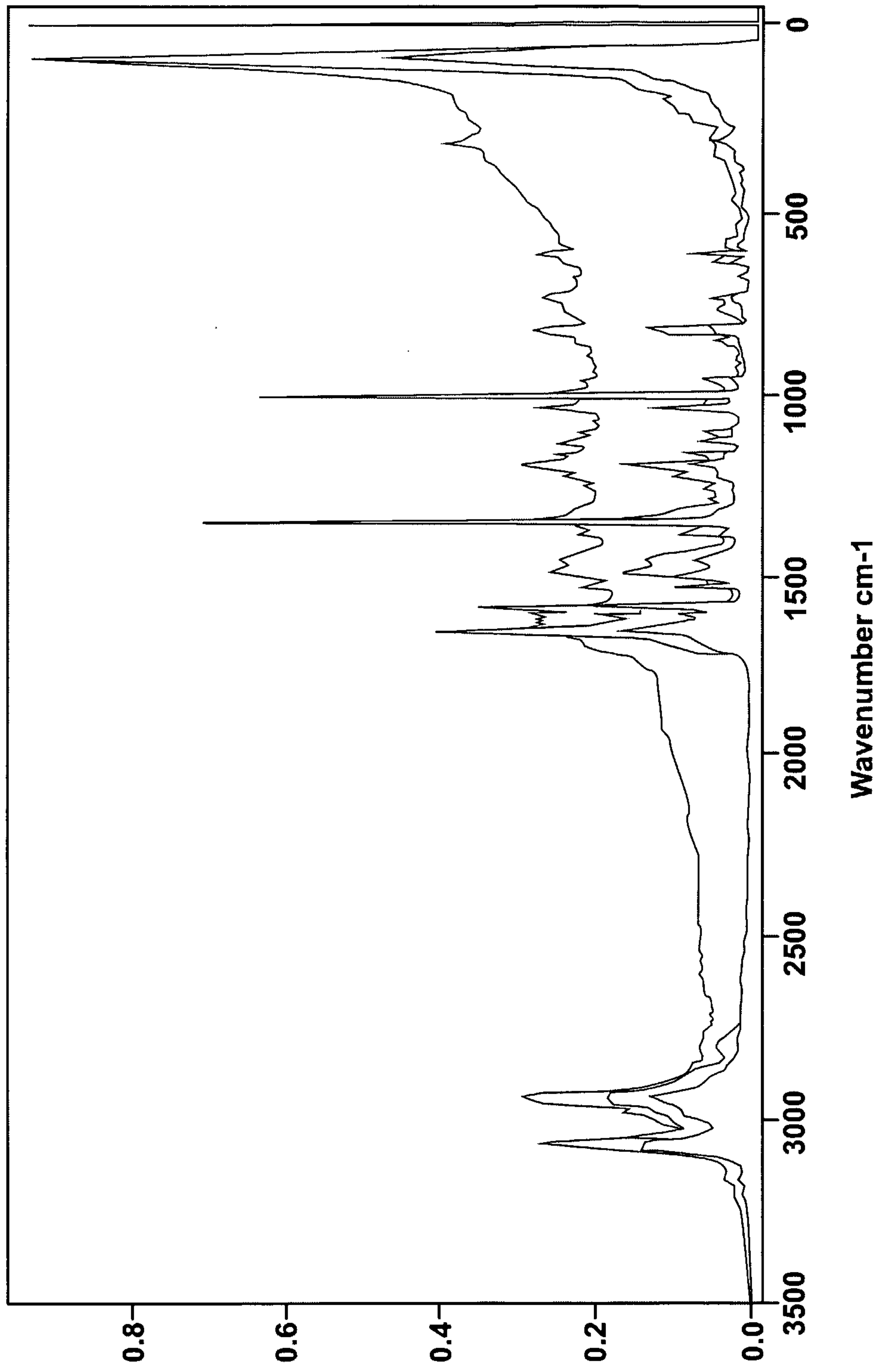
0.0
0.2
0.4
0.6
0.8
3500
3000
2500
2000
1500
1000
500
0
Wavenumber cm-1

Figure 7

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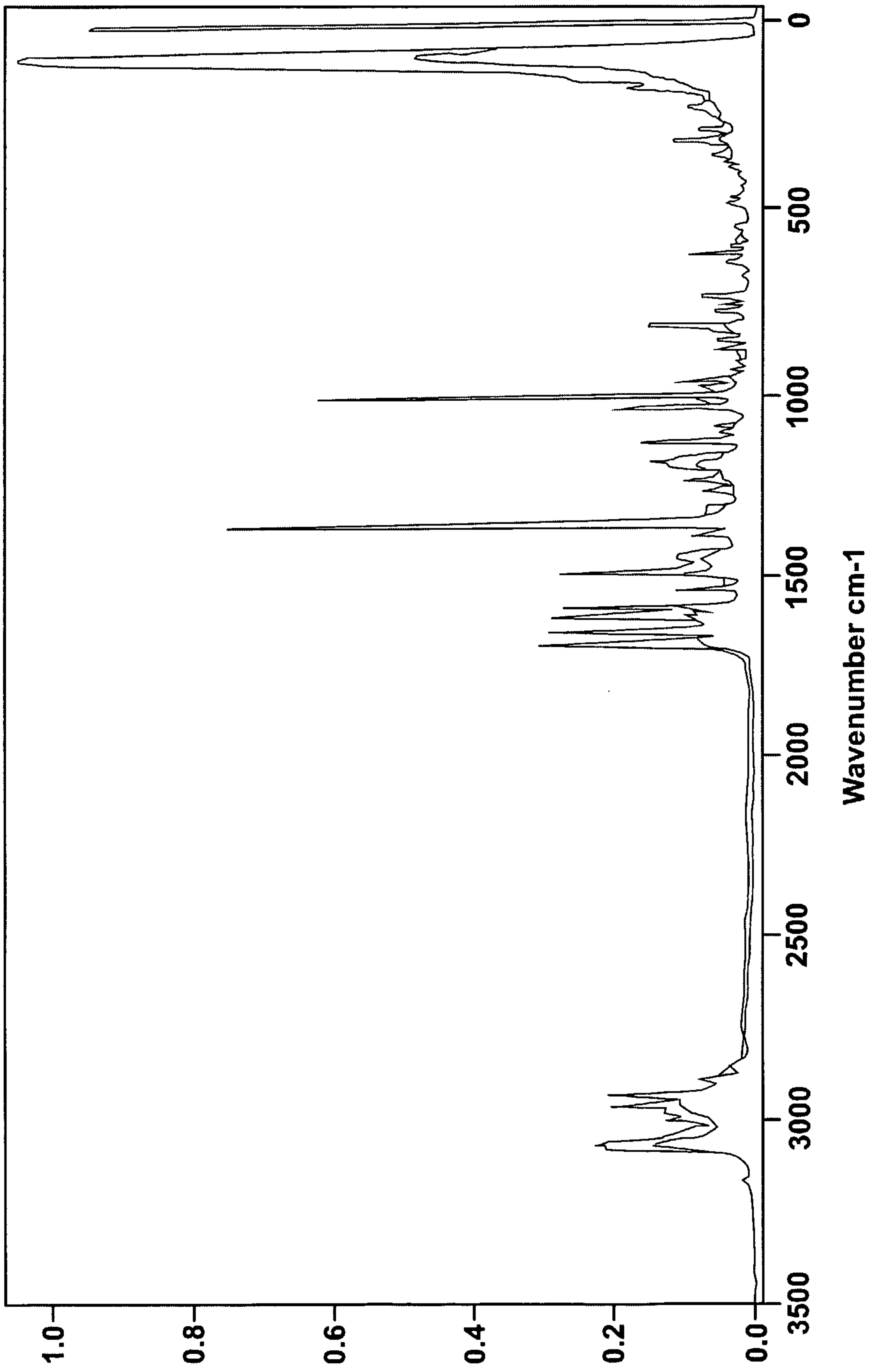
1.0
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
2000
2500
3000
3500
Wavenumber cm-1

Figure 8