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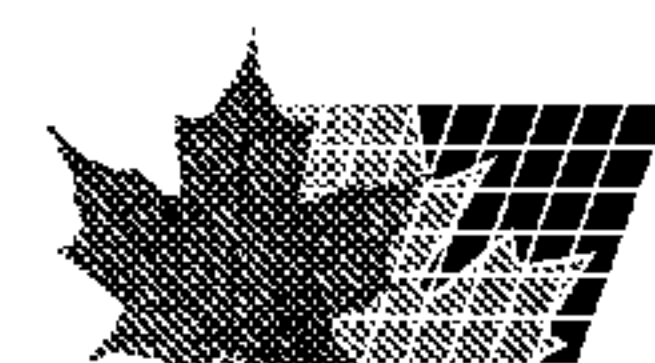
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(54) Titre : NOUVELLES FORMES BRUTES ET CRISTALLINES DE CHLOHYDRATE DE LERCANIDIPINE
(54) Title: NOVEL CRUDE AND CRYSTALLINE FORMS OF LERCANIDIPINE HYDROCHLORIDE

(57) **Abrégé/Abstract:**

The invention describes novel lercanidipine crude Forms (A) and (B), novel lercanidipine hydrochloride crystalline Forms (I) and (II) obtained from said crude Forms, novel crystalline Forms (III) and (IV), and lercanidipine solvates, and pharmaceutical, antihypertensive compositions containing as active agent at least one of the lercanidipine hydrochloride crystalline Forms (I) - (IV) or lercanidipine solvates and methods of use thereof



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ABSTRACT

The invention describes novel lercanidipine crude Forms (A) and (B), novel
5 lercanidipine hydrochloride crystalline Forms (I) and (II) obtained from said crude
Forms, novel crystalline Forms (III) and (IV), and lercanidipine solvates, and
pharmaceutical, antihypertensive compositions containing as active agent at least one of
the lercanidipine hydrochloride crystalline Forms (I) – (IV) or lercanidipine solvates and
methods of use thereof

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5 **NOVEL CRUDE AND CRYSTALLINE FORMS OF LERCANIDIPINE
HYDROCHLORIDE**

FIELD OF THE INVENTION

10 The invention is directed to novel crude forms, crystalline forms, and solvate of
lercanidipine hydrochloride, and to processes for the preparation of these forms.
Pharmaceutical compositions comprising the novel crystalline forms are also
contemplated.

15 **BACKGROUND OF THE INVENTION**

 Lercanidipine (methyl 1,1,N-trimethyl-N-(3,3-diphenylpropyl)-2-aminoethyl 1,4-
dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate) is a highly lipophilic
dihydropyridine calcium antagonist with long duration of action and high vascular
selectivity. Its mechanism of antihypertensive activity is attributed to a direct relaxant
20 effect on vascular smooth muscle, which lowers total peripheral resistance. The
recommended starting dose of lercanidipine as monotherapy is 10 mg daily by oral route,
with a drug titration as necessary to 20 mg daily. Lercanidipine is rapidly absorbed
following oral administration with peak plasma levels occurring 2-3 hours following
dosing. Elimination is essentially via the hepatic route.

25 By virtue of its high lipophilicity and high membrane coefficient, lercanidipine
combines a short plasma half life with a long duration of action. In fact, the preferential
distribution of the drug into membranes of smooth muscle cells results in membrane-
controlled pharmacokinetics characterized by a prolonged pharmacological effect. In

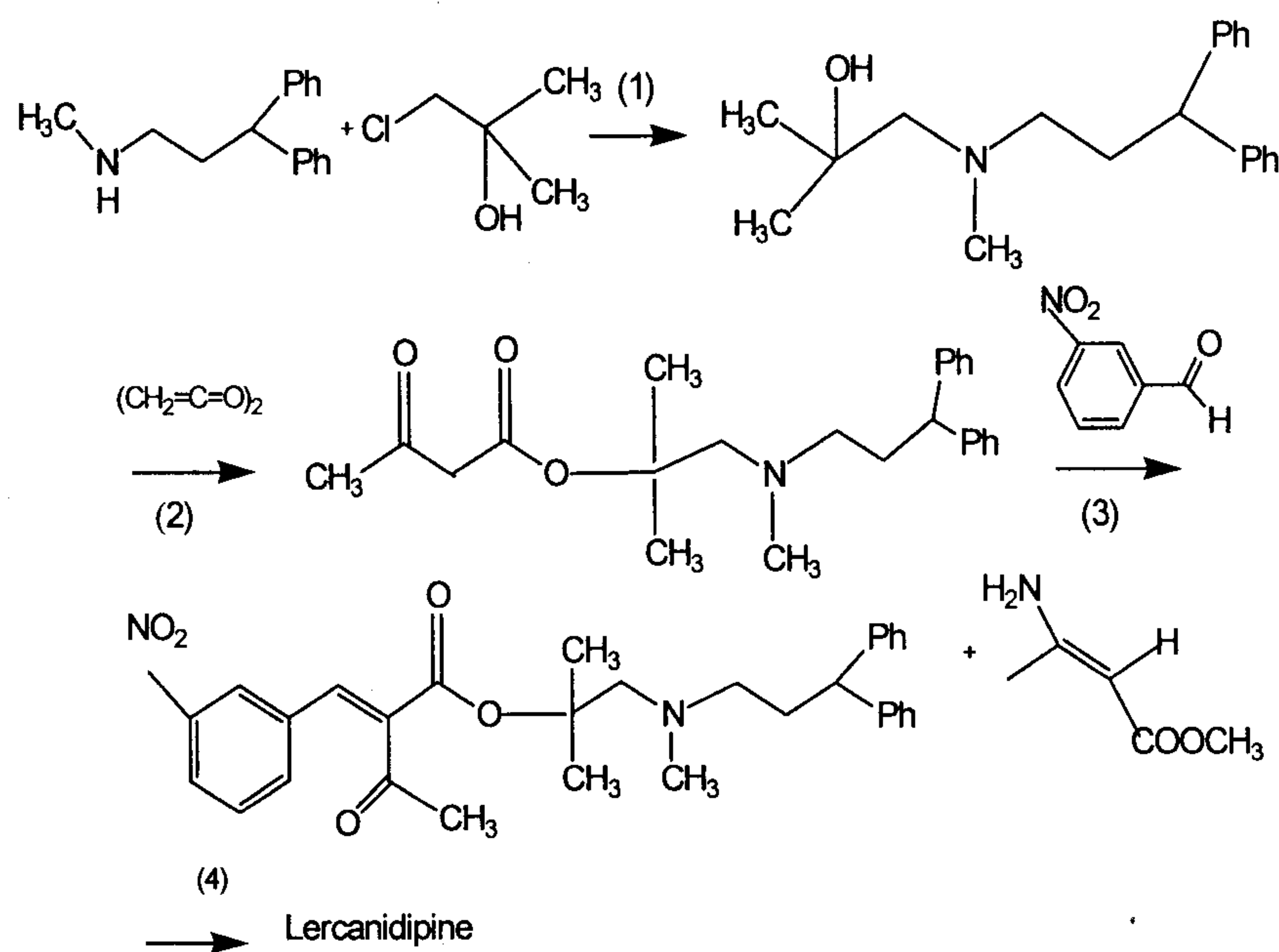
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comparison to other calcium antagonists, lercanidipine is characterized by gradual onset and long-lasting duration of action despite decreasing plasma levels. *In vitro* studies show that isolated rat aorta response to high K^+ may be attenuated by lercanidipine, even after the drug has been removed from the environment of the aortic tissue for 6 hours.

5 Lercanidipine is commercially available from Recordati S.p.A. (Milan, Italy) and has been described along with methods for making it and resolving it into individual enantiomers in U.S. Patents 4,705,797; 5,767,136; 4,968,832; 5,912,351; and 5,696,139.

A process for preparing lercanidipine described in U.S. Patent No. 4,705,797 involves the following scheme:



(1): xylene at reflux; (2): toluene, 85°C; (3) HCl + $CHCl_3$; 0°C; (4) $HO-CH(CH_3)_2$ at reflux

10

Crude lercanidipine is an oily residue that must be purified by flash chromatography using chloroform, containing increasing amounts of acetone, as the eluant. The solvent is then evaporated to dryness and remaining residue is dissolved in methanol adding a small excess of hydrochloric acid in ethanol. After evaporation of the solvent, the hemi-

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hydrated hydrochloride salt is prepared by treatment with diluted hydrochloric acid in the presence of sodium chloride.

A major disadvantage of the process of preparing lercanidipine, as it is described in U.S. Patent No. 4,705,797, is that the disclosed cyclization reaction generates several
5 by-products, which results in a lower yield for the desired product. Moreover, the purification and isolation of lercanidipine from the reaction mixture is quite complex, since it requires numerous treatments with different solvents. Finally, the purification and isolation steps are difficult to perform on an industrial scale because of the necessity of purifying the product by column chromatography.

10 U.S. Patent 5,912,351 describes a simpler process for the preparation of lercanidipine hydrochloride. It involves reaction of 1,4-dihydro-2,6-dimethyl-5-methoxycarbonyl-4- (3-nitrophenyl) pyridine-3-carboxylic acid with thionyl chloride in dichloromethane and dimethylformamide at a temperature between -4 and $+1^{\circ}\text{C}$ and subsequent esterification of the obtained acid chloride with 2, N-dimethyl-N-(3,3-
15 diphenylpropyl)-1-amino-2-propyl alcohol at a temperature between -10 and 0°C . 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.

However, the isolation of lercanidipine hydrochloride in crystalline form is again
20 quite complex. After evaporating the solvent from the reaction mixture and dissolving the residue thus obtained in ethyl acetate, the solution is washed first with brine, then washed further five times with a 10% solution of sodium carbonate, five times with 1N hydrochloric acid, and eventually once again with brine.

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Therefore, there is a need in the art for a process for the preparation of lercanidipine hydrochloride in crystalline form which avoids one more of the disadvantages of the currently used processes.

In addition, it was observed that lercanidipine, as produced by the second-
5 described process above, displayed batch-to-batch variability despite careful process control and even observation of the melting point believed to be characteristic of the solid product obtained by the process of Example 3 of USP 5,767,136 of 186-188EC. This variability was manifest in seemingly unpredictably appearing (and disappearing) differences in one or more of product appearance (e.g., color), melting point and
10 solubility. This raised issues as to whether assurances of purity and/or reproducibility can be made (e.g., to regulatory authorities) that the product is always the same.

Further research by the present inventors revealed batch-to-batch differences in bioavailability in animals, and differences in crystal size. In the course of researching the causes of the variability problem, the inventors surprisingly discovered novel
15 lercanidipine hydrochloride polymorphs. They also discovered more suitable processes for the preparation and isolation of crystalline lercanidipine hydrochloride products from the reaction mixture. It was surprisingly determined that lercanidipine hydrochloride shows polymorphic features and crystallizes into different crystalline forms depending on the process followed and on the solvents used. Furthermore, the isolation of each of
20 individual crystalline polymorphs has become possible, thus decreasing the possibility of batch to batch variability of lercanidipine, which the present inventors determined was due to mixtures of different solid forms being present by the same batch and to such mixtures of different composition having melting points within the same narrow range as

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the individual forms. As a result, more reproducible batches of lercanidipine more suitable for large scale manufacture and quality control were needed.

Accordingly, herein Applicants disclose crude lercanidipine Forms (A) and (B) and two crystalline forms formed therefrom, as well as two additional novel crystalline
5 forms which are formed from novel solvate forms of lercanidipine.

SUMMARY OF THE INVENTION

The present invention provides novel crude forms, crystalline forms and solvates of lercanidipine hydrochloride and processes for making them.

10 In one embodiment, the invention provides novel crude lercanidipine hydrochloride Form (A), which has a melting point of about 150-152EC (DSC peak) and comprises about 3-4% (w/w) ethyl acetate.

In another embodiment, the invention provides novel crude lercanidipine hydrochloride Form (B) which has a melting point of about 131-135EC (DSC peak) and
15 comprises about 0.3-0.7% (w/w) ethyl acetate.

Methods are provided for the independent syntheses of crude lercanidipine hydrochloride Form (A) and crude lercanidipine hydrochloride Form (B), making possible to obtain each crude form in isolated form.

In a further embodiment, isolated lercanidipine hydrochloride crystalline Form (I)
20 is provided which has the following X-ray diffraction pattern, at wavelength $K\alpha$ wherein distances between peaks (D in $\text{\AA}$), relative intensity ratios (I/I_0) ratios, and angles of significant peaks (2θ) are:

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	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
5	16.3	83	5.4
	6.2	47	14.2
	4.78	29	18.6
	4.10	63	21.7
	4.06	36	21.9
	3.90	100	22.8

The lercanidipine hydrochloride crystalline Form (I) has a melting point of about
 10 197-201EC, when said melting point is determined as DSC peak.

In an alternative embodiment, isolated lercanidipine hydrochloride crystalline
 Form (II) is provided, which has the following X-ray diffraction pattern, at wavelength
 Kα, as shown wherein distances, (I/I₀) ratios, and 2 θ angles of significant peaks are:

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
15	9.3	35	9.5
	6.0	45	14.7
	5.49	65	16.1
20	4.65	52	19.1
	4.27	74	20.8
	3.81	41	23.4
	3.77	100	23.6
	3.58	44	24.8
25	3.54	29	25.2

The lercanidipine hydrochloride crystalline Form (II) has a melting point of about
 207-211EC, when said melting point is determined as DSC peak.

The present invention thus permits obtaining mixtures of Form I and Form II
 30 having a predetermined and reproducible content of each form, and optionally, also other
 forms of lercanidipine, such as amorphous.

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Also provided are methods of syntheses in which each of isolated lercanidipine hydrochloride crystalline Form (I) and Form (II) may be obtained, independently, from the starting material of lercanidipine hydrochloride crude Form (A) or crude Form (B).

Also provided are pharmaceutical compositions comprising (1) crystalline lercanidipine hydrochloride and optionally other forms of lercanidipine, such as amorphous, wherein the crystalline lercanidipine hydrochloride is selected from the group consisting of lercanidipine hydrochloride crystalline Form (I), lercanidipine hydrochloride crystalline Form (II), and combinations thereof comprising a predetermined content of each crystalline form, and (2) at least one component selected from the group consisting of a pharmaceutically acceptable carrier or diluent, a flavorant, a sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a colorant, a disintegrant, an excipient, a lubricant, a plasticizer, and an edible oil.

In certain embodiments the aforementioned pharmaceutical compositions are provided as a dosage form comprising lercanidipine hydrochloride crystalline Form (I) or Form (II) or a combination thereof having a predetermined formulation of each crystalline Form.

In further embodiments, the invention also provides for methods of treating a subject with arterial hypertension, the method comprising administering a therapeutically effective amount of lercanidipine hydrochloride crystalline Form (I), lercanidipine hydrochloride crystalline Form (II), or combinations thereof comprising a predetermined content of each form to a subject in need of such treatment.

In other embodiments, a method of treating or preventing atherosclerotic lesions in arteries of a subject is provided, the method comprising administering a therapeutically effective amount of lercanidipine hydrochloride crystalline Form (I),

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lercanidipine hydrochloride crystalline Form (II), or combinations thereof comprising a predetermined amount of each form, to a subject in need of such treatment. In preferred aspect, a subject in need of treatment is a mammal. Most preferably the subject in need of treatment is a human.

5 In certain embodiments, the invention provides solvates of lercanidipine hydrochloride comprising lercanidipine hydrochloride and an organic solvent. In preferred embodiments, the solvent is selected from the group consisting of methylene chloride, acetone, anisole, tetrahydrofuran, terbutyl methyl ether, isopropanol, 2-butanol, heptane, methyl ethyl ketone, and ethyl acetate.

10 In one embodiment, the invention provides a solvate of lercanidipine hydrochloride wherein the solvent is methylene chloride, the lercanidipine hydrochloride-methylene chloride content is 1:1 (mole/mole), and the solvate has, at wavelength $K\alpha$, an X-ray diffraction image expressed by the following Table:

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
15	6.6	40	13.4
	5.87	42	15.1
	5.04	39	17.6
	4.00	96	22.2
	3.90	29	22.8
20	3.86	34	23.0
	3.67	100	24.2
	2.04	31	44.4

In another embodiment the invention provides a solvate of lercanidipine
 25 hydrochloride wherein the solvent is anisole, the lercanidipine hydrochloride-anisole content is 1:0.4 (mole/mole), and the solvate (a) form has, at wavelength $K\alpha$, an X-ray diffraction image expressed by the following Table:

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	<u>d (Å)</u>	<u>Relative intensity (%)</u>	<u>Angle (°2θ)</u>
	17.4	62	5.1
	7.6	34	11.6
5	5.71	43	15.5
	5.57	58	15.9
	4.99	47	17.7
	4.62	40	19.2
	4.44	29	20.0
10	4.28	98	20.8
	4.04	100	22.0
	3.19	43	27.9
	2.92	36	30.6
15	2.86	42	31.3

In another embodiment the invention provides a solvate of lercanidipine hydrochloride wherein the solvent is anisole, the lercanidipine hydrochloride-anisole content is 1:0.4 (mole/mole), and the solvate (b) form has, at wavelength K α , an X-ray diffraction image expressed by the following Table:

	<u>d (Å)</u>	<u>Relative intensity (%)</u>	<u>Angle (°2θ)</u>
20	6.9	49	12.8
	6.7	63	13.3
	5.82	86	15.2
25	5.27	41	16.8
	5.15	53	17.2
	4.00	47	22.2
	3.89	46	22.8
	3.66	100	24.3
30			

In another embodiment the invention provides a solvate of lercanidipine hydrochloride wherein the solvent is acetone, the lercanidipine hydrochloride-acetone content is 1:1.2 (mole/mole), and the solvate has, at wavelength K α , an X-ray diffraction image expressed by the following Table:

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	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
	10.1	42	8.8
	7.3	100	12.1
5	5.87	31	15.1
	4.07	41	21.8
	3.96	52	22.4
	3.79	49	23.5
	3.71	37	24.0
10	3.34	33	26.7

In another embodiment the invention provides a solvate of lercanidipine hydrochloride wherein the solvent is ethyl acetate, the lercanidipine hydrochloride-ethyl acetate content is 1:1 (mole/mole), and the solvate has, at wavelength K α , an X-ray

15 diffraction image expressed by the following Table:

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
	6.9	100	12.8
	6.3	29	14.0
20	5.80	45	15.3
	5.65	31	15.7
	5.43	44	16.3
	4.74	53	18.7
	4.53	49	19.6
25	4.00	84	22.2
	3.91	91	22.7
	3.67	77	24.2
	3.60	34	24.7
	3.53	34	25.2
30	3.49	43	25.5

In another embodiment the invention provides a solvate of lercanidipine hydrochloride wherein the solvent is terbutyl methyl ether, the lercanidipine hydrochloride- terbutyl methyl ether content is 1:0.8 (mole/mole), and the solvate has, at

35 wavelength K α , an X-ray diffraction image expressed by the following Table:

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	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
5	6.2	77	14.2
	4.88	29	18.2
	4.52	64	19.6
	4.02	48	22.1
	3.93	100	22.6
10	3.43	46	26.0

In another embodiment the invention provides a solvate of lercanidipine hydrochloride wherein the solvent is isopropanol, the lercanidipine hydrochloride-isopropanol content is 1:1 (mole/mole), and the solvate has, at wavelength K α , an X-ray diffraction image expressed by the following Table:

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
15	6.6	35	13.5
	5.85	48	15.1
	5.06	41	17.5
20	4.04	64	22.0
	3.90	39	22.8
	3.72	37	23.9
	3.67	100	24.2

25 In another embodiment the invention provides a solvate of lercanidipine hydrochloride wherein the solvent is 2-butanol, the lercanidipine hydrochloride-2-butanol content is 1:0.8 (mole/mole), and the solvate has, at wavelength K α , an X-ray diffraction image expressed by the following Table:

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
30	6.8	34	13.1
	5.86	36	15.1
	5.13	42	17.3

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4.03	51	22.0
3.90	36	22.8
3.67	100	24.2

- 5 In another embodiment the invention provides a solvate of lercanidipine hydrochloride wherein the solvent is heptane, the lercanidipine hydrochloride-heptane content is 1:0.9 (mole/mole), and the solvate has, at wavelength $K\alpha$, an X-ray diffraction image expressed by the following Table:

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
10	7.3	54	12.2
	6.0	44	14.7
	4.03	85	22.0
	3.85	100	23.1
15	3.76	93	23.6
	3.63	67	24.5
	3.38	39	26.4
	3.01	47	29.6

- 20 In another embodiment the invention provides a solvate of lercanidipine hydrochloride wherein the solvent is methyl ethyl ketone, the lercanidipine hydrochloride-methyl ethyl ketone content is 1:0.7 (mole/mole), and the solvate has, at wavelength $K\alpha$, an X-ray diffraction image expressed by the following Table:

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
25	6.8	50	13.1
	6.1	43	14.5
	5.87	47	15.1
	5.10	53	17.4
30	3.99	100	22.2
	3.87	48	22.9
	3.74	36	23.8
	3.69	65	24.1
	3.61	70	24.6

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In another embodiment the invention provides a solvate of lercanidipine hydrochloride wherein the solvent is tetrahydrofuran, the lercanidipine hydrochloride-tetrahydrofuran content is 1:0.9 (mole/mole), and the solvate has, at wavelength $K\alpha$, an

5 X-ray diffraction image expressed by the following Table:

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
10	6.6	100	13.5
	5.88	32	15.1
	5.12	56	17.3
	4.25	38	20.9
	4.06	50	21.9
	3.92	42	22.7
15	3.75	44	23.7
	3.70	90	24.0
	3.64	31	24.4

In yet another embodiment, the invention provides isolated lercanidipine hydrochloride crystalline form (III), having a melting point in the range of 137-150°C

20 and having an X-ray diffraction image, at wavelength $K\alpha$, expressed by the following Table:

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
25	11.5	39	7.7
	9.1	38	9.7
	9.0	37	9.8
	8.0	50	11.0
	6.6	48	13.5
	5.58	57	15.9
30	5.49	34	16.1
	5.13	43	17.3
	4.09	63	21.7
	3.92	43	22.7
	3.72	100	23.9

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3.60	85	24.7
3.47	31	25.6

In another embodiment, the invention provides crystalline form (IV), having a
 5 melting point in the range of 116-135°C and having an X-ray diffraction image, at
 wavelength $K\alpha$, expressed by the following Table:

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
	7.9	71	11.2
10	6.9	53	12.7
	5.21	57	17.0
	5.13	46	17.3
	4.73	66	18.8
	4.69	95	18.9
15	4.53	53	19.6
	4.40	81	20.2
	4.34	43	20.4
	3.99	44	22.2
	3.89	52	22.8
20	3.77	100	23.6
	3.69	35	24.1

Also provided are pharmaceutical compositions comprising (1) lercanidipine
 hydrochloride crystalline Form (III) or lercanidipine hydrochloride crystalline Form
 25 (IV), and combinations thereof, comprising a predetermined content of each crystalline
 form, and optionally including other forms of lercanidipine, such as, amorphous
 lercanidipine, lercanidipine hydrochloride crystalline Form (I) or lercanidipine
 hydrochloride crystalline Form (II), and (2) at least one component selected from the
 group consisting of a pharmaceutically acceptable carrier or diluent, a flavorant, a
 30 sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a
 colorant, a disintegrant, an excipient, a lubricant, a plasticizer, and an edible oil.

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In certain embodiments the aforementioned pharmaceutical compositions are provided as a dosage form comprising lercanidipine hydrochloride crystalline Form (III) or Form (IV) or a combination thereof having a predetermined formulation of each crystalline Form, optionally including other forms of lercanidipine, such those set forth
5 above.

In further embodiments, the invention provides lercanidipine hydrochloride crystalline forms (III) or (IV) or mixtures thereof, including the dosage forms set forth above, wherein said crystalline forms are in micronized form, preferably with an average size of D(50%) 2-8 μm , D(90%) < 15 μm .

10 In another embodiment, a method is provided for treating a subject with arterial hypertension, the method comprising administering a therapeutically effective amount of lercanidipine hydrochloride crystalline Form (III), lercanidipine hydrochloride crystalline form (IV), or combinations thereof to a subject in need of such treatment.

In another embodiment, the invention provides a method of treating or preventing
15 atherosclerotic lesions in arteries in a subject, which comprises administering a therapeutically effective amount of lercanidipine hydrochloride crystalline Form (III), lercanidipine hydrochloride crystalline Form (IV), or combinations thereof having a predetermined content in each of said Form (III) and (IV) to a subject in need of such treatment.

20 In other embodiments, the invention provides an antihypertensive composition comprising predetermined amounts of lercanidipine hydrochloride crystalline Form (III) and lercanidipine hydrochloride crystalline Form (IV). In certain embodiments, the ratio of Form (III) : Form (IV) is between about 1:9 to 9:1. e.g., wherein the ratio of Form (III) : Form (IV) is selected from the group consisting of 9:1, 7:3, 1:1, 3:7 and 1:9.

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Also provided are methods of making a lercanidipine hydrochloride-methylene chloride solvate or a lercanidipine hydrochloride-methyl ethyl ketone solvate from the starting material of lercanidipine hydrochloride crystalline Form I, methods for preparing lercanidipine hydrochloride crystalline Form (III) by the removal of solvent from a lercanidipine hydrochloride solvate by evaporation under vacuum or in nitrogen stream to form said crystalline Form (III) and a method for preparing lercanidipine hydrochloride crystalline Form (IV) by removal of acetone from a lercanidipine hydrochloride-acetone solvate by evaporation under vacuum or in a nitrogen stream.

According to one aspect of the present invention, there is provided isolated lercanidipine hydrochloride crystalline Form (I), which has the X-ray diffraction pattern, at wavelength $K\alpha$, wherein distances, (I/I₀) ratios, and 2θ angles of significant peaks are:

	<u>D (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2θ angle</u>
15	16.3	83	5.4
	6.2	47	14.2
	4.78	29	18.6
	4.10	63	21.7
	4.06	36	21.9
20	3.90	100	22.8

According to another aspect of the present invention, there is provided a method of producing lercanidipine hydrochloride crystalline Form (I), which has an X-ray diffraction pattern, at wavelength $K\alpha$, wherein distances, (I/I₀) ratios, and 2θ angles of significant peaks are:

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	<u>D (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2θ angle</u>
	16.3	83	5.4
	6.2	47	14.2
	4.78	29	18.6
5	4.10	63	21.7
	4.06	36	21.9
	3.90	100	22.8 ;

which comprises: d) adding a C1-C5 alcohol solvent containing a maximum of 5% water (v/v) to a crude lercanidipine hydrochloride Form and heating under reflux and
 10 with stirring to produce a clear solution; e) cooling the solution of step d) and stirring until the concentration of lercanidipine hydrochloride dissolved in the crystallization solvent is $\leq 2\%$ by weight; and f) recovering the solid obtained from step e), and drying said solid to produce the lercanidipine hydrochloride crystalline Form (I).

According to still another aspect of the present invention, there is
 15 provided a method of producing lercanidipine hydrochloride crystalline Form (I), which has an X-ray diffraction pattern, at wavelength $K\alpha$, wherein distances, (I/I₀) ratios, and 2θ angles of significant peaks are:

	<u>D (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2θ angle</u>
	16.3	83	5.4
20	6.2	47	14.2
	4.78	29	18.6
	4.10	63	21.7
	4.06	36	21.9
	3.90	100	22.8 ;

25 which comprises: d') providing a mixture of ethanol and lercanidipine hydrochloride, refluxing under stirring and cooling and adding crystalline seeds of Form (I); e') further

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cooling the seeded mixture of step d') and stirring until the concentration of lercanidipine hydrochloride dissolved in the crystallization solvent is $\leq 2\%$ by weight; and f') recovering the solid of step e') to form lercanidipine hydrochloride Form (I).

According to yet another aspect of the present invention, there is
5 provided an antihypertensive pharmaceutical composition comprising (1) crystalline lercanidipine hydrochloride and optionally other forms of lercanidipine, wherein the crystalline lercanidipine hydrochloride is lercanidipine hydrochloride crystalline Form (I), comprising a predetermined content of each crystalline form, and (2) at least
10 one component selected from the group consisting of a pharmaceutically acceptable carrier or diluent, a flavorant, a sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a colorant, a disintegrant, an excipient, a lubricant, a plasticizer, and an edible oil.

According to a further aspect of the present invention, there is provided
a unit dosage form comprising the antihypertensive pharmaceutical composition
15 described herein.

According to yet a further aspect of the present invention, there is
provided a use of lercanidipine hydrochloride crystalline Form (I) for treating
hypertension, coronary heart disease or congestive heart failure in a subject in need
thereof.

20 According to still a further aspect of the present invention, there is
provided a use of lercanidipine hydrochloride crystalline Form (I) for treating or
preventing atherosclerotic lesions in arteries in a subject in need thereof.

According to another aspect of the present invention, there is provided
a use of lercanidipine hydrochloride crystalline Form (I) for treating or preventing
25 heart failure in a subject in need thereof.

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According to yet another aspect of the present invention, there is provided an antihypertensive composition comprising lercanidipine hydrochloride crystalline Form (I) and lercanidipine hydrochloride crystalline Form (II).

These and other aspects of the present invention will be apparent to those of ordinary skill in the art in light of the present description, claims and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph of DSC analysis carried out on crystalline Form (I), according to the working conditions described in Example 12. The ordinate indicates heat flow in mW and the abscissa temperature in °C.

Figure 2 is a graph of DSC analysis carried out on crystalline Form (II), according to the working conditions described in Example 12. The ordinate indicates heat flow in mW and the abscissa temperature in °C.

Figure 3 is a graph of the results of the thermogravimetric tests carried out on Form (I) and Form (II), respectively, as described in Example 13. The abscissa indicates temperature in °C and the ordinate indicates percent mass variation.

Figure 4 is a graph of solubility at 25°C of Forms (I) and (II) in ethanol at increasing water concentrations. The experiments are described in Example 15. The

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ordinate indicates % solubility expressed as w/w and the abscissa % by weight of water in ethanol.

Figure 5 is a graph of solubility at 40°C of Forms (I) and (II) in ethanol at increasing water concentrations. The tests are described in Example 15. The ordinate indicates % solubility expressed as w/w and the abscissa % by weight of water in ethanol.

Figure 6 shows ^{13}C NMR spectra in solid phase of crystalline Form (I). The signals and attributes of the corresponding carbon atoms can be found in Table 4.

Figure 7 shows ^{13}C NMR spectra in solid phase of crystalline Form (II). The signals and attributes of the corresponding carbon atoms can be found in Table 5.

Figure 8 shows IR spectra of Form (I). The signal and corresponding attributes can be found in Table 6.

Figure 9 shows IR spectra of Form (II). The signal and corresponding attributes can be found in Table 7.

Figure 10 represents percent average concentration of lercanidipine hydrochloride in dog plasma after administration of crystalline Form (I) and of crystalline Form (II) in an amount of 3 mg/kg, in the form of a hard gelatin capsule. The ordinate indicates the mean value of concentration in plasma and the abscissa indicates time (in minutes).

Figures 11 and 12 show X-ray diffraction spectra at wavelength $\text{K}\alpha$ of crystalline Forms (I) and (II), respectively. The distances (d) in Å, the (I/I₀) ratios and values of 2θ angles of the most significant peaks can be found in Tables 1 and 2 below. The ordinate indicates the number of counts/sec and the abscissa shows the values of 2θ angles.

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Figures 13 and 14 are plots of percent mass change as a function of time in hygroscopicity tests carried out on Forms (I) and (II) of lercanidipine hydrochloride, respectively. The ordinate on the left indicates percent mass changes and the ordinate on the right percent relative humidity; the abscissa indicates time in minutes. The protocol
5 for the hygroscopicity tests are described in Example 14.

Figures 15 and 16 show X-ray diffraction spectra at wavelength $K\alpha$ of crude lercanidipine hydrochloride Form (A) and of crude lercanidipine hydrochloride Form (B), respectively.

Figures 17 and 18 show Raman spectra of crude lercanidipine hydrochloride
10 Form (A) and of crude lercanidipine hydrochloride Form (B), respectively, where the ordinate represents Raman units and the abscissa represents wave number (cm^{-1}).

Figures 19 and 20 show the results of the thermogravimetric analysis carried out on crude lercanidipine hydrochloride Form (A) and on crude lercanidipine hydrochloride Form (B), respectively. In these figures, the abscissa indicates temperature (in $^{\circ}\text{C}$) and
15 the ordinate indicates percent mass variation.

Figure 21 shows the X-ray diffraction spectrum at wavelength $K\alpha$ of the solvate of lercanidipine hydrochloride with methylene chloride having a lercanidipine hydrochloride-methylene chloride content of 1:1 (mole/mole). The ordinate indicates the number of counts per second and the abscissa represents the values of 2θ angles.

20 **Figure 22** shows the X-ray diffraction spectrum at wavelength $K\alpha$ of crystalline form (III) of lercanidipine hydrochloride.

Figures 23 and 24 show plots referring to the solvate of lercanidipine hydrochloride with methylene chloride having a lercanidipine hydrochloride-methylene chloride content of 1:1 (mole/mole) and of lercanidipine hydrochloride crystalline form

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(III) and the thermogravimetric analysis carried out according to the operating modes described in Example 36B. The ordinate indicates % mass variation and the abscissa the temperature.

Figures 25 and 26 show Raman spectrums referring to the solvate of lercanidipine hydrochloride with methylene chloride having a lercanidipine hydrochloride-methylene chloride content of 1:1 (mole/mole) and of lercanidipine hydrochloride crystalline form (III), respectively. The ordinate indicates Raman units and the abscissa represents wave number (in cm^{-1}).

Figure 27 shows the X-ray diffraction spectrum of lercanidipine hydrochloride crystalline form (IV).

Figure 28 shows the X-ray diffraction spectrum of the solvate lercanidipine hydrochloride-acetone having a lercanidipine hydrochloride-acetone content of 1:1.2(mole/mole).

Figure 29 shows the X-ray diffraction spectrum of the solvate lercanidipine hydrochloride-ethyl acetate having a lercanidipine hydrochloride-ethyl acetate content of 1:1 (mole/mole).

Figure 30 shows the X-ray diffraction spectrum of the solvate lercanidipine hydrochloride-tetrahydrofuran having a lercanidipine hydrochloride-tetrahydrofuran content of 1:0.9(mole/mole).

Figure 31 shows the X-ray diffraction spectrum of the solvate lercanidipine hydrochloride-terbutyl methyl ether having a lercanidipine hydrochloride-terbutyl methyl ether content of 1:0.8 (mole/mole).

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Figure 32 shows the X-ray diffraction spectrum of the solvate lercanidipine hydrochloride-anisole (a) form having a lercanidipine hydrochloride- anisole content of 1:0.4 (mole/mole).

Figure 33 shows the X-ray diffraction spectrum of the solvate lercanidipine hydrochloride-anisole (b) form having a lercanidipine hydrochloride-anisole content of 1:0.4 (mole/mole).

Figure 34 shows the X-ray diffraction spectrum of the solvate lercanidipine hydrochloride-isopropanol having a lercanidipine hydrochloride-isopropanol content of 1:1 (mole/mole).

Figure 35 shows the X-ray diffraction spectrum of the solvate lercanidipine hydrochloride-isobutanol having a lercanidipine hydrochloride-isobutanol content of 1:0.8 (mole/mole).

Figure 36 shows the X-ray diffraction spectrum of the solvate lercanidipine hydrochloride-heptane having a lercanidipine hydrochloride-heptane content of 1:0.9 (mole/mole).

Figure 37 shows the Raman spectrum of lercanidipine hydrochloride crystalline form (IV).

Figure 38 shows the Raman spectrum of the solvate lercanidipine hydrochloride-acetone having a lercanidipine hydrochloride-acetone content of 1:1.2(mole/mole).

Figure 39 shows the Raman spectrum of the solvate lercanidipine hydrochloride-ethyl acetate having a lercanidipine hydrochloride-ethyl acetate content of 1:1 (mole/mole).

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Figure 40 shows the Raman spectrum of the solvate lercanidipine hydrochloride-tetrahydrofuran having a lercanidipine hydrochloride-tetrahydrofuran content of 1:0.9 (mole/mole).

Figure 41 shows the Raman spectrum of the solvate lercanidipine hydrochloride-
5 terbutyl methyl ether having a lercanidipine hydrochloride-terbutyl methyl ether content of 1:0.8 (mole/mole).

Figure 42 shows the Raman spectrum of the solvate lercanidipine hydrochloride-anisole (a) form having a lercanidipine hydrochloride-anisole content of 1:0.4(mole/mole).

10 **Figure 43** shows the Raman spectrum of the solvate lercanidipine hydrochloride-anisole (b) form having a lercanidipine hydrochloride-anisole content of 1:0.4(mole/mole).

Figure 44 shows the Raman spectrum of the solvate lercanidipine hydrochloride-isopropanol having a lercanidipine hydrochloride-isopropanol content of 1:1
15 (mole/mole).

Figure 45 shows the Raman spectrum of the solvate lercanidipine hydrochloride-isobutanol having a lercanidipine hydrochloride-isobutanol content of 1:0.8 (mole/mole).

Figure 46 shows the Raman spectrum of the solvate lercanidipine hydrochloride-heptane having a lercanidipine hydrochloride-heptane content of 1:0.9 (mole/mole).

20 **Figure 47** shows the results of the thermogravimetric analysis carried out on the solvate lercanidipine hydrochloride-anisole (b) form having a lercanidipine hydrochloride-anisole content of 1:0.4 (mole/mole).

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Figure 48 shows the results of the thermogravimetric analysis carried out on the solvate lercanidipine hydrochloride-ethyl acetate having a lercanidipine hydrochloride-ethyl acetate content of 1:1 (mole/mole).

Figure 49 shows the results of the thermogravimetric analysis carried out on the solvate lercanidipine hydrochloride-acetone having a lercanidipine hydrochloride-acetone content of 1:1.2 (mole/mole).

Figure 50 shows the results of the thermogravimetric analysis carried out on the solvate lercanidipine hydrochloride-tetrahydrofuran having a lercanidipine hydrochloride-tetrahydrofuran content of 1:0.9 (mole/mole).

Figure 51 shows the results of the thermogravimetric analysis carried out on the solvate lercanidipine hydrochloride-anisole (a) form having a lercanidipine hydrochloride-anisole content of 1:0.4 (mole/mole).

Figure 52 shows the results of the thermogravimetric analysis carried out on the solvate lercanidipine hydrochloride-terbutyl methyl ether having a lercanidipine hydrochloride-terbutyl methyl ether content of 1:0.8 (mole/mole).

Figure 53 shows the results of the thermogravimetric analysis carried out on the solvate lercanidipine hydrochloride-isopropanol having a lercanidipine hydrochloride-isopropanol content of 1:1 (mole/mole).

Figure 54 shows the results of the thermogravimetric analysis carried out on the solvate lercanidipine hydrochloride-isobutanol having a lercanidipine hydrochloride-isobutanol content of 1:0.8 (mole/mole).

Figure 55 shows the results of the thermogravimetric analysis carried out on the solvate lercanidipine hydrochloride-heptane having a lercanidipine hydrochloride-heptane content of 1:0.9 (mole/mole).

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Figure 56 shows the results of the thermogravimetric analysis carried out on lercanidipine hydrochloride crystalline form (IV).

Figure 57 shows the results of the thermogravimetric analysis carried out on the solvate lercanidipine hydrochloride-methyl ethyl ketone having a lercanidipine hydrochloride-methyl ethyl ketone content of 1:0.7 (mole/mole).

Figure 58 shows the X-ray spectrum of the solvate lercanidipine hydrochloride-methyl ethyl ketone having a lercanidipine hydrochloride-methyl ethyl ketone content of 1:0.7 (mole/mole).

Figure 59 shows the Raman spectrum of the solvate lercanidipine hydrochloride-methyl ethyl ketone having a lercanidipine hydrochloride-methyl ethyl ketone content of 1:0.7 (mole/mole).

DETAILED DESCRIPTION OF THE INVENTION

According to one aspect of the present invention, there is provided isolated lercanidipine hydrochloride crystalline Form (I), which has the X-ray diffraction pattern, at wavelength $K\alpha$, as shown in Figure 11.

According to another aspect of the present invention, there is provided a method of producing lercanidipine hydrochloride crystalline Form (I), which has an X-ray diffraction pattern, at wavelength $K\alpha$, as shown in Figure 11, which comprises: d) adding a C1-C5 alcohol solvent containing a maximum of 5% water (v/v) to a crude lercanidipine hydrochloride Form and heating under reflux and with stirring to produce a clear solution; e) cooling the solution of step d) and stirring until the concentration of lercanidipine hydrochloride dissolved in the crystallization solvent is $\leq 2\%$; and f) recovering the solid obtained from step e), and drying said solid to produce the lercanidipine hydrochloride crystalline Form (I).

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According to still another aspect of the present invention, there is provided a method of producing lercanidipine hydrochloride crystalline Form (I), which has an x-ray diffraction pattern, at wavelength $K\alpha$, as shown in Figure 12, which comprises: d') providing a mixture of ethanol and lercanidipine hydrochloride, refluxing under stirring
5 and cooling and adding crystalline seeds of Form (I); e') further cooling the seeded mixture of step d') and stirring until the concentration of lercanidipine hydrochloride dissolved in the crystallization solvent is $\leq 2\%$; and f') recovering the solid of step e') to form lercanidipine hydrochloride Form (I).

According to yet another aspect of the present invention, there is provided an
10 antihypertensive pharmaceutical composition comprising (1) crystalline lercanidipine hydrochloride and optionally other forms of lercanidipine, wherein the crystalline lercanidipine hydrochloride is lercanidipine hydrochloride crystalline Form (I), and (2) at least one component selected from the group consisting of a pharmaceutically acceptable carrier or diluent, a flavorant, a sweetener, a preservative, a dye, a binder, a suspending
15 agent, a dispersing agent, a colorant, a disintegrant, an excipient, a lubricant, a plasticizer, and an edible oil.

According to a further aspect of the present invention, there is provided a unit dosage form comprising the antihypertensive pharmaceutical composition described herein.

20 According to yet a further aspect of the present invention, there is provided a use of lercanidipine hydrochloride crystalline Form (I) for treating hypertension, coronary heart disease or congestive heart failure in a subject in need thereof.

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According to still a further aspect of the present invention, there is provided a use of lercanidipine hydrochloride crystalline Form (I) for treating or preventing atherosclerotic lesions in arteries in a subject in need thereof.

According to another aspect of the present invention, there is provided a use of
5 lercanidipine hydrochloride crystalline Form (I) for treating or preventing heart failure in a subject in need thereof.

According to yet another aspect of the present invention, there is provided an antihypertensive composition comprising lercanidipine hydrochloride crystalline Form (I) and lercanidipine hydrochloride crystalline Form (II).

10 The present invention discloses novel crude forms and crystalline forms and novel solvate forms of lercanidipine hydrochloride and processes for making them. Applicants have determined that lercanidipine hydrochloride exhibits polymorphism and crystallizes in different forms depending on the process followed and on the solvents used, especially for crystallization. Additionally, the various novel forms have distinct
15 chemical and physical properties and bioavailability profiles in animals, including man, as discussed herein.

The novel methods for preparation of crude of lercanidipine hydrochloride are suitable for highly reproducible commercial scale production of reproducible solid compositions of lercanidipine hydrochloride. The methods advantageously produce
20 novel crude Forms (A) and (B) of lercanidipine hydrochloride which also exhibit characteristics desirable for industrial applications. Crude Forms (A) and (B), e.g., exhibit higher solubility and faster drying rates compared to other crude forms of lercanidipine hydrochloride that have previously been reported. Crude Forms (A) and

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(B) further allow simplified crystallization procedures to be used for production of novel isolated crystalline forms of lercanidipine hydrochloride.

The novel isolated crystalline forms of lercanidipine hydrochloride of the present invention can be obtained from lercanidipine hydrochloride crude Forms (A) and (B) and are termed lercanidipine hydrochloride crystalline Form (I) and Form (II). Either of isolated Form (I) or isolated Form (II) may be reproducibly obtained from the (A) and (B) intermediates by varying the crystallization conditions as described below. Forms (I) and (II) may also be obtained using other starting materials. Both of Forms (I) and (II) may be obtained using, for example, crude lercanidipine Form (C) as starting material, as described herein. Form (II) may also be obtained using Form (I) as starting material, as described herein.

Both lercanidipine hydrochloride crystalline Forms (I) and (II) exhibit good stability. Form (I) is characterized by a paler yellow color, smaller crystal size, higher solubility in aqueous media (all compared to Form (II)), and a melting point (DSC peak) within the range of about 197EC to about 201EC, more specifically, about 198.7EC, and the X-ray diffraction pattern set forth, supra.

Form (II) is characterized by a more pronounced yellow color, larger crystal size, slightly lower solubility in aqueous media (all compared to Form (I)), and a melting point (DSC peak) within the range of about 207-211EC, more specifically about 209.3EC.

Both Form (I) and Form (II) are stable. Form II exhibited higher bioavailability in the dog, and was also non equivalent to form I in man, showing a higher plasma concentration (AUC_{0-t}) and a delayed time of maximum concentration (t_{max}), compared to Form (I).

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Methods known in the art for producing crystalline lercanidipine hydrochloride were inconsistent in producing lercanidipine hydrochloride with predictable physical and chemical characteristics. Hence, prior art methods had the undesirable property of producing lercanidipine hydrochloride that varied, e.g., in physico-chemical properties, from batch to batch, even among batches produced by the same process and under the same conditions. The present inventors have discovered that the source of inconsistency exhibited by the prior art methods of producing lercanidipine hydrochloride is the presence of varying and unpredictable amounts of crystalline lercanidipine hydrochloride Form (II). In contrast to prior art methods of producing lercanidipine hydrochloride, the invention provides the novel crystalline Forms (I) and (II) that represent crystalline forms of lercanidipine hydrochloride of a purity and uniformity that has not been obtained with previously achieved solid forms of lercanidipine hydrochloride.

The purity and uniformity of Forms (I) and (II) allow for increased ease in production of lercanidipine dosage forms, due to, e.g., more precisely defined physico-chemical characteristics, such as, for example, increased uniformity of particle size following micronization and more reproducible solubility. Forms (I) and (II) also provide dosage forms with more precisely defined pharmacological characteristics, e.g., bioavailability, compared to previously achieved dosage forms that varied from batch-to-batch in their physico-chemical characteristics.

In a human study in man, where the plasma levels of lercanidipine were assessed after administration of a single dose of either lercanidipine hydrochloride Form (I) or (II), Form (I) had shorter time in obtaining the maximum concentration in plasma, relative to Form (II). Hence, Form (I) is more suited for immediate release formulations and dosage forms. From the same study, Form (II) showed a higher bioavailability,

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relative to Form (I), and is thus suited for use in controlled release formulations and dosage forms. Accordingly, the availability of pure Forms (I) and (II) provides for the ability to blend the two polymorphs into dosage forms with novel controlled characteristics, e.g., a dosage form with both a rapid onset and sustained biological
5 action.

The novel methods for preparation of solvates of lercanidipine hydrochloride described herein are suitable for highly reproducible commercial scale production of reproducible solid compositions of lercanidipine hydrochloride. The methods advantageously produce novel solvates and crystalline forms starting with crude Forms
10 (A) or (B) of lercanidipine hydrochloride or crystalline Forms (I) and (II) that are disclosed in Italian patent application no. MI 2001A 001726, filed August 6, 2001, and which exhibit characteristics desirable for industrial applications. Methods of preparing crude Forms (A) and (B) are described herein, *infra*. Crude Forms (A) and (B), e.g., exhibit higher solubility and faster drying rates compared to other crude forms of
15 lercanidipine hydrochloride that have previously been reported. Hence, it is desirable to produce crystalline forms of lercanidipine hydrochloride using crude Form (A) or (B) as starting material. The solvates and crystalline forms of the present invention may also be produced using other forms of lercanidine, such as, for example and without limitation, amorphous lercanidipine and lercanidipine crude Form (C). As used herein, the term
20 “crude form” refers to precipitated solid forms comprising crystals of a compound that have not been washed and/or recrystallized to remove impurities (including but not limited to solvent) that may be present and which lack, e.g., melting point and x-ray spectra characteristic of crystalline forms. In the present specification, the crude forms are referred to as Forms (A) and (B) of lercanidipine hydrochloride.

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As used herein, the term “crystalline form” refers to crystals of a compound that have been crystallized and treated to remove impurities, e.g., a form obtained after evaporation of solvent from a solvate, or having melting point and x-ray spectra characteristic of crystalline forms. Crystalline Forms (I) and (II) of lercanidipine hydrochloride are disclosed herein and in Italian patent application no. MI 2001A 001726, filed August 6, 2001. These crystalline forms have an HPLC purity $\geq$ 99.5 % and residual solvents content of < 3000 ppm. Lercanidipine hydrochloride crystalline Forms (III) and (IV) are described by their X-ray structure, Raman spectra and melting points, which are discussed below. Alternatively, these crystalline forms can be described by a process that yields them, e.g., removal of solvent from a solvate under specified conditions. These crystalline forms have an HPLC purity of > 99 % and residual solvents content of ≤ 3000 ppm. These additional lercanidipine hydrochloride crystalline forms, i.e., lercanidipine hydrochloride crystalline Forms (III) and (IV) are described in Italian patent application no. MI 2001A 001727, filed August 6, 2001, and the attached Appendix I, application of Leonardi et al., for " NOVEL SOLVATE AND CRYSTALLINE FORMS OF LERCANIDIPINE HYDROCHLORIDE," filed August 6, 2002.

As used herein, the term “polymorphism” refers to a property of a compound to crystallize 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.

As used herein, a “subject in need of treatment” is a mammalian (e.g., human) subject suffering from or at risk of developing the particular condition to be treated, e.g.,

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essential hypertension, secondary hypertension, isolated systolic hypertension , coronary heart disease (e.g., chronic stable angina, myocardial infarction), congestive heart failure.

A subject in need of treatment for arterial hypertension may be identified using methods well known in the art such as, for example, by direct measurement of blood pressure
5 using, for example, a manual sphygmomanometer, automatic/electronic devices or ambulatory blood pressure monitoring.

As used herein, a “therapeutically effective amount” of an agent is an amount sufficient to ameliorate at least one symptom associated with a pathological, abnormal or otherwise undesirable condition, an amount sufficient to prevent or lessen the probability
10 that such a condition will occur or re-occur, or an amount sufficient to delay worsening of such a condition. An amount sufficient to lower blood pressure to values lower than 140/90 is recommended. Recent World Health Organization guidelines recommended a diastolic blood pressure lower than 85 mm Hg and a systolic blood pressure lower than 130 mm Hg in younger patients and in diabetic patients. Treatment of other pathologies,
15 such as heart failure or arteriosclerosis is also specifically contemplated as per, e.g., U.S. Patent No. 5,696,139 and 5,767,136.

The present invention contemplates any method that may be used to produce the novel crude forms of lercanidipine hydrochloride described herein. These forms have different physico-chemical properties, e.g., melting points (which can be determined by
20 DSC analysis), than the crude form of lercanidipine hydrochloride produced by other known methods, e.g., by the method described in U.S. Patent No. 5,912,351; termed Form (C). Form (A) has a melting point of about 150EC to about 152EC (DSC peak), Form (B) has a melting point of about 131EC to about 135EC (DSC peak), and Form (C) has a melting point of about 186EC to about 192EC (DSC peak). Additionally,

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thermogravimetric studies show that Form (A) comprises 3 - 4 % residual ethyl acetate and Form (B) comprises 0.3-0.7 % residual ethyl acetate, by weight. Comparatively, the residual solvent present in Form (C) has been determined to be 0-0.1%.

Aspects of the invention are directed to processes for the preparation of
5 lercanidipine hydrochloride, each resulting in a different crude form of the product. The first two steps in producing either crude form are identical and are:

(a) reacting 2, 6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid (prepared as described in German patent DE 2847
237) with thionyl chloride or oxalyl chloride in a mixture of an aprotic dipolar solvent
10 and of an aprotic polar solvent to yield a chloride compound, and

(b) in-situ reaction of the chloride obtained from the above step with 2, N-dimethyl-N-(3,3-diphenylpropyl)-1-amino-2-propyl alcohol, at a temperature preferably between -5 and +5°C, in a mixture of an aprotic dipolar solvent and of an aprotic polar solvent.

15 In a preferred embodiment, the mixture of an aprotic dipolar solvent and of an aprotic polar solvent is ethyl acetate and dimethylformamide used at a ratio of 4:1.

After the in-situ reaction, the lercanidipine hydrochloride is isolated and recovered from the mixture. The method of isolation used determines the crude form of lercanidipine hydrochloride obtained. Following the protocol below (a protocol) yields
20 Form (A):

- i) washing the mixture of step (b), preferably with water,
- ii) removing water from the reaction mixture of step i), preferably by azeotropic distillation under vacuum at 200-300 mmHg at a temperature below about 60°C (preferably at 40-50°C);

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- iii) concentrating the mixture of step ii) preferably to about 1/3 of the initial volume at the same temperature and pressure as in step (ii), adding fresh solvent (e.g., ethyl acetate) preferably to obtain the initial volume, thus obtaining a suspension with a water content, as determined according to Karl Fischer (U.S. Pharmacopoeia 25, Method 921) preferably between 0.10 and 0.15%;
- 5 iv) cooling the suspension of step iii) preferably to 0-5°C;
- v) filtering the solid of step iv);
- vi) re-suspending the solid of step v) preferably in ethyl acetate and stirring preferably at 60-65°C for about 1 hour; and
- 10 vii) cooling to 5-10°C, filtering and drying the obtained solid (e.g., in an oven at about 70°C).

The second process (β protocol; used to prepare Form (B)) is performed using the following steps:

- i') washing the mixture of step (b) preferably with water,
- 15 ii') removing the water from step i') preferably by azeotropically refluxing the product of step i') with a Dean Stark apparatus until a water content of about 2%, measured according to Karl Fischer, is obtained;
- iii') concentrating the mixture of step ii') to preferably $\frac{3}{4}$ of the initial volume and adding fresh solvent (ethyl acetate) to the mixture preferably until (1) the initial
- 20 volume is achieved and (2) a water content, measured according to Karl Fischer, between 0.9 and 1.1% is obtained;
- iv') cooling the solution of step iii') preferably to 0-5°C to obtain a solid;
- v') filtering the solid of step iv');

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vi') re-suspending the solid of step v') preferably in ethyl acetate and stirring at preferably 60-65°C for about 1 hour; and

vii') cooling the suspension of step vi') preferably to 5-10°C, filtering and drying the solid obtained, preferably in an oven at about 70°C.

5 The temperature of step vii') should be carefully controlled at 5-10°C to maximize yield.

These novel crude forms of lercanidipine hydrochloride present the advantage of higher solubility and faster drying rate compared to Form (C) and make a simplified further crystallization process possible (which can advantageously be used to prepare
10 Form (I) or Form (II)). Compared to the crude form produced by the method of U.S. Patent No. 5,912,351, these forms permit use of less solvent to recrystallize the compound. This also increases yield by reducing loss of compound. Additionally, the methods used to produce these crude forms are more adaptable to use in a large scale setting and commercial setting.

15 It has been surprisingly found that each of crude lercanidipine hydrochloride Form (A) and Form (B), when undergoing different purification treatments, result in two novel and different crystalline forms of lercanidipine hydrochloride. Studies indicate that these novel crystalline forms have different physical and chemical properties. DSC analysis of crystalline Form (I) indicates that it has a melting peak of about 197EC to
20 about 201EC, specifically about 198.7EC. DSC analysis of crystalline Form (II) indicates that it has a melting peak of about 207EC to about 211EC, specifically about 209.3EC.

One purification process (γ process), that leads to formation of one of the novel crystalline forms (Form (I)) comprises the following steps:

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Process for Making Form (I)

- d) adding isopropanol to crude lercanidipine hydrochloride (Form (A) or Form (B)) and heating under reflux with stirring to produce a solution (if the solution is
5 not clear, it should be filtered hot);
- e) cooling the solution of step d) preferably to a temperature between 30 and 40°C and stirring for a period of time preferably between 12 and 48 hours to produce a solid; and
- f) filtering the solid obtained from step e), washing the solid with
10 isopropanol, re-filtering the solid, and drying the solid (*e.g.*, in an oven) at preferably 70°C for a period of time preferably between 12-48 hours.

Crude Form (C) may be also be used as starting material in step d). In such case, however, there is the risk of decreased yield of product because the solution should be filtered hot, resulting in the increased loss of lercanidipine hydrochloride in step d). In
15 step e), crystallization is considered complete when the content of the solution is #2% lercanidipine HCl. Other alcohols may also be used as the solvent in step d). An alternatively preferred solvent is a C₁-C₅ alcohol containing a maximum of 5% water, *e.g.*, anhydrous ethanol. Crystalline Form (I) may be added in step (e) as seeds to further promote crystal formation.

20 **Alternative Process for Making Form (I)**

The present application also contemplates an alternative method of producing lercanidipine hydrochloride having crystalline Form (I) which comprises the steps of:

- d') adding ethanol to crude lercanidipine hydrochloride, preferably at a weight/volume ratio of lercanidipine hydrochloride solvent of 1:4 to 1:6, most preferably

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1:4, refluxing under stirring in order to obtain a solution (if the solution is not clear it should preferably be filtered hot), cooling under stirring, preferably to 20°C, and adding crystalline seeds of Form (I);

e') cooling the seeded mixture of step d'), preferably to a temperature
5 between 10 and 15°C, and stirring at this temperature for a period of time preferably between 24 and 96 hours to form a solid; and

f') filtering and drying the solid of step e'), it preferably in an oven at preferably 70°C to obtain lercanidipine hydrochloride Form (I).

In step e'), crystallization is considered complete when the content of the solution
10 is # 2% lercanidipine hydrochloride. Crystalline seeds of Form (I) may also be added to steps e') to further promote crystal formation .

Process for Making Form (II)

The second purification process (δ process), which yields crystalline Form (II), comprises the steps of:

15 d'') adding acetonitrile to crude lercanidipine hydrochloride (Form (A) or Form (B)) and heating the mixture under reflux and stirring,

e'') cooling of the mixture of step d'') to room temperature and stirring preferably for 24 hours to form a solid,

f'') filtering the solid obtained from step e'') and drying it preferably in an
20 oven.

In step e''), crystallization is considered complete when the content of the solution is # 2% lercanidipine HCl.

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The present application also contemplates two additional methods for producing Form (II).

First Alternative Process for Making Form (II)

The first alternative method comprises the steps of:

- 5 d''') adding isopropanol or ethanol, preferably ethanol, with a water content preferably between 5 to 10% by weight to lercanidipine hydrochloride, refluxing with stirring to produce a solution;
- e''') cooling the mixture to a temperature preferably between 20 and 40°C and stirring for a period preferably between 24 and 96 hours to form a solid;
- 10 f''') filtering the solid and drying (e.g., in an oven) at preferably 70°C for 12-18 hours to produce lercanidipine hydrochloride Form (II).

In step e'''), crystallization is considered complete when the content of the solution is # 2% lercanidipine HCl.

Second Alternative Method for Making Form II

- 15 The second alternative method of obtaining the Form (II) polymorph comprises the steps of:
- d''') dissolving crude lercanidipine hydrochloride or its crystalline Form (I) in a protic polar or an aprotic dipolar solvents preferably containing up to 50% by weight of water at a temperature preferably between 20 and 70°C to produce a solution;
- 20 e''') stirring the solution of step d''') at a temperature preferably between 20 and 25°C to produce a solid;
- f''') filtering the solid of step e''') and drying (e.g., in an oven) at preferably 70°C for preferably 12-18 hours.

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The second alternative method may optionally comprise the step of adding up to 60% water to the solution of step d''') prior to step e'''). The second alternative method may further comprise irradiating with ultrasound and/or adding preferably authentic crystalline seeds of Form (II) to step e'''). In step e'''), crystallization is considered

5 complete when the content of the solution is #2% lercanidipine HCl. In a preferred embodiment, the protic polar solvent is an alcohol solvent such as, but not limited to, methanol, ethanol, n-propanol, isopropanol. In another preferred embodiment, the aprotic dipolar solvent is N-methylpyrrolidone.

The preferred process for preparing Form (I) is the γ process and the preferred

10 process for preparing Form (II) is the δ process. Applicants have determined that Form (I) can be quantitatively obtained by use of C₁-C₅ anhydrous alcohol (preferably anhydrous ethanol or isopropanol) or C₁-C₅ alcohol containing up to 5% water under controlled conditions d' -f). In fact, the foregoing processes, especially the γ and δ processes can be used to produce the desired polymorph reproducibly and consistently.

15 In addition to differences in melting point, the two crystalline forms exhibit differences in x-ray structure, solubility, and bioavailability. Solubility studies show that Form (I) is more soluble than Form (II) in water, ethanol, and mixtures thereof (See Tables 2 & 3). Bioavailability studies in dogs and humans indicate that Form (II) is more bioavailable than Form (I). The study in humans also indicates, however, that

20 Form (I) has a shorter time to maximum concentration attainable and is thus suitable for use in immediate release formulations and dosage forms. Finally, x-ray diffraction studies show that these two forms have different diffraction patterns (see Figures 11 and 12 and Example 20). Form I has a smaller crystal and hence particle size before

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micronization and so is easier and faster to process than Form II, which presents with larger crystals.

The present application further discloses pharmaceutical formulations and unit dosage forms that comprise one of the isolated polymorphs of the present invention or a
5 mixture thereof of predetermined polymorph content.

The present invention is also directed to a method of treating a subject with hypertension (e.g., essential hypertension, secondary hypertension or isolated systolic hypertension), coronary heart disease (e.g., chronic stable angina, myocardial infarction) or congestive heart failure the method comprising administering a therapeutically
10 effective amount of isolated lercanidipine hydrochloride crystalline Form (I), lercanidipine hydrochloride crystalline Form (II), or combinations thereof of predetermined polymorph content (optionally with other form of lercanidipine, such as amorphous form) to a subject in need of such treatment.

The invention also contemplates a method of treating and preventing
15 atherosclerotic lesions in arteries of a subject, the method comprising administering a therapeutically effective amount of isolated lercanidipine hydrochloride crystalline Form (I), isolated lercanidipine hydrochloride crystalline Form (II), or combinations thereof to a subject in need of such treatment.

Subjects suffering from and in need of treatment of hypertension and the other
20 conditions mentioned above can be treated by the administering a therapeutically effective amount of isolated lercanidipine hydrochloride crystalline Form (III), lercanidipine hydrochloride crystalline Form (IV), or combinations thereof, of predetermined polymorph content (optionally with one or more other form of lercanidipine, such as, for example, lercanidipine hydrochloride crystalline Form (I),

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lercanidipine hydrochloride crystalline Form (II) or amorphous form) formulated according to, for example and without limitation, the compositions and dosage forms described herein.

The invention also contemplates a method of treating and preventing atherosclerotic lesions in arteries of a subject, the method comprising administering a therapeutically effective amount of isolated lercanidipine hydrochloride crystalline Form (III), isolated lercanidipine hydrochloride crystalline Form (IV), or combinations thereof to a subject in need of such treatment (optionally with other form of lercanidipine, such as, for example, lercanidipine hydrochloride crystalline Form (I), lercanidipine hydrochloride crystalline Form (II) or amorphous form).

Pharmaceutical Compositions

The present invention contemplates novel solvates of lercanidipine hydrochloride. The solvates of the present invention include, but are not limited to, lercanidipine in combination with methylene chloride, methyl ethyl ketone, acetone, anisole, ethyl acetate, tetrahydrofuran, terbutyl methyl ether, isopropanol, 2-butanol, or heptane. These solvates are advantageous because they can be obtained under defined conditions.

The present application contemplates any method that produces the solvates of the present invention. These solvates are defined by specific X-ray diffraction patterns (see **Figures 8-16 and 38**), Raman spectra (see **Figures 18-26 and 39**), and thermogravimetric results (see **Figures 27-35 and 37**). Specific methods of producing the solvates of the invention are disclosed herein.

A lercanidipine hydrochloride-methylene chloride solvate can be prepared with a method comprising the steps of:

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- (i) suspending crystalline Form (I) of lercanidipine hydrochloride in methylene chloride to produce a mixture;
- (ii) placing the mixture of step (i) in a closed vessel and stirring under mild conditions, e.g., at a temperature between about 20 to 50°C to produce a solid; and
- 5 (iii) isolating the solid produced in step (ii), e.g., by filtration.

In step (ii), stirring is typically performed for eight days. Similar results may be obtained, however, with longer or shorter times. The methods can also be practiced using lercanidipine crude form (C) as starting materia.

A lercanidipine hydrochloride-methyl ethyl ketone solvate can be prepared by:

- 10 (i') dissolving lercanidipine hydrochloride crystalline Form (I) in methyl ethyl ketone to produce a solution;
- (ii') cooling the solution of step (i') to preferably 20-25 °C while stirring and keeping the solution at the temperature for preferably at least two days to produce a solid; and
- 15 (iii') filtering the solid and drying.

Step (i') is preferably performed, for example, at 80°C. Also preferred is where the lercanidipine hydrochloride-methyl ethyl ketone solution of step (i') comprises 0 to 5% (v/v) water.

- Independent preferences for step (ii') are cooling the solution to room temperature
- 20 and stirring for at least two days. Further preferred are simultaneous preferences where the solution in step (ii') is cooled to room temperature and stirred at room temperature for at least two days.

The preferred conditions for drying in step (iii') are in an oven at 60°C for 24 hours under vacuum.

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The other solvates of the present invention can be obtained by suspending a lercanidipine hydrochloride-methylene chloride solvate prepared, for example and without limitation by the method in steps (i) – (iii), with a solvent selected from the group consisting of acetone, anisole, ethyl acetate, tetrahydrofuran, terbutyl methyl ether, isopropanol, 2-butanol, and heptane, at a temperature between 20 and 50°C for 114 to 420 hours to produce a solid. The solid produced by this method is a novel solvate comprising lercanidipine hydrochloride with the solvent used in the reaction. Therefore, if heptane is used as the solvent then the final solvate would be lercanidipine hydrochloride-heptane.

It has been determined that when anisole is used as the solvate, that two different forms of the solvate may be produced ((a) and (b) forms). The differences between these forms are clear from their x-ray spectra. When using the method disclosed above lercanidipine hydrochloride-anisole (b) form is produced.

As an alternative method, the solvates can be prepared by suspending lercanidipine hydrochloride crystalline Form (III), which is described in further detail below, in a solvent selected from the group consisting of anisole, ethyl acetate, tetrahydrofuran, terbutyl methyl ether, or acetone to produce a solution. The solution that is prepared is kept under mild stirring in a closed vessel at a temperature between 20 and 50°C for 114 to 420 hours to produce a solid. The solid that is formed is then filtered. When anisole is used as the solvent with this method, lercanidipine hydrochloride-anisole (a) form solvate is produced. In a preferred embodiment, the temperature is 20-50°C and the solution is stirred from 114 to 420 hours.

In another alternative embodiment, the solvates of the present invention can be prepared by suspending crude lercanidipine hydrochloride Form (A) or (B) in a solvent

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selected from the group consisting of anisole, ethyl acetate, tetrahydrofuran, terbutyl methyl ether, acetone, or methylene chloride to produce a suspension. The suspension is maintained under mild stirring in a closed vessel at a temperature between 20 and 50°C for 114 to 420 hours. The solid that is produced is then filtered to give the final product.

- 5 When anisole is used as the solvent in this method, lercandipine hydrochloride-anisole (a) form solvate is produced. In a preferred embodiment, the temperature is 20-50°C and the solution is stirred for 114 to 420 hours.

The preparation of the these solvates, both starting from the solvate of lercanidipine hydrochloride or from the crude (A) or (B) or (C) forms, may be preferably
10 carried out at room temperature. Alternatively, the method may include a series of thermal cycles performed after the solvent is added to lercanidipine. The length and number of the cooling and heating steps, as well as the temperatures, may be determined by one of ordinary skill in the art. In a preferred embodiment, the steps are about 3 hours each. In another embodiment, the heating step is performed at 35°C and the cooling step
15 is performed at 25°C. In a most preferred embodiment, the thermal cycle is composed of a cooling step at 25°C, heating step at 35°C, and a cooling step at 25°C (written as 25°C-35°C-25°C), where each step is about 3 hours. The number of cycles can preferably range from 10 to 20. Preferably, after completion of the final cycle the sample is stirred at a temperature of 25°C for a period of time of 24 –240 h.

20

Crystalline Forms III and IV

Under specific conditions, removal of the solvents from the solvates disclosed above produces novel crystalline forms. These forms have been termed lercanidipine hydrochloride crystalline Form (III) and (IV).

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The present application contemplates any and all methods that may be used to prepare the forms described herein. In the present application, preferred methods of preparing these forms are described.

In one method, evaporation of solvent from a solvate, under a nitrogen stream or
5 under vacuum, produces lercanidipine hydrochloride crystalline Form (III). A preferred set of conditions for evaporation is, without limitation, a vacuum of 1-0.01 mbarr for 20-30 hours at a temperature of 50-90°C. Preferably, the solvent is selected from the group consisting of methylene chloride, tetrahydrofuran, heptane, anisole, ethyl acetate, isopropanol and 2-butanol. In one embodiment, the solvate is selected from any of the
10 solvates described herein, except lercanidipine hydrochloride-anisole (a) form that was described previously.

To prepare lercanidipine hydrochloride crystalline form (IV), acetone is removed from a lercanidipine hydrochloride-acetone solvate, under a nitrogen stream or under vacuum. A preferred set of conditions for acetone removal is, without limitation, a
15 vacuum of 1-0.01 mbar for 20-30 hours at a temperature of 50-90°C.

The compounds and polymorphs of the present invention may be formulated into a pharmaceutical composition. The pharmaceutical composition may also include optional additives, such as a pharmaceutically acceptable carrier or diluent, a flavorant, a sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a
20 colorant, a disintegrant, an excipient, a film forming agent, a lubricant, a plasticizer, an edible oil or any combination of two or more of the foregoing.

The crystalline forms can undergo micronization, using any method known in the art. The average size of particle produced by this method are preferably D(50%)2-8 µm, D(90%)<15 µm.

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Suitable pharmaceutically acceptable carriers or diluents include, but are not limited to, 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.

- 5 Suitable binders include, but are not limited to, 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.

- Suitable disintegrants include, but are not limited to, starch, e.g., corn starch,
10 methyl cellulose, agar, bentonite, xanthan gum, sodium starch glycolate, crosspovidone and the like.

 Suitable lubricants include, but are not limited to, sodium oleate, sodium stearate, sodium stearyl fumarate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

- 15 A suitable suspending agent is, but is not limited to, 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.

- Suitable dispersing and suspending agents include, but are not limited to,
20 synthetic and natural gums, such as vegetable gum, tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone and gelatin.

 Suitable film forming agents include, but are not limited to, hydroxypropylmethylcellulose, ethylcellulose and polymethacrylates.

Suitable plasticizers include, but are not limited to, polyethylene glycols of different molecular weights (e.g., 200-8000 Da) and propylene glycol.

Suitable colorants include, but are not limited to, ferric oxide(s), titanium dioxide and natural and synthetic lakes.

5 Suitable edible oils include, but are not limited to, cottonseed oil, sesame oil,
coconut oil and peanut oil.

Examples of additional additives include, but are not limited to, sorbitol, talc, stearic acid, dicalcium phosphate and polydextrose.

10 *Unit Dosage Forms*

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. Parenteral preparations (e.g., injectable preparations and preparations for powder jet systems) also are preferred.

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Solid unit dosage forms may be prepared by mixing an active agent 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 agent is dispersed evenly throughout the composition. In this case, the compositions can be formed as dry or moist granules.

Dosage forms with predetermined amounts of lercanidipine hydrochloride may be formulated starting with compositions with known quantities of lercanidipine hydrochloride using methods well known in the art. In a preferred embodiment a dosage form is obtained by mixing compositions comprising known quantities of crystalline lercanidipine hydrochloride, e.g., Form (I) or (II), optionally including non-crystalline lercanidipine hydrochloride. Further preferred is where a dosage form with predetermined amounts of crystalline lercanidipine hydrochloride is formulated by mixing compositions comprising essentially pure crystalline lercanidipine hydrochloride are mixed to form dosage forms comprising a predetermined ratio of crystalline, e.g., Forms (I) and (II).

Dosage forms can be formulated as, for example, "immediate release" dosage forms. "Immediate release" dosage forms are typically formulated as tablets that release at least 70%-90% of the active ingredient within 30-60 min when tested in a drug dissolution test, e.g., U.S. Pharmacopeia standard <711>. In a preferred embodiment, immediate dosage forms release at 75% of active ingredient in 45 min.

Dosage forms can also be formulated as, for example, "controlled release" dosage forms. "Controlled," "sustained," "extended" or "time release" dosage forms are equivalent terms that describe the type of active agent delivery that occurs when the

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active agent is released from a delivery vehicle at an ascertainable and manipulatable rate over a period of time, which is generally on the order of minutes, hours or days, typically ranging from about sixty minutes to about 3 days, rather than being dispersed immediately upon entry into the digestive tract or upon contact with gastric fluid. A controlled release rate can vary as a function of a multiplicity of factors. Factors influencing the rate of delivery in controlled release include the particle size, composition, porosity, charge structure, and degree of hydration of the delivery vehicle and the active ingredient(s), the acidity of the environment (either internal or external to the delivery vehicle), and the solubility of the active agent in the physiological environment, i.e., the particular location along the digestive tract. Typical parameters for dissolution test of controlled release forms are found in U.S. Pharmacopeia standard <724>.

Dosage forms can also be formulated to deliver active agent in multiphasic stages whereby a first fraction of an active ingredient is released at a first rate and at least a second fractions of active ingredient is released at a second rate. In a preferred embodiment, a dosage form can be formulated to deliver active agent in a biphasic manner, comprising a first "immediate release phase", wherein a fraction of active ingredient is delivered at a rate set forth above for immediate release dosage forms, and a second "controlled release phase," wherein the remainder of the active ingredient is released in a controlled release manner, as set forth above for controlled release dosage forms.

Tablets or pills can be coated or otherwise compounded to form a unit dosage form which has delayed and/or prolonged action, such as time release and controlled release unit dosage forms. For example, the tablet or pill can comprise an inner dosage

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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 an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release.

5 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, polydihydro-pyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

For liquid dosage forms, the active substances or their physiologically acceptable
10 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
15 used. A mixture of the various solvents mentioned may further be used in the present invention.

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
20 dosage forms include, but are not limited to, topical gels, lotions, ointments, transmucosal systems and devices, and iontophoretic (electrical diffusion) delivery system. Transdermal dosage forms may be used for timed release and controlled release of the active agents of the present invention.

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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.

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.

The polymorphs 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-eneoxidepolylysine substituted with palmitoyl residues.

The present application further discloses pharmaceutical formulations and unit dosage forms that comprise one of the isolated polymorphs of the present invention or a mixture thereof of predetermined polymorph content. Dosage forms with predetermined amounts of lercanidipine hydrochloride may be formulated starting with compositions with known quantities of lercanidipine hydrochloride using methods well known in the art. In a preferred embodiment a dosage form is obtained by mixing compositions comprising known quantities of crystalline lercanidipine hydrochloride, e.g., Form (III) or (IV), optionally including other forms of crystalline lercanidipine hydrochloride, e.g., Form (I) or (II), or non-crystalline forms or lercanidipine hydrochloride, e.g., amorphous. Further preferred is where a dosage form with predetermined amounts of crystalline

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lercanidipine hydrochloride is formulated by mixing compositions comprising essentially pure crystalline lercanidipine hydrochloride are mixed to form dosage forms comprising a predetermined ratio of crystalline Forms (III) and (IV).

Dosage forms preferably comprise a predetermined amount of any one of

5 crystalline lercanidipine hydrochloride Form (I), (II), (III) or (IV). Also preferred are dosage forms that simultaneously comprise predetermined amounts of at least two crystalline lercanidipine hydrochloride Forms, e.g., Forms (I) and (II), Forms (I) and (III), Forms (I) and (IV), Forms (II) and (III), Forms (II) and (IV), or Forms (III) and (IV). Also preferred are dosage forms that simultaneously comprise predetermined

10 amounts of at least three crystalline lercanidipine hydrochloride Forms, e.g., Forms (I), (II) and (III), Forms (I), (II) and (IV), Forms (I), (III) and (IV), or Forms (II), (III) and (IV). Also preferred are dosage forms that simultaneously comprise predetermined amounts of at least four crystalline lercanidipine hydrochloride Forms, e.g., Forms (I), (II), (III) and (IV). Each of the aforementioned may optionally include other forms of

15 lercanidipine such as, for example and without limitation, indeterminate or amounts of crystalline lercanidipine hydrochloride, e.g., Forms (I), (II), (III) and (IV), that have not been predetermined, or other forms of lercanidipine, e.g., crude or amorphous.

Administration

The pharmaceutical composition or unit dosage forms of the present invention

20 may be administered by a variety of routes such as intravenous, intratracheal, subcutaneous, oral, mucosal parenteral, buccal, sublingual, ophthalmic, pulmonary, transmucosal, transdermal, and intramuscular. Unit dosage forms also can be administered in intranasal form via topical use of suitable intranasal vehicles, or via

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transdermal routes, using those forms of transdermal skin patches known to those of ordinary skill in the art. Oral administration is preferred.

The pharmaceutical composition or unit dosage forms of the present invention may be administered to an animal, preferably a human being, in need of antihypertensive treatment. The pharmaceutical composition or unit dosage form of the present invention may be administered according to a dosage and administration regimen defined by routine testing in light of the guidelines given above in order to obtain optimal antihypertensive activity and a decreased in blood pressure while minimizing toxicity or side-effects for a particular patient. However, such fine turning of the therapeutic regimen is routine in light of the guidelines given herein.

The dosage of the composition containing polymorphs or mixtures of the present invention may vary according to a variety of factors such as underlying disease state, the individual's condition, weight, sex and age and the mode of administration. For oral administration, the pharmaceutical compositions can be provided in the form of scored or unscored solid unit dosage forms.

A pharmaceutical composition comprising (1) lercanidipine hydrochloride, where the lercanidipine hydrochloride is selected from the group consisting of isolated lercanidipine hydrochloride crystalline Form (I), isolated lercanidipine hydrochloride crystalline Form (II), or combinations thereof of predetermined polymorph composition; and (2) at least one component selected from the group consisting of a pharmaceutically acceptable carrier or diluent, a flavorant, a sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a colorant, a disintegrant, an excipient, a diluent, a lubricant, a plasticizer, and an edible oil. In a preferred embodiment, the pharmaceutical composition or dosage form comprises 0.1 to 400 mg lercanidipine hydrochloride.

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Preferably, the composition or dosage form comprises 1 to 200 mg lercanidipine hydrochloride, for all uses disclosed herein. More preferably, the composition or dosage form comprises 5 to 40 mg lercanidipine hydrochloride. Smaller amounts may be selected when a preferred enantiomer having higher activity for a particular therapeutic goal is used.

A pharmaceutical composition comprising (1) lercanidipine hydrochloride, where the lercanidipine hydrochloride is selected from the group consisting of isolated lercanidipine hydrochloride crystalline Form (III), isolated lercanidipine hydrochloride crystalline Form (IV), or combinations thereof of predetermined polymorph composition; and (2) at least one component selected from the group consisting of a pharmaceutically acceptable carrier or diluent, a flavorant, a sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a colorant, a disintegrant, an excipient, a diluent, a lubricant, a plasticizer, and an edible oil. In a preferred embodiment, the pharmaceutical composition or dosage form comprises 0.1 to 400 mg lercanidipine hydrochloride, for all uses disclosed herein. Preferably, the composition or dosage form comprises 1 to 200 mg lercanidipine hydrochloride. More preferably, the composition or dosage form comprises 5 to 40 mg lercanidipine hydrochloride. Smaller amounts may be selected when a preferred enantiomer having a higher activity for a particular therapeutic goal is used.

The pharmaceutical composition or unit dosage form may be administered in a single daily dose, or the total daily dosage may be administered in divided doses. In addition, co-administration or sequential administration of other active agents may be desirable. The polymorphs and mixtures thereof of the invention may be combined with any known drug therapy, preferably for treatment of hypertension. For example,

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bimodal therapy involving in addition a diuretic, a β -receptor blocker, an ACE inhibitor or an angiotensin II receptor antagonist is contemplated by the present invention (see, *e.g.*, U.S. Provisional Application No. 60/344,601, filed October 23, 2001 and Italian Application No. MI 2001 A 002136 filed October 16, 2001).

5 For combination therapy the compounds may initially be provided as separate dosage forms until an optimum dosage combination and administration regimen is achieved. Therefore, the patient may be titrated to the appropriate dosages for his/her particular hypertensive condition. After the appropriate dosage of each of the compounds is determined to achieve a decrease of the blood pressure without untoward
10 side effects, the patient then may be switched to a single dosage form containing the appropriate dosages of each of the active agents, or may continue with a dual dosage form.

 The exact dosage and administration regimen utilizing the combination therapy of the present invention is selected in accordance with a variety of factors including type,
15 species, age, weight, sex and medical condition of the patient; the severity and etiology of the hypertension to be treated; the route of administration; the renal and hepatic function of the patient; the treatment history of the patient; and the responsiveness of the patient. Optimal precision in achieving concentrations of compounds within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the
20 drug's availability to target sites. This involves a consideration of the absorption, distribution, metabolism, excretion of a drug, and responsiveness of the patient to the dosage regimen. However, such fine tuning of the therapeutic regimen is routine in light of the guidelines given herein.

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A pharmaceutical composition for parenteral administration contains not below 0.1%, preferably from about 0.5% to about 30%, by weight of a polymorph or mixture of the present invention, based upon the total weight of the pharmaceutical composition. Individual isolated polymorphs are preferred for parenteral administration.

5 Generally, transdermal dosage forms contain from about 0.01% to about 100% by weight of the active agents, based upon 100% total weight of the dosage.

In a preferred embodiment of the present invention, the composition is administered daily to the patient. In a further preferred embodiment, the pharmaceutical composition or dosage form 0.1 to 400 mg lercanidipine hydrochloride. Preferably, the
10 composition or dosage form comprises 1 to 200 mg lercanidipine hydrochloride. More preferably, the composition or dosage form comprises 5 to 40 mg lercanidipine hydrochloride.

EXAMPLES

15 The following examples of preparation of lercanidipine hydrochloride crude Forms (A) and (B) and crystalline Forms (I) and (II) are now disclosed for illustrative non-limiting purposes, together with the results of DSC analysis and solubility, stability and hygroscopicity tests; the bioavailability tests for the new crystalline forms are also disclosed.

20

EXAMPLE 1 Initial preparation

Thionyl chloride (36 g) diluted in ethyl acetate (25 g) was slowly added to a solution of 2,6-dimethyl-5-methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid (90 g) prepared, e.g., as disclosed in German patent DE 2847 237, in

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dimethylformamide (115 g) and ethyl acetate (396 g), keeping temperature between -1 and +1°C. A solution of 2, N-dimethyl-N-(3,3-diphenylpropyl)-1-amino-2-propanol (84 g) in ethyl acetate (72 g) was slowly added to the mixture thus obtained. The whole was kept under stirring at the same temperature for 3 hours. The mixture was then heated to 20-25°C and kept under stirring for 12 hours. Water (340 ml) was then added, the whole was stirred for 30 min and after settling the aqueous phase was discarded. The organic phase was washed again with water (340 ml).

EXAMPLE 2 Crude lercanidipine hydrochloride Form (A)

The organic phase obtained from Example 1 was then subjected to azeotropic distillation under vacuum at about 250 mmHg, without going above a temperature of 60°C. After removing about 50 ml of water, the solution was concentrated to about 1/3 of the initial volume in the same conditions of temperature and pressure and then brought to its initial volume with fresh ethyl acetate until the K.F. value (Karl Fisher value) was about 0.10-0.15%. The final suspension was cooled to 0-5°C. The solid was filtered, suspended in ethyl acetate (350 g) and stirred at 60-65°C for 1 hour. The whole was cooled to 5-10°C and then filtered. The solid was dried in an oven at 70°C. 133 g of dry raw lercanidipine hydrochloride Form (A) was obtained (75% yield), DSC peak 150-152°C.

20

EXAMPLE 3 Crude lercanidipine hydrochloride Form (B)

The organic phase obtained at the end of Example 1 was heated under reflux (70-75°C) and the water contained in the solution was removed with a Dean Stark apparatus (Spaziani Rolando, Nettuno, Rome, Italy) until a K.F. value of about 2% was obtained.

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The whole was then distilled at atmospheric pressure to reach $\frac{3}{4}$ of initial volume. The solution was brought to its initial volume by adding fresh ethyl acetate. The K.F. value at the end of this operation was 0.9-1.1%. The final solution was cooled to 0-5°C. A solid slowly precipitates which was filtered. The solid thus obtained was suspended in ethyl acetate (350 g) and stirred at 60-65°C for 1 hour. The whole was cooled to 5-10°C, then filtered and dried in an oven at 70°C, thus obtaining 133 g of crude lercanidipine hydrochloride Form (B), DSC peak 131-135°C; 75% yield.

EXAMPLE 3A Crude lercanidipine hydrochloride Form (B)

The organic phase obtained at the end of Example 1 was heated under reflux (70-75°C) and the water contained in the solution was removed with a Dean Stark apparatus until a K.F. value of about 2% was obtained. The whole was then distilled at atmospheric pressure to reach $\frac{3}{4}$ of initial volume. The solution was brought to its initial volume by adding fresh ethyl acetate. The K.F. value at the end of this operation was 0.9-1.1%. The final solution was cooled to 20°C, seeded with 0.1% of crude lercanidipine hydrochloride Form (B) and cooled to 0-5°C. A solid slowly precipitated and was then filtered. The solid thus obtained was suspended in ethyl acetate (350 g) and stirred at 60-65°C for 1 hour. The whole was cooled at 5-10°C, then filtered and dried in an oven at 70°C for 24 hours, thus obtaining 133 g of crude lercanidipine hydrochloride Form (B), DSC peak 131-135°C; 75% yield.

EXAMPLE 4 Preparation of lercanidipine hydrochloride crystalline Form (I)

In separate representative experiments, 100 g of crude lercanidipine hydrochloride Form (A), (B), or (C) was loaded into a reactor, followed by 400 ml of 2-

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propanol. The mixture was heated under strong reflux and under stirring, thus obtaining an almost complete dissolution of the crude substance. The mixture was hot filtered to eliminate a slight opalescence and the clear solution kept under stirring was cooled to 40°C. Temperature was then set at 35°C. The whole was kept for 24 hours under stirring at 35°C, then temperature was set at 30°C, and stirring was continued at said temperature for another 24 hours. The solid was filtered at 30°C and washed with 50 ml of 2-propanol, then dried in an oven at 70°C under vacuum for 24 hours. Weight of dry product in each case was (lercanidipine HCl (I)) 90 g (HPLC purity of the product in Form (I) > 99.5%).

10

EXAMPLE 4A Preparation of lercanidipine hydrochloride crystalline Form (I)

In separate representative experiments, 100 g of crude lercanidipine hydrochloride Form (A), (B), or (C) was loaded into a reactor, followed by 400 ml of 2-propanol. The mixture was heated under strong reflux and under stirring, thus obtaining an almost complete dissolution of the crude substance. The mixture was hot filtered to eliminate a slight opalescence and the clear solution kept under stirring is slowly cooled to 40°C. Precipitation was then triggered with 100 mg of lercanidipine hydrochloride Form (I) and temperature was set at 35°C, keeping the mixture under stirring. The whole was kept for 24 hours under stirring at 35°C, then temperature was set at 30°C, keeping under stirring at said temperature for another 24 hours. The solid was filtered at 30°C and washed with 50 ml of 2-propanol, then dried in an oven at 70°C under vacuum for 24 hours. Weight of dry product (lercanidipine HCl (I)) was 90 g (HPLC purity of the product in Form (I) > 99.5%).

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EXAMPLE 5 Preparation of lercanidipine hydrochloride crystalline Form (I)

In independent preparations, 25 kg of crude lercanidipine hydrochloride, Form (A) or (B), and then 100 mL of 95% ethanol were loaded and brought to strong reflux under stirring. The solution was cooled under stirring at 20°C and then seeded with
5 crystalline Form (I). The whole was then cooled to a temperature between 10 and 15°C, keeping the reaction mixture under stirring for 4 days. The solid thus obtained was filtered and washed with 95% ethanol, the precipitate was filtered and dried in an oven under vacuum at 70°C for 24 hours. 20.2 kg of product was obtained, corresponding to a yield of 81%; HPLC purity in Form (I) > 99.5%. Comparable results are obtained with
10 Form (C) as starting material.

EXAMPLE 6 Preparation of lercanidipine hydrochloride crystalline Form (II)

100 g of crude lercanidipine hydrochloride Form (C) and then 200 ml of acetonitrile was loaded into a reactor. The mixture was heated under strong reflux and
15 under stirring, thus obtaining a complete dissolution. The mixture was brought to 20-30°C under slight stirring and kept at said temperature for 24 hours. The precipitate was filtered and dried in an oven at 70°C for 24 hours. 95 g of dry product was obtained, corresponding to a 95% yield; HPLC purity > 99.5% in lercanidipine hydrochloride Form (II). Comparable results are obtained when lercanidipine hydrochloride Form (A)
20 or (B) is used as starting material.

EXAMPLE 7 Preparation of lercanidipine hydrochloride crystalline Form (II)

In separate representative experiments, 100 g of crude lercanidipine hydrochloride Form (A), (B), or (C) in 200 ml of 95% ethanol was loaded into a reactor,

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the mixture thus obtained was heated under stirring and under strong reflux and then cooled at 25°C always under stirring. The solution was kept at said temperature for 24 hours under stirring. The precipitate thus obtained was then filtered and dried in an oven at 70°C for 24 hours. 90 g of Form (II), HPLC purity > 99.5% was obtained.

5

EXAMPLE 7A Preparation of lercanidipine hydrochloride crystalline Form (II)

25 g of lercanidipine HCl crude substance or Form (C) was dissolved at 60°C in 100 ml of a mixture ethanol-H₂O (8:2). The whole was filtered by gravity to eliminate the possible insoluble portion and diluted with 100 ml of H₂O. The solution thus
10 obtained was stirred at 25°C as such, or it was added with 0.1 g of lercanidipine hydrochloride Form (II) or it was sonicated for 6 seconds at 20 kHz and 100 Watts, always at 25°C. Whatever the choice, after 48 hours under stirring the precipitate thus formed was collected and dried in an oven at 70°C for 24 hours, obtaining a 80-85% yield of Form (II). Comparable results are obtained using crude Forms (A) or (B) or
15 lercanidipine hydrochloride crystalline Form (I) as starting material.

As an alternative, the initial clear solution is diluted with 100 ml of ethanol and seeded with lercanidipine hydrochloride Form (II) (0.1 g). After 48 hours with stirring at 25°C, 80% yield with respect to stoichiometric lercanidipine hydrochloride Form (II) is obtained.

20

EXAMPLE 8 Preparation of lercanidipine hydrochloride crystalline Form (II) in aqueous methanol

In representative independent examples, 40 g of lercanidipine hydrochloride crude Form (C) or crystalline Form (I) was dissolved in 100 ml of methanol at 30°C.

25 The whole was filtered by gravity to eliminate the possible insoluble portion and 25 ml

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of water was added. The solution thus obtained was stirred at 25°C as such, or was mixed with 0.1 g of lercanidipine hydrochloride Form (II), or was sonicated for 6 seconds at 20 kHz and 100 Watts, always at 25°C. Whichever the choice, after 48 hours under stirring the precipitate thus formed was collected and dried, with yields of 80-85% with respect to stoichiometric lercanidipine hydrochloride Form (II). Comparable results are obtained using crude Form (A) or (B).

EXAMPLE 9 Preparation of lercanidipine hydrochloride crystalline Form (II) in aqueous 1-propanol

60 g of lercanidipine HCl crude Form (C) was dissolved at 60°C in 100 ml of 1-propanol-H₂O (8:2). After filtering by gravity the possible insoluble portion the solution was cooled in two hours to 25°C and stirred for 120 hours at said temperature, with or without sonication for 6 seconds at 20 kHz and 100 Watts. The precipitate thus formed was collected, obtaining 90% yield with respect to stoichiometric lercanidipine hydrochloride Form (II) after a drying step. Comparable results are obtained using crude Forms (A) or (B) or lercanidipine hydrochloride crystalline Form (I) as starting material.

EXAMPLE 10 Preparation of lercanidipine hydrochloride crystalline Form (II) in aqueous 2-propanol

30 g of lercanidipine hydrochloride crude Form (C) was dissolved at 60°C in 100 ml of 2-propanol-H₂O (8:2). After filtering by gravity the possible insoluble portion the solution was cooled in two hours to 25°C and stirred for 72 hours at said temperature, with or without sonication for 6 seconds at 20 kHz and 100 Watts. The precipitate thus formed was collected, obtaining 85% yield with respect to stoichiometric lercanidipine hydrochloride Form (II) after a drying step. The same result is obtained by stirring for

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168 hours at 10°C. Comparable results are obtained using crude Forms (A) or (B) or lercanidipine hydrochloride crystalline Form (I) as starting material.

EXAMPLE 11 Preparation of lercanidipine hydrochloride crystalline Form (II) in aqueous N-methylpyrrolidone

A suspension of 50 g of lercanidipine hydrochloride crude Form (C) in 30 ml of N-methylpyrrolidone/water (1:1) was stirred at 20-25°C for 12 days. The solid thus formed was collected by filtration and dried, yielding 40 g of lercanidipine hydrochloride Form (II). Comparable results are obtained using crude Forms (A) or (B) or lercanidipine hydrochloride crystalline Form (I) as starting material.

EXAMPLE 12 DSC analysis of lercanidipine hydrochloride crystalline Forms (I) and (II)

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).

DSC of Form (I): 3.8 mg of Form (I) was placed in a golden pan of the apparatus Perkin Elmer DSC7. The heating speed during the test was 10°C/min.

DSC Form (II): 4.6 mg of Form (II) was placed in a golden pan of the apparatus Perkin Elmer DSC7. The heating speed during the test was 10°C/min.

The data are shown in Figures 1 and 2 and the characteristic points of the figures are briefly summarized in the following Table 1.

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Table 1.

	<u>Compound</u>	<u>Melting T (Tpeak) [°C]</u>	<u>Onset T [°C]</u>
	Form (I)	198.7	179.8
5	Form (II)	209.3	169.0

Immediately after melting of Form (I) or (II) an exothermic event due to salt decomposition can be observed.

10 **EXAMPLE 13 Thermogravimetry**

A gravimetric analysis associated with an IR analysis was carried out on both crystalline Forms (I) and (II), and also on crude lercanidipine hydrochloride Form (A) and on crude lercanidipine hydrochloride Form (B), using a Netsch Thermomicrobalance 209 in combination with a spectrometer FTIR Bruker Vector 22.

15 The tests were carried out according to the following working conditions: 2-5 mg of sample was heated in a steel crucible in nitrogen atmosphere, with a heating speed of 10°C/min. The results obtained with crystalline Forms (I) and (II) are shown in Figure 3, from which it can be inferred that in both crystalline forms no weight loss can be observed up to their melting point (*i.e.*, until about 190-200°C).

20 During degradation, which takes places as indicated above after melting, a CO₂ loss can be observed.

The results obtained with crude lercanidipine hydrochloride Form (A) are shown in Figure 19, where a weight loss of 3.4% can be observed in the temperature range 25-153°C. The volatile compound has been identified by its corresponding IR spectrum and

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is ethyl acetate. During degradation ($T > 170^{\circ}\text{C}$) a small amount of ethyl acetate in gas phase could be observed.

The results obtained with crude lercanidipine hydrochloride Form (B) are shown in Figure 20, where a weight loss of 0.5% in temperature range 25-153°C can be
5 observed. The volatile compound identified with its corresponding IR spectrum is ethyl acetate (0.4%) and water (0.1%). During degradation ($T > 170^{\circ}\text{C}$) a small amount of ethyl acetate in gas phase can be observed.

EXAMPLE 14 Hygroscopicity of crystalline Forms (I) and (II)

10 The hygroscopicity of both crystalline Forms (I) and (II) was measured with DVS analysis by means of a water absorption analyzer (SURFACE MEASUREMENT SYSTEM, Marion, Buckinghamshire, UK) according to the following working conditions:

10-15 mg of Form (I) and (II) respectively were placed in a quartz sample-holder,
15 placed in its turn on a microbalance, and the sample underwent humidity cycles between 0 and 95%, starting from 50% of relative humidity (25°C, relative humidity (RH): 50-95-0-95-0-50% at RH/h:5%).

The results of the tests are shown in the diagrams of Figures 13 and 14.

20 14-1 Results obtained with crystalline Form (I)

The exposure of Form (I) to humidity in the DVS analyzer results in a mass change of +0.15% at 95% RH, and of -0.3% at 0% RH, with almost no hysteresis during mass increase and loss. These slight variations are probably due to a reversible surface absorption of water.

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14-2 Results obtained with crystalline Form (II)

The exposure of Form (II) to humidity in DVS causes a negligible mass variation (< 0.05%) in the whole RH range tested.

5 EXAMPLE 15 Solubility of crystalline Forms (I) and (II)*15.1 Solubility in water and in ethanol at room temperature*

The solubility at 23°C of both crystalline Forms (I) and (II) was evaluated by UV-Visible spectroscopy in bi-distilled water (at the pH value spontaneously reached by the system) and in absolute ethanol. The molar absorptivity had been previously determined in acetonitrile. The same molar absorptivity was considered for the determination in water and in ethanol. Solubility in water certainly depends on pH. The residual solid obtained by filtration of the suspension was immediately analyzed with Raman spectroscopy. The results are shown in the following Tables 2 and 3.

15 TABLE 2. Solubility in water (about 40 mg/ml as initial condition).

<u>Starting material</u>	<u>Time [min]</u>	<u>Solubility [mg/ml]</u>	<u>Residual material</u>
Form (I)	5/25/45/990	0.4/0.5/0.5/0.5	Form (I)
Form (II)	5/25/45/990	0.2/0.2/0.3/0.3	Form (II)

20 TABLE 3. Solubility in ethanol (100 mg/ml as initial condition)

<u>Starting material</u>	<u>Time [min]</u>	<u>Solubility [mg/ml]</u>	<u>Residual material</u>
Form (I)	15/45/120	28/27/27	Form (I)
Form (II)	15/45/120	11/12/12	Form (II)

25 Form (II) is less soluble than Form (I) in both solvents.

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15.2 Solubility in mixtures of water-ethanol at 25°C and at 40°C, with increasing water concentrations

Figures 4 and 5 show solubility in water-ethanol at 25°C and at 40°C of Form (I) and of Form (II). The maximum solubility is reached for both forms, at both
5 temperatures, when water concentration is of 20%. Also in this case the solubility of crystalline Form (I) is higher than that of crystalline Form (II).

EXAMPLE 16 Solid phase ^{13}C -NMR studies

The high resolution ^{13}C -NMR solid phase spectra were carried out with the
10 Bruker, ASX300 Instrument equipped with a 7 mm Rotor accessory, using several combined techniques:

Magic angle spinning (MAS). About 300 mg of the sample was placed in the rotor spinning at 4.3 kHz around an axis oriented at the magic angle ($54^\circ 70'$) to the magnetic field to overcome the dipolar broadening caused by CSA (Chemical Shift
15 Anisotropy). The experiments were conducted at room temperature.

Dipolar Coupling. Since much of line broadening in ^{13}C spectra of organic solids is due to coupling to protons, it was removed by heteronuclear decoupling (decoupling power level was almost 1 Kilowatt).

Cross polarization (CP). Cross polarization allowed carbon magnetization from
20 larger proton magnetization via the dipolar coupling to increase signal intensity.

Total suppression of sidebands (TOSS). TOSS was performed using spin-echoes synchronized with the rotation of the sample to cause phase alteration of the spinning sidebands, resulting in cancellation when successive spectra were added together.

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Crystalline Forms (I) and (II) show different ^{13}C -NMR spectra in solid phase.

The signals (chemical shift) and attribution of the corresponding carbon atoms (as numbered in the formula of lercanidipine hydrochloride shown below) are represented in the following Tables 4 and 5, respectively.

5

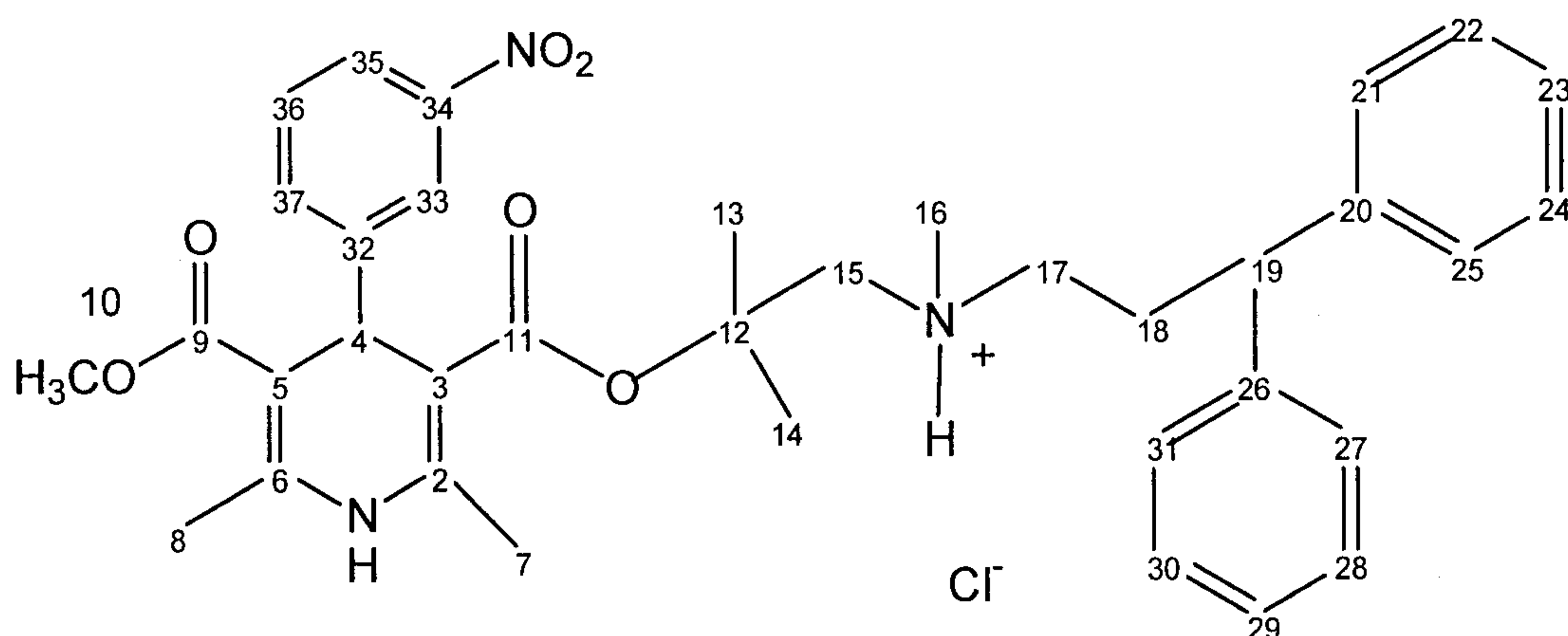


Table 4. Lercanidipine hydrochloride crystalline Form (I)

10

<u>Chemical shift (δ, ppm)</u>	<u>Attribution of carbon atoms</u>
168.7; 167.7	9; 11 or 11; 9
150.1 to 120.4	2; 6 and 20 to 37
104.3; 100.9	3; 5 or 5; 3
79.7	12
63.0; 60.1 (weak)	15; 17 or 17; 15
48.6	10
47.7	16
45.4	19
41.1	4
31.6	18
27.7; 26.4	13; 14 or 14; 13
19.6; 18.0	7; 8 or 8; 7

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Table 5. Lercanidipine hydrochloride crystalline Form (II)

	<u>Chemical shift (δ, ppm)</u>	<u>Attribution of carbon atoms</u>
5	168.1; 166.6	9; 11 or 11; 9
	151.9 to 121.9	2; 6 and from 20 to 37
	104.0; 102.8	3; 5 or 5; 3
	79.0	12
	66.0; 58.0 (weak)	15; 17 or 17; 15
10	49.7	10
	48.8	16
	44.3	19
	40.5	4
	29.8	18
15	27.6; 23.5	13; 14 or 14; 13
	19.6; 18.3	7; 8 or 8; 7

EXAMPLE 17 IR Studies

The IR (infrared) spectra were recorded in KBr powder by Diffuse Reflectance Technique using a Perkin Elmer Spectrum-one instrument. IR spectra, whose wave lengths and corresponding attribution are shown in the following Tables 6 and 7, are clearly different for the new Forms (I) and (II).

Table 6. IR spectrum in KBr powder of lercanidipine hydrochloride Form (I)

	<u>Wavelength (cm⁻¹)</u>	<u>Attribution</u>
25	3186	NH stretching
	3100-2800	Alkyl and phenyl stretching
	2565	N ⁺ H stretching
	1673	C=O stretching
	1525; 1348	Asymmetric and symmetric stretching of NO ₂
30	group	
	1405; 1386	Bending of geminal methyl groups
	785-685	Out-of-plane bending of 5 and 3 adjacent hydrogens on aromatic rings

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Table 7. IR spectrum in KBr powder of lercanidipine hydrochloride Form (II)

	<u>Wavelength (cm⁻¹)</u>	<u>Attribution</u>
5	3183	NH stretching
	3100-2800	Alkyl and phenyl stretching
	2684	N ⁺ H stretching
	1705;1675	C=O stretching
	1526; 1350	Asymmetric and symmetric stretching of NO ₂ group
10	1402; 1380	Bending of geminal methyl groups
	800-680	Out-of-plane bending of 5 and 3 adjacent hydrogens on aromatic rings

EXAMPLE 18: Raman Spectra

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.

The following Tables 8 and 9 show the most significant peaks of Raman spectra of Form (I) and Form (II), respectively.

Table 8. Raman spectrum of crystalline Form (I)

	<u>Wave number (cm⁻¹)</u>	<u>Peak intensity *</u>
20	3054	M
	3040	M
	2981	M
	2941	M
	1675	S
25	1646	M
	1583	M
	1489	M
	1349	Vs
	1236	M
30	1005	S
	821	M
	174	M
	98	S
	73	Vs

* M= moderate; S= strong, Vs =very strong

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Table 9. Raman spectrum of crystalline Form (II)

	<u>Wave number (cm⁻¹)</u>	<u>Peak intensity *</u>
5	3074	M
	3064	M
	3055	M
	3048	M
	3030	M
10	2973	M
	2940	M
	1675	S
	1647	S
	1630	M
15	1584	M
	1489	M
	1351	Vs
	1005	M
	995	M
20	103	Vs
	85	S

* M= moderate; S= strong, Vs =very strong

EXAMPLE 19 Bioavailability of crystalline Forms (I) and (II)**25 19a-Dog**

A study was carried out on six Beagle dogs to evaluate the bioavailability of crystalline Forms (I) and (II).

The products, in micronized form, were administered orally by hard gelatin capsules filled up with the active agent, Form (I) and (II), at a dosage of 3 mg/kg, administered once in the morning of the day of the experiment.

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Blood samples were taken at given times and plasma concentrations of lercanidipine were determined with a stereoselective analytical method HPLC-MS/MS, according to the following working conditions;

Lercanidipine was extracted from dog plasma by means of a liquid-liquid
5 extraction with a mixture of n-hexane and ethyl ether. The dry residue of the organic phase was taken up with a mixture of methanol and water and a liquid-phase chromatographic separation (LC) was carried out; the two enantiomers of lercanidipine were separated on a CHIROBIOTIC V column (Vancomycin) (particle size 5 μ m, column size 150 x 4.6 mm (ASTEC, NJ, USA)) and were detected with a mass spectrometer
10 (MS/MS) by using an electrospray technique.

The analytical method was validated in a concentration range between 0.1 and 20 ng/ml of plasma for both enantiomers. The method has shown to be specific with an accuracy of 15%. The average concentrations of lercanidipine in the tables represent the sum of both enantiomers.

15 The profiles referring to the average concentrations of lercanidipine for both forms are shown in Figure 10. The following Tables 10 and 11 show single values referring to AUC, T_{max}, C_{max} and to plasma concentrations.

TABLE 10. Mean values (n=5) of AUC_{0-t}, C_{max} and T_{max} of lercanidipine hydrochloride
20 (S+R) crystalline Form (I) and crystalline Form (II), in dogs, after oral administration at a dosage of 3 mg/kg.

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Form (I)

Parameter	Dog 1	Dog 2*	Dog 3	Dog 4	Dog 5	Dog 6	Mean	SD
AUC _{0-t} ng/h/ml	15.41	263.83	27.544	46.57	70.39	28.72	37.73	19.12
T _{max} (h)	2.00	4.00	6.00	3.00	3.00	6.00	4.00	1.67
C _{max} (ng/ml)	8.29	128.87	11.62	27.17	22.58	17.83	17.50	6.91

Form (II)

Parameter	Dog 1	Dog 2*	Dog 3	Dog 4	Dog 5	Dog 6	Mean	SD
AUC _{0-t} ng/h/ml	54.59	119.77	75.62	173.82	142.34	61.91	104.68	43.99
T _{max} (h)	3.00	1.50	1.50	4.00	2.00	6.00	3.00	1.61
C _{max} (ng/ml)	18.46	52.19	19.78	52.64	55.38	18.56	36.17	17.27

* not included in the calculation of mean value

5

Table 11. Average concentration in plasma of lercanidipine hydrochloride (S+R) crystalline Form (I) and crystalline Form (II), in dogs, after oral administration at a dosage of 3 mg/kg.

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Form (I)

Time (h)	Dog 1	Dog 2*	Dog 3	Dog 4	Dog 5	Dog 6	Mean	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.1	0.20	0.00	0.00	0.00	0.00	0.00	0.02
1	0.59	0.29	0.00	0.00	0.00	0.00	0.12	0.22
1.5	1.83	1.06	0.32	0.00	1.33	0.00	0.70	0.73
2	8.29	8.94	0.94	0.35	17.11	0.28	5.39	6.34
3	4.44	36.39	0.92	27.17	22.58	1.29	11.28	11.11
4	1.81	128.87	9.42	11.07	16.39	6.26	8.99	5.56
6	0.80	26.65	11.62	2.53	9.73	17.83	8.50	6.50

Form (II)

5

Time (h)	Dog 1	Dog 2*	Dog 3	Dog 4	Dog 5	Dog 6	Mean	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.00	22.67	6.99	0.00	0.00	0.00	1.40	2.61
1	0.00	52.13	16.61	5.50	3.28	0.00	5.08	5.91
1.5	0.23	52.19	19.78	35.43	32.69	3.49	18.32	14.88
2	7.63	35.45	17.81	38.10	55.38	10.19	25.82	19.23
3	18.46	17.43	15.80	28.36	40.57	14.10	23.46	12.56
4	14.83	5.17	14.10	52.64	23.66	13.24	23.69	16.26
6	8.05	4.50	3.62	17.46	6.76	18.56	10.89	6.82

* not included in the calculation of mean value

The formulation containing Form (II) is more bioavailable than the one containing crystalline Form (I) in 5 animals out of 6.

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To simplify the comparison, dog 2 was excluded from the evaluation, since after the administration of Form (I) dog 2 shows a plasma AUC of 264 ng/h/ml versus a mean value of 38 ± 19 (SD) of the other 5 dogs. On the other hand, its AUC after administration of Form (I) is similar to that of the other animals, the value being 120
5 versus 105 ± 44 ng/h/ml.

The bioavailability of lercanidipine hydrochloride (Form (II)), expressed as increase in the AUC of lercanidipine (R+S) obtained after administration of Form (II), is about 3 times higher than that obtained with Form (I). The average profile of plasma concentrations for both crystalline forms is shown in Figure 10.

10 The analysis of these results shows that the amount of lercanidipine (S+R) absorbed after administration of crystalline Form (II) is 3 times higher that of Form (I), whereas the absorption speed, expressed as T_{max} , is practically unchanged.

Plasma concentrations 6 hours after administration (last sampling time) are similar, the concentrations being of 8.5 ± 6.5 ng/ml after administration of Form (I) and
15 of 10.9 ± 6.8 ng/ml after administration of Form (II).

19b-Man

A study was carried out on 16 healthy volunteers to assess the relative bioavailability of lercanidipine hydrochloride Form (I) and Form (II). Form (I) was represented by a tablet of Zanedip^R corresponding to 10 mg of lercanidipine
20 hydrochloride (Reference –R). Form (II) was administered in form of a 10 mg tablet prepared exactly in the same way and with the same composition of Zanedip^R 10mg, starting from micronized Form (II) having the same particle size of Form I (Test-T). Blood samples were taken at 15 points from time 0 to 24 h post-dosing and plasma concentrations of lercanidipine were determined with a stereoselective analytical method

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HPLC-MS/MS as described in Example 19a, as validated for man at the same concentration intervals.

The pharmacokinetic parameters obtained are given in the following table

	Form (I) geom. least square mean	Form (II) geom. least square mean	Point Estimate (T/R)	90%C.I.
AUC_{0-t} (ng·h/mL)	8.82	10.36	1.17	0.93 – 1.48
C_{max} (ng/mL)	3.18	3.22	1.01	0.73 – 1.42
t_{max} (h)	1.50*	2.50*	0.75**	0.00 – 1.25
C_{max}/AUC	0.386^	0.329^	0.85	0.69 – 1.02
* median ** median difference ^ least square mean				

5

The obtained results indicated that lercanidipine hydrochloride Form (II) was not bioequivalent to Form I, with Form (II) obtaining higher plasma levels, that lercanidipine hydrochloride Form (I) has a t_{max} that is shorter than that of Form (II), suggesting its use in immediate release formulations.

10

EXAMPLE 20 X-ray diffraction studies

Philips PW 1710 and Philips X pert PW 3040 powder diffractometer (Copper K α radiation) were used, under the following typical conditions: about 5-70 mg sample (without any previous treatment) with application of a slight pressure to obtain a flat surface. Ambient air atmosphere. 0.02° 2 θ stepsize, 2 sec step-1, 2-50 2 θ .

15

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The obtained spectra are given in Figures 11 and 12 and the corresponding main peaks are described in Tables 12 and 13. The data are clearly different for new isolated Forms (I) and (II).

5 **Table 12.** X RD spectrum of lercanidipine hydrochloride Form (I).

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
10	16.3	83	5.4
	6.2	47	14.2
	4.78	29	18.6
	4.10	63	21.7
	4.06	36	21.9
	3.90	100	22.8

15 **Table 13.** X RD spectrum of lercanidipine hydrochloride Form (II).

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
20	9.3	35	9.5
	6.0	45	14.7
	5.49	65	16.1
	4.65	52	19.1
	4.27	74	20.8
	3.81	41	23.4
	3.77	100	23.6
25	3.58	44	24.8
	3.54	29	25.2

EXAMPLE 21 Melting point determination of various mixtures of lercanidipine

30 hydrochloride crystalline Forms (I) and (II)

The melting points of compositions consisting of known ratios of lercanidipine hydrochloride crystalline Forms (I) and (II) were determined manually. Conditions consisted of using a set point of 177°C and introducing the capillary into the instrument

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(Melting Point Apparatus model 535, Büchi Labortechnik AG, Flawil, Switzerland) at approximately 5°C below the melting point. Results are shown in Table 14.

Table 14. Melting points of compositions consisting of known ratios of lercanidipine hydrochloride crystalline Forms (I) and (II). Samples in Series A and Series B were heated at a gradient of 1°C/min and 0.5°C/min, respectively. Results are given in °C.

Sample	Pure Form (I)	Ratio lercanidipine hydrochloride crystalline Form (I): Form (II)					Pure Form (II)
		9:1	7:3	1:1	3:7	1:9	
Series A	186.8	188.0	189.5	190.0	192.2	194.2	194.3
Series B	185.9-186.8	184.4-186.1	184.5-187.0	186.7-187.4	186.5-189.4	188.7-190.5	190.6-192.9

U.S. Patent No. 5,767,136 discloses crystalline lercanidipine hydrochloride as having a melting point of 186-188°C. Table 14 shows that this melting point is exhibited by mixtures of Form (I) and Form(II) in which the ratio of Form (I):Form (II) varies between 9:1 to 3:7. Bianchi et al. (Drugs of the Future, 1987, 12:1113-1115) report a melting point of 186-188EC (non DSC) for a lercanidipine product they characterize as “crystals”. Hence, the melting point of a preparation of lercanidipine hydrochloride is not sufficient by itself to distinguish the particular form or forms present therein, and many mixtures of different compositions have the same melting point range.

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EXAMPLE 22. Micronization of lercanidipine hydrochloride.

Micronization is carried out by a jet-mill process using a MICRONETTE M300 from the firm NUOVA GUSEO (Villanova sull'Arda -PC- Italy). Parameters are as follows: Injection pressure, 5 Kg/cm²; micronization pressure, 9 Kg/cm²; and cyclone pressure, 2.5 Kg/cm². 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 (50%) 2-8 µm and D (90%) < 15 µm.

EXAMPLE 23**10 Preparation of the solvate of lercanidipine hydrochloride with methylene chloride**

Lercanidipine hydrochloride Form (I) (5.34 g), prepared as described *supra*, was combined with 20 ml of methylene chloride in a closed vessel, the suspension was kept under mild stirring for 192 hours at 20-25°C to produce a solid. The solid was then filtered with a glass filter G4 and washed with fresh methylene chloride. A product of 15 7.4 g of lercanidipine hydrochloride-methylene chloride solvate (1:1 mol/mol) was obtained.

EXAMPLE 24**Preparation lercanidipine hydrochloride form (III)**

20 3.9 g of solvate of lercanidipine hydrochloride with methylene chloride solvate, prepared by the method of Example 1, was placed in a glove hood under constant nitrogen stream (25 l/h) at ambient temperature. The sample was then dried at 90°C and 1 millibar, then placed in a stoppered flask and isolated with parafilm.

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EXAMPLES 25-49 describe preparation of solvates of lercanidipine hydrochloride with solvents other than methylene chloride

EXAMPLES 25-28**Preparation of solvates of lercanidipine hydrochloride with anisole, ethyl acetate****5 and *tert*-butyl methyl ether**

The solvate of lercanidipine hydrochloride with methylene chloride prepared as described in Example 1, the lercanidipine hydrochloride crystalline form (III) obtained as described in Example 2, or the lercanidipine crude (A) or (B) forms prepared as described *supra*, were introduced in a closed vessel together with a solvent chosen from
10 the group consisting of anisole, ethyl acetate and *tert*-butyl methyl ether, under mild stirring, with 10-20 thermal cycles: 25°C-35°C-25°C (3 hours each). After these thermal cycles the samples were kept at 25°C for 24-240 hours. The solvate was then isolated by filtration. The solvent used, the concentration of the starting product in the solvation solvent, and the solvate stoichiometry are shown in Table 1.

15

EXAMPLES 29-31**Preparation of solvates of lercanidipine hydrochloride with isopropanol, 2-butanol, heptane**

The solvate of lercanidipine hydrochloride with methylene chloride prepared as
20 described in Example 1 was placed in a closed vessel together with a solvent chosen from the group consisting of isopropanol, 2-butanol and heptane, kept under mild stirring and subjected to 10-20 thermal cycles 25°C-35°C-25°C (heating step 3 hours, cooling step 3 hours). After these thermal cycles the sample was kept at 25°C for 24-240 hours

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and then filtered. The solvent used, the concentrations of the starting product in the solvation solvent and the solvate stoichiometry are shown in Table 1.

EXAMPLES 32-33

5 Preparation of solvates of lercanidipine hydrochloride with acetone and tetrahydrofuran

The solvate of lercanidipine hydrochloride with methylene chloride, prepared as described in Example 1, and a solvent chosen from the group consisting of acetone and tetrahydrofuran were placed in a closed vessel, kept under mild stirring and subjected to 10-20 thermal cycles: 25°C-35°C-25°C (heating step 3 hours, cooling step 3 hours). After these thermal cycles the samples were kept at 25°C for 24-240 hours and then filtered. The solvent used, the concentrations of the starting product in the solvation solvent and the solvate stoichiometry are shown in Table 1.

15 TABLE 15

EXAMPLE	CONCENTRATION (mg/ml)	SOLVENT	SOLID SOLVATE OBTAINED [content of solvent:lercanidipine hydrochloride (mole/mole)]
3	500	Anisole	lercanidipine hydrochloride- anisole (b) form [0.4]
4	508	Ethyl acetate	lercanidipine hydrochloride- ethyl acetate [1]
5	164	Anisole	lercanidipine hydrochloride- anisole (a) form [0.4]
6	229	Terbutyl methyl	lercanidipine hydrochloride-

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		ether	terbutyl methyl ether [0.8]
7	447	Isopropanol	lercanidipine hydrochloride- isopropanol [1]
8	390	2-butanol	lercanidipine hydrochloride-2- butanol [0.8]
9	348	Heptane	lercanidipine hydrochloride- heptane [0.9]
10	297	Acetone	lercanidipine hydrochloride- acetone [1.2]
11	308	Tetrahydrofuran	lercanidipine hydrochloride- tetrahydrofuran [0.9]

EXAMPLES 34-41

Preparation of solvates of lercanidipine hydrochloride with 2-propanol, 2-butanol, tetrahydrofuran, terbutyl methyl ether, anisole, acetone, ethyl acetate, heptane,

5 using lercanidipine-hydrochloride-methylene chloride

The solvate of lercanidipine hydrochloride with methylene chloride, obtained as described in Example 1, was suspended in a closed vessel in a solvent chosen from the group consisting of 2-propanol, 2-butanol, tetrahydrofuran, terbutyl methyl ether, anisole, acetone, ethyl acetate and heptane. The suspension that was produced was

10 stirred at 20-50°C for 114-420 hours to produce the solvates. The solvates were then filtered. The solvent used, the concentration of the starting product in the solvation solvent, and the solvate obtained are shown in Table 2.

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TABLE 16

EXAMPLE	CONCENTRATION (mg/ml)	SOLVENT	SOLID SOLVATE OBTAINED
12	320	2-propanol	lercanidipine hydrochloride- 2-propanol
13	323	2-butanol	lercanidipine hydrochloride- 2-butanol
14	323	Tetrahydrofuran	lercanidipine hydrochloride- tetrahydrofuran
15	306	Terbutyl methyl ether	lercanidipine hydrochloride-terbutyl methyl ether
16	306	Anisole	lercanidipine hydrochloride-anisole (b) form
17	320	Acetone	lercanidipine hydrochloride-acetone
18	320	Ethyl acetate	lercanidipine hydrochloride- ethyl acetate
19	330	Heptane	lercanidipine hydrochloride-heptane

EXAMPLES 42-46

- 5 **Preparation of solvates of lercanidipine hydrochloride with the following solvents chosen in the group comprising: tetrahydrofuran, terbutyl methyl ether, anisole, acetone, ethyl acetate**

Lercanidipine hydrochloride crystalline form (III), obtained as described in Example 2, was suspended in a solvent chosen from the group consisting of

10 tetrahydrofuran, terbutyl methyl ether, anisole, acetone and ethyl acetate. The suspension then was stirred at 20-50°C for 114-240 hours. The solvent used, the

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concentration of the starting product in the solvent and the solvate obtained are shown in the following Table 3.

TABLE 17

EXAMPLE	CONCENTRATION (mg/ml)	SOLVENT	SOLID OBTAINED
20	317	Tetrahydrofuran	lercanidipine hydrochloride-tetrahydrofuran
21	313	Terbutyl methyl ether	lercanidipine hydrochloride-terbutyl methyl ether
22	317	Anisole	lercanidipine hydrochloride-anisole (a) form
23	313	Acetone	lercanidipine hydrochloride-acetone
24	327	Ethyl acetate	lercanidipine hydrochloride-ethyl acetate

5

EXAMPLES 47-55**De-solvation of the solvates obtained in Examples 3-11**

The solvent was removed from the solvates by heating under vacuum. The starting solvate (also indicated with the number of the preparation example), the operating conditions applied in the removal of the inclusion solvent and the crystalline form of lercanidipine hydrochloride obtained are shown in Table 4.

10

TABLE 18

Ex.	STARTING SOLVATE	STARTING SOLVATE PREPARATION	SOLVENT REMOVAL CONDITIONS	CRYSTALLINE LERCANIDIPINE HCl FORM OBTAINED*
25	lercanidipine hydrochloride-anisole (b form)	Example 3	90°C/<1 mbar/ 24 hours	Form (III)
26	lercanidipine hydrochloride-ethyl acetate	Example 4	90°C/<1 mbar/ 24 hours	Form (III)
27	lercanidipine	Example 5	50°C/<1 mbar/	Form (I)

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	hydrochloride-anisole (a form)		24 hours	
28	lercanidipine hydrochloride-terbutyl methyl ether	Example 6	90°C/<1 mbar/ 24 hours	Form (I)
29	lercanidipine hydrochloride-acetone	Example 10	90°C/<1 mbar/ 24 hours	Form (IV)
30	lercanidipine hydrochloride- tetrahydrofurane	Example 11	90°C/<1 mbar/ 24 hours	Form (III)
31	lercanidipine hydrochloride- isopropanol	Example 7	90°C/<1 mbar/ 22 hours	Form (III)
32	lercanidipine hydrochloride-2-butanol	Example 8	90°C/<1 mbar/ 22 hours	Form (III)
33	lercanidipine hydrochloride-heptane	Example 9	90°C/<1 mbar/ 22 hours	Form (III)

*determined by Raman spectroscopy and X-ray diffraction

EXAMPLE 56

5 Preparation of the solvate lercanidipine hydrochloride-methyl ethyl ketone

100 g of lercanidipine hydrochloride crystalline Form (I) was suspended in 250 ml of methyl ethyl ketone/water (95/5) and heated at 80°C until complete dissolution.

The solution was cooled under stirring, kept at room temperature, and then filtered. The product was dried in an oven at 60°C under vacuum (about 200 mmHg). 93 g of product

10 was obtained having a lercanidipine hydrochloride-methyl ethyl ketone content of 1:0.7 (mole/mole).

EXAMPLE 57

X-ray diffraction

The new crystalline forms are hereinafter identified by their X-ray spectrums.

15 Philips PW 1710 and Philips X pert PW 3040 powder diffractometer (Copper K α

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radiation) were used, under the following typical conditions: about 5-70 mg sample (without any previous treatment) with application of a slight pressure to obtain a flat surface. Ambient air atmosphere. 0.02° 2θ stepsize, 2 sec step-1, 2-50 2θ .

Lercanidipine hydrochloride crystalline form (III) showed an X-ray diffraction
5 image at wavelength $K\alpha$ as expressed in Table 5 and shown in Figure 2.

TABLE 19

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
10	11.5	39	7.7
	9.1	38	9.7
	9.0	37	9.8
	8.0	50	11.0
	6.6	48	13.5
15	5.58	57	15.9
	5.49	34	16.1
	5.13	43	17.3
	4.09	63	21.7
	3.92	43	22.7
20	3.72	100	23.9
	3.60	85	24.7
	3.47	31	25.6

Lercanidipine hydrochloride crystalline form (IV) showed an X-ray diffraction
25 image, at wavelength $K\alpha$ as expressed in Table 6 and shown in Figure 7.

TABLE 20

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
30	7.9	71	11.2
	6.9	53	12.7
	5.21	57	17.0
	5.13	46	17.3
	4.73	66	18.8

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	4.69	95	18.9
	4.53	53	19.6
	4.40	81	20.2
	4.34	43	20.4
5	3.99	44	22.2
	3.89	52	22.8
	3.77	100	23.6
	3.69	35	24.1

10 The solvate of lercanidipine hydrochloride with methylene chloride showed an X-ray diffraction image, at wavelength $K\alpha$ as expressed in Table 7 and shown in Figure 1.

TABLE 21

15	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
	6.6	40	13.4
	5.87	42	15.1
	5.04	39	17.6
20	4.00	96	22.2
	3.90	29	22.8
	3.86	34	23.0
	3.67	100	24.2
	2.04	31	44.4
25			

The solvate of lercanidipine hydrochloride with anisole (a) form showed an X-ray diffraction image, at wavelength $K\alpha$ as expressed in Table 8 and shown in Figure 12.

TABLE 22

30	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
	17.4	62	5.1
	7.6	34	11.6
	5.71	43	15.5
35	5.57	58	15.9
	4.99	47	17.7
	4.62	40	19.2

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	4.44	29	20.0
	4.28	98	20.8
	4.04	100	22.0
	3.19	43	27.9
5	2.92	36	30.6
	2.86	42	31.3

The solvate of lercanidipine hydrochloride with anisole (b) form showed an X-ray diffraction image, at wavelength $K\alpha$ expressed in Table 9 and shown in Figure 13.

10

TABLE 23

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
	6.9	49	12.8
15	6.7	63	13.3
	5.82	86	15.2
	5.27	41	16.8
	5.15	53	17.2
	4.00	47	22.2
20	3.89	46	22.8
	3.66	100	24.3

The solvate of lercanidipine hydrochloride with acetone showed an X-ray diffraction image, at wavelength $K\alpha$ as expressed in Table 10 and shown in Figure 8.

25

TABLE 24

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
	10.1	42	8.8
30	7.3	100	12.1
	5.87	31	15.1
	4.07	41	21.8
	3.96	52	22.4
	3.79	49	23.5
35	3.71	37	24.0
	3.34	33	26.7

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The solvate of lercanidipine hydrochloride with ethyl acetate showed an X-ray diffraction image, at wavelength $K\alpha$ as expressed in Table 11 and shown in Figure 9.

TABLE 25

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
5	6.9	100	12.8
	6.3	29	14.0
	5.80	45	15.3
10	5.65	31	15.7
	5.43	44	16.3
	4.74	53	18.7
	4.53	49	19.6
	4.00	84	22.2
15	3.91	91	22.7
	3.67	77	24.2
	3.60	34	24.7
	3.53	34	25.2
	3.49	43	25.5
20			

The solvate of lercanidipine hydrochloride with terbutyl methyl ether showed an X-ray diffraction image, at wavelength $K\alpha$, as expressed in Table 12 and shown in Figure 11.

25 **TABLE 26**

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
	6.2	77	14.2
	4.88	29	18.2
30	4.52	64	19.6
	4.02	48	22.1
	3.93	100	22.6
	3.43	46	26.0

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The solvate of lercanidipine hydrochloride with isopropanol showed an X-ray diffraction image, at wavelength $K\alpha$ as expressed in Table 13 and shown in Figure 14.

5

TABLE 27

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
10	6.6	35	13.5
	5.85	48	15.1
	5.06	41	17.5
	4.04	64	22.0
	3.90	39	22.8
15	3.72	37	23.9
	3.67	100	24.2

The solvate of lercanidipine hydrochloride with 2-butanol showed an X-ray diffraction image, at wavelength $K\alpha$ the image as expressed in Table 14 and shown in Figure 15.

20

TABLE 28

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
25	6.8	34	13.1
	5.86	36	15.1
	5.13	42	17.3
	4.03	51	22.0
	3.90	36	22.8
30	3.67	100	24.2

The solvate of lercanidipine hydrochloride with heptane showed an X-ray diffraction image, at wavelength $K\alpha$ as expressed in Table 15 and shown in Figure 16.

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TABLE 29

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
5	7.3	54	12.2
	6.0	44	14.7
	4.03	85	22.0
	3.85	100	23.1
	3.76	93	23.6
10	3.63	67	24.5
	3.38	39	26.4
	3.01	47	29.6

The solvate of lercanidipine hydrochloride with tetrahydrofuran showed an X-ray
 15 diffraction image, at wavelength Kα as expressed in Table 16 and shown in Figure 10.

TABLE 30

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
20	6.6	100	13.5
	5.88	32	15.1
	5.12	56	17.3
	4.25	38	20.9
	4.06	50	21.9
25	3.92	42	22.7
	3.75	44	23.7
	3.70	90	24.0
	3.64	31	24.4

30 The solvate of lercanidipine hydrochloride with methyl ethyl ketone showed an
 X-ray diffraction image, at wavelength Kα as expressed in Table 17 and shown in Figure
 38.

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TABLE 31

	<u>d (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2 θ angle</u>
5	6.8	50	13.1
	6.1	43	14.5
	5.87	47	15.1
	5.10	53	17.4
	3.99	100	22.2
10	3.87	48	22.9
	3.74	36	23.8
	3.69	65	24.1
	3.61	70	24.6

EXAMPLE 58**15 Description of the crystals and their thermal characterization**EXAMPLE 58 A Thermomicroscopic analysis

A few mg of each sample were placed on a microscope slide provided with cover slip and placed on a Mettler model FP82 hotplate (Mettler, Volketswil, Switzerland) with a heating speed of 10°C/min, and analyzed with a Leitz Orthoplan Pol light microscope (Wild Leitz, Zurich, Switzerland) The sample was not hermetically sealed. The analysis provided the following results.

Solvate of lercanidipine hydrochloride with methylene chloride prepared according to Example 23: The sample consisted of irregular striated birefringent crystals (examined with a crossed polarizer). The heating of the solvate resulted in the melting of the powder in a range between 138 and 150°C. No other transition phase was visible.

Lercanidipine hydrochloride crystalline Form (III) obtained as described in Example 24: The sample consisted of small and very small birefringent crystals (examined with a crossed polarizer) with an irregular shape and having breaks and

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cracks. The heating of the crystalline Form (III) resulted in a melting in a range of 137-150°C. No other transition phase was visible.

Solvate lercanidipine hydrochloride-anisole (b) form obtained as described in

Example 25: The sample consisted of small birefringent cylinders (examined with a
5 crossed polarizer), having breaks and cracks. No transition phase was observed up to the
melting temperature of 144-146°C.

Solvate lercanidipine hydrochloride-ethyl acetate obtained as described in

Example 26: The sample consisted of small birefringent cylinders (examined with a
crossed polarizer), having breaks and cracks. Some small drops built up at 106°C. No
10 transition phase was observed up to the melting temperature of 135-145°C.

Solvate lercanidipine hydrochloride-anisole (a) form obtained as described in

Example 27: The sample consisted of birefringent crystals (examined with a crossed
polarizer). Formation of microdrops together with the presence of several microcrystals
was observed at 95°C; no other transformation was seen by heating to melting at 188°C.

15 Solvate lercanidipine hydrochloride-terbutyl methyl ether obtained as described
in Example 28: The sample consisted of non-birefringent crystals (examined with a
crossed polarizer). Some small drops built up upon pressing the sample with a spatula.
No transition phase was observed up to the melting temperature of 172-190°C.

Solvate lercanidipine hydrochloride-isopropanol (Example 29): The sample
20 consisted of small birefringent cylinders (with a crossed polarizer) without breaks or
cracks. From a range of 135-148°C the crystals de-solvate and remained bathed in the
liquid. The crystals melted at 177-200°C.

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Solvate lercanidipine hydrochloride-2-butanol (Example 30): The sample consisted of birefringent cylinders (with a crossed polarizer) having several breaks and cracks. No transition phase was observed when the crystals were heated up to their melting temperature of 125-145°C.

5 Solvate lercanidipine hydrochloride-heptane (Example 31): The sample consisted of small irregular birefringent crystals (with a crossed polarizer). No transition phase was observed when the crystals were heated up to their melting point at 125-150°C.

10 Solvate lercanidipine hydrochloride-acetone (Example 32): The sample consisted of large irregular birefringent crystals (with a crossed polarizer). No transition phase was observed when the crystals were heated up to their melting temperature at 125-135°C.

15 Solvate lercanidipine hydrochloride-tetrahydrofuran (Example 33): The sample consisted of irregular crystals having breaks and cracks, which were birefringent (examined with a crossed polarizer). No transition phase was observed if the crystals were heated up to their melting point of 125-160°C.

20 Lercanidipine hydrochloride crystalline Form IV (Example 51): The sample consisted of large crystals having several breaks and cracks that were practically non birefringent (examined with a crossed polarizer). No transition phase was observed when the crystals were heated up to their melting temperature of 116-135°C. A few crystals kept their solid form and melted only at 195°C.

Solvate lercanidipine hydrochloride-methyl ethyl ketone (Example 55): The sample consisted of small cylinder-shaped birefringent crystals (with a crossed polarizer)

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having breaks and cracks. No transition phase was observed when the sample was heated up to the melting temperature (135-155°C).

EXAMPLE 58B Thermogravimetric analysis (TG and TGFTIR)

5 Each sample weighing 2 to 5 mg was placed in an aluminum crucible of an apparatus PERKIN ELMER TGS-2 Thermogravimetric System (Perkin-Elmer International, Inc., Rotkreuz, Switzerland) and heated in nitrogen stream at a rate of 10°C/min. The thermogravimetric analysis together with an IR analysis in Fourier transform was carried out according to the following operating modes. Each sample
10 weighing 2 to 5 mg was placed in an aluminum crucible of an apparatus Netzsch Thermomicrobalance TG209 (Netzsch Gerätebau, Selb, Germany) coupled with a spectrometer in Fourier transform BRUKER FTIR Vector 22 (Spectrospin, Fällanden, Switzerland) and heated in nitrogen stream at a rate of 10°C/min.

The thermogravimetric analyses gave the following results:

15 Solvate of lercanidipine hydrochloride with methylene chloride prepared according to Example 23: A weight loss of 10.1% was observed in the temperature range between 25 and 150°C. (Fig. 3).

The volatile compound was identified by the corresponding IR spectrum and was found to be methylene chloride. The stoichiometric compound monosolvate
20 corresponded to a weight loss of 11.6%. Since methylene chloride has a high vapor pressure and since the sample already lost small amounts of dichloromethane at 25°C, it can be inferred that the product obtained in Example 1 corresponded to a solvate of lercanidipine hydrochloride with 1 molecule of methylene chloride.

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Lercanidipine hydrochloride crystalline Form (III) obtained as described in

Example 24: A weight loss of 0.3% corresponding to the presence of dichloromethane, as identified by the corresponding IR spectrum, was observed in the temperature range 25-165°C (See Fig. 4).

5 Solvate lercanidipine hydrochloride-anisole (b) form obtained as described in

Example 25: A weight loss of 6.1% was observed in the range 25-170°C (Fig. 27).

Anisole was mainly present in the gas phase.

Solvate lercanidipine hydrochloride-ethyl acetate obtained as described in

10 Example 26: A weight loss of 11.4% was observed in the temperature range between 25 and 160°C (Fig. 28). The volatile compound, as identified by the IR spectrum, was found to be ethyl acetate.

Solvate lercanidipine hydrochloride-anisole (a) form obtained as described in

Example 27: A weight loss of 5.9% was observed in the temperature range between 25 and 175°C (Fig. 31). The volatile compound was found to be anisole.

15 Solvate lercanidipine hydrochloride-terbutyl methyl ether obtained as described

in Example 28: A weight loss of 10% was observed in the temperature range between 25 and 130°C (Fig. 32). The volatile compound, as identified by the IR spectrum, was found to be terbutyl methyl ether. Degradation was observed at a temperature above 180°C (only CO₂ is present).

20 Solvate lercanidipine hydrochloride-isopropanol obtained as described in

Example 29: A weight loss of 8.4% is observed in the temperature range between 25 and 160°C (Fig. 33). The volatile component is found to be isopropanol.

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Solvate lercanidipine hydrochloride-2-butanol obtained as described in Example

30: A weight loss of 8.6% was observed in the temperature range 25-155°C (Fig. 34).

The volatile component was found to consist of 2-butanol.

Solvate lercanidipine hydrochloride-heptane obtained as described in Example

5 31: A weight loss of 12.4% was observed in the temperature range 25-160°C (Fig. 35).

Solvate lercanidipine hydrochloride-acetone obtained as described in Example

32: A weight loss of 10.1% was observed in the temperature range 25-175°C (Fig. 29).

Solvate lercanidipine hydrochloride-methyl ethyl ketone obtained as described in

10 Example 55: A weight loss of 7.4% was observed in the temperature range 25-160°C,
(Fig. 37). The volatile compound identified was found to be methyl ethyl ketone.

Solvate lercanidipine hydrochloride-tetrahydrofuran (Example 33): A weight
loss of 9.3% was observed at 25-180°C. The volatile component was found to be THF
(Fig. 35).

15 Lercanidipine hydrochloride Form (IV) (Example 51): A weight loss of 0.3%
was observed between 25 and 140°C; the volatile component was water (Fig. 36).

For some samples, mass loss did not correspond to stoichiometric values, which can be
due to the presence of inclusion complexes.

* * *

20 The present invention is not to be limited in scope by the specific embodiments
described herein. Indeed, various modifications of the invention in addition to those
described herein will become apparent to those skilled in the art from the foregoing

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description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

It is further to be understood that values are approximate, and are provided for description.

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CLAIMS:

1. Isolated lercanidipine hydrochloride crystalline Form (I), which has the X-ray diffraction pattern, at wavelength $K\alpha$, wherein distances, (I/I₀) ratios, and 2θ angles of significant peaks are:

5	<u>D (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2θ angle</u>
	16.3	83	5.4
	6.2	47	14.2
	4.78	29	18.6
	4.10	63	21.7
10	4.06	36	21.9
	3.90	100	22.8

2. A method of producing lercanidipine hydrochloride crystalline Form (I), which has an X-ray diffraction pattern, at wavelength $K\alpha$, wherein distances, (I/I₀) ratios, and 2θ angles of significant peaks are:

15	<u>D (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2θ angle</u>
	16.3	83	5.4
	6.2	47	14.2
	4.78	29	18.6
	4.10	63	21.7
20	4.06	36	21.9
	3.90	100	22.8 ;

which comprises:

d) adding a C1-C5 alcohol solvent containing a maximum of 5% water (v/v) to a crude lercanidipine hydrochloride Form and heating under reflux and with stirring to produce a clear solution;

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e) cooling the solution of step d) and stirring until the concentration of lercanidipine hydrochloride dissolved in the crystallization solvent is $\leq 2\%$ by weight; and

5 f) recovering the solid obtained from step e), and drying said solid to produce the lercanidipine hydrochloride crystalline Form (I).

3. The method of claim 2, wherein step f) comprises filtering the solid obtained from step e), washing the solid with isopropanol and re-filtering the solid before drying.

10 4. The method of claim 2, wherein the alcohol of step d) is selected from the group consisting of isopropanol, ethanol and anhydrous ethanol.

5. The method of claim 2, wherein the crude Form is lercanidipine hydrochloride crude Form (A), lercanidipine hydrochloride crude Form (B) or lercanidipine crude Form (C).

15 6. The method of claim 2, wherein said step d) further comprises filtering the heated solution.

7. The method of claim 2, wherein said step e) comprises cooling the solution to a temperature between 30 and 40°C.

8. The method of claim 7, wherein said step e) further comprises stirring for a period of time of 12-48 hours.

20 9. The method of claim 2, wherein said drying in step f) takes place in an oven.

10. A method of producing lercanidipine hydrochloride crystalline Form (I), which has an X-ray diffraction pattern, at wavelength $K\alpha$, wherein distances, (I/I_0) ratios, and 2θ angles of significant peaks are:

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	<u>D (Å)</u>	<u>Relative intensity (I/I₀)</u>	<u>2θ angle</u>
	16.3	83	5.4
	6.2	47	14.2
	4.78	29	18.6
5	4.10	63	21.7
	4.06	36	21.9
	3.90	100	22.8 ;

which comprises:

10 d') providing a mixture of ethanol and lercanidipine hydrochloride,
refluxing under stirring and cooling and adding crystalline seeds of Form (I);

e') further cooling the seeded mixture of step d') and stirring until the concentration of lercanidipine hydrochloride dissolved in the crystallization solvent is $\leq 2\%$ by weight; and

15 f') recovering the solid of step e') to form lercanidipine hydrochloride
Form (I).

11. The method of claim 10, wherein the ratio of lercanidipine hydrochloride to volume of solvent in step d') on a weight volume ratio is within the range of about 1:4 to 1:6.

12. The method of claim 11, wherein said ratio is 1:4.

20 13. The method of claim 10, wherein said step d') further comprises filtering the heated solution.

14. The method of claim 10, wherein cooling in said step d') is to a temperature of 20°C while stirring.

25 15. The method of claim 10, wherein cooling in said step e') is to a temperature between 10 and 15°C.

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16. The method of claim 10, wherein the drying in said step f') takes place in an oven at 70°C.

17. The method of claim 14, wherein authentic seeds of lercanidipine Form (I) are added at the end of cooling in steps e') and d').

5 18. An antihypertensive pharmaceutical composition comprising (1) crystalline lercanidipine hydrochloride and optionally other forms of lercanidipine, wherein the crystalline lercanidipine hydrochloride is lercanidipine hydrochloride crystalline Form (I), comprising a predetermined content of each crystalline form, and
10 (2) at least one component selected from the group consisting of a pharmaceutically acceptable carrier or diluent, a flavorant, a sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a colorant, a disintegrant, an excipient, a lubricant, a plasticizer, and an edible oil.

19. A unit dosage form comprising the antihypertensive pharmaceutical composition of claim 18.

15 20. The unit dosage form of claim 19, wherein the dosage form is a lercanidipine immediate release dosage form.

21. The unit dosage form of claim 19, wherein the dosage form is a lercanidipine controlled release dosage form.

22. The unit dosage form of claim 19, wherein the dosage form comprises a
20 lercanidipine immediate release phase and a lercanidipine controlled release phase.

23. The unit dosage form of claim 19, wherein the composition comprises 0.1 to 400 mg lercanidipine hydrochloride.

24. The unit dosage form of claim 23, wherein the composition comprises 1 to 200 mg lercanidipine hydrochloride.

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25. The unit dosage form of claim 24, wherein the composition comprises 5 to 40 mg lercanidipine hydrochloride.

26. A use of lercanidipine hydrochloride crystalline Form (I) in preparation of a pharmaceutical composition for treating hypertension, coronary heart disease or
5 congestive heart failure in a subject in need thereof.

27. A use of lercanidipine hydrochloride crystalline Form (I) in preparation of a pharmaceutical composition for treating or preventing atherosclerotic lesions in arteries in a subject in need thereof.

28. A use of lercanidipine hydrochloride crystalline Form (I) in preparation
10 of a pharmaceutical composition for treating or preventing heart failure in a subject in need thereof.

29. The use of any one of claims 26 to 28, wherein said subject is a mammal.

30. The use of claim 29, wherein said subject is a human.

31. A use of lercanidipine hydrochloride crystalline Form (I) for treating
15 hypertension, coronary heart disease or congestive heart failure in a subject in need thereof.

32. A use of lercanidipine hydrochloride crystalline Form (I) for treating or preventing atherosclerotic lesions in arteries in a subject in need thereof.

33. A use of lercanidipine hydrochloride crystalline Form (I) for treating or
20 preventing heart failure in a subject in need thereof.

34. The use of any one of claims 31 to 33, wherein said subject is a mammal.

35. The use of claim 34, wherein said subject is a human.

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36. Lercanidipine hydrochloride crystalline Form (I) for treating hypertension, coronary heart disease or congestive heart failure in a subject in need thereof.
37. Lercanidipine hydrochloride crystalline Form (I) for treating or
5 preventing atherosclerotic lesions in arteries in a subject in need thereof.
38. Lercanidipine hydrochloride crystalline Form (I) for treating or preventing heart failure in a subject in need thereof.
39. The lercanidipine hydrochloride crystalline Form of any one of claims 36 to 38, wherein said subject is a mammal.
- 10 40. The lercanidipine hydrochloride crystalline Form of claim 39, wherein said subject is a human.
41. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and lercanidipine hydrochloride crystalline Form (I) for treating hypertension, coronary heart disease or congestive heart failure in a subject in need
15 thereof.
42. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and lercanidipine hydrochloride crystalline Form (I) for treating or preventing atherosclerotic lesions in arteries in a subject in need thereof.
43. A pharmaceutical composition comprising a pharmaceutically acceptable
20 carrier or diluent and lercanidipine hydrochloride crystalline Form (I) for treating or preventing heart failure in a subject in need thereof.
44. The pharmaceutical composition of any one of claims 41 to 43, wherein said subject is a mammal.
45. The pharmaceutical composition of claim 44, wherein said subject is a
25 human.

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46. An antihypertensive composition comprising lercanidipine hydrochloride crystalline Form (I) and lercanidipine hydrochloride crystalline Form (II).

47. The antihypertensive composition of claim 46, wherein the lercanidipine hydrochloride crystalline Form (I) has a melting point of about 197-201°C and the
5 lercanidipine hydrochloride crystalline Form (II) has a melting point of about 207-211°C, when said melting points are determined as DSC peaks.

48. The antihypertensive composition of claim 46 or 47, wherein the ratio of Form (I): Form (II) is between 1:9 to 9:1.

49. The antihypertensive composition of claim 46 or 47, wherein the ratio of
10 Form (I): Form (II) is 9:1.

50. The antihypertensive composition of claim 46 or 47, wherein the ratio of Form (I): Form (II) is 7:3.

51. The antihypertensive composition of claim 46 or 47, wherein the ratio of Form (I): Form (II) is 1:1.

15 52. The antihypertensive composition of claim 46 or 47, wherein the ratio of Form (I): Form (II) is 3:7.

53. The antihypertensive composition of claim 46 or 47, wherein the ratio of Form (I): Form (II) is 1:9.

54. The antihypertensive pharmaceutical composition of claim 18, wherein
20 said lercanidipine hydrochloride crystalline Forms (I) has an average particle size of D (50%) 2-8 μm and D (90%) < 15 μm .

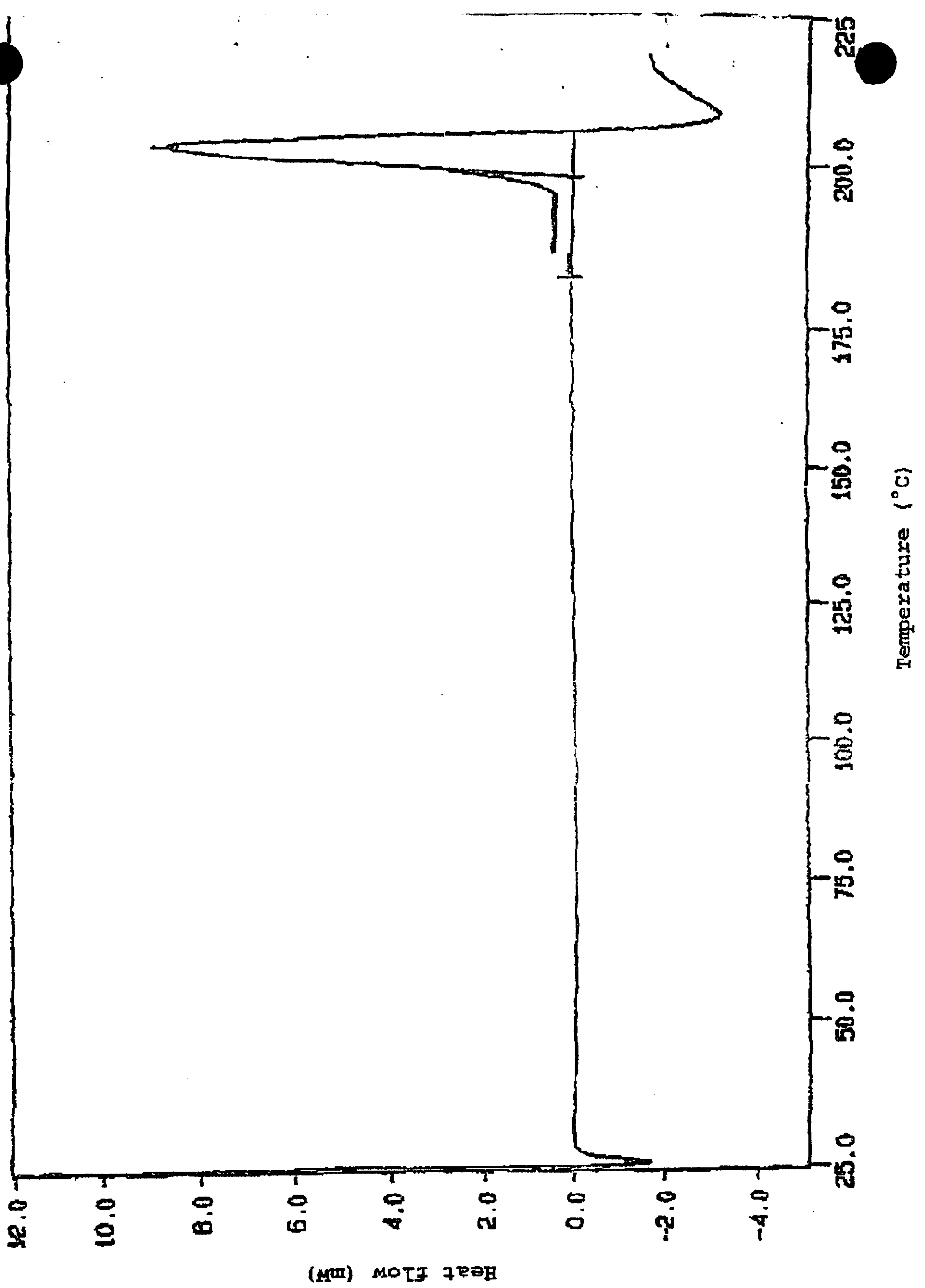
55. The antihypertensive composition of any one of claims 46 to 53, wherein said lercanidipine crystalline Forms (I) and (II) each have an average particle size of D (50%) 2-8 μm and D (90%) < 15 μm .

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56. The lercanidipine crystalline Form of claim 1, wherein the lercanidipine crystalline Form is present in the form of particles having an average particle size of D (50%) 2-8 μm and D (90%) < 15 μm .

FIGURE 1



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A.

FIGURE 2

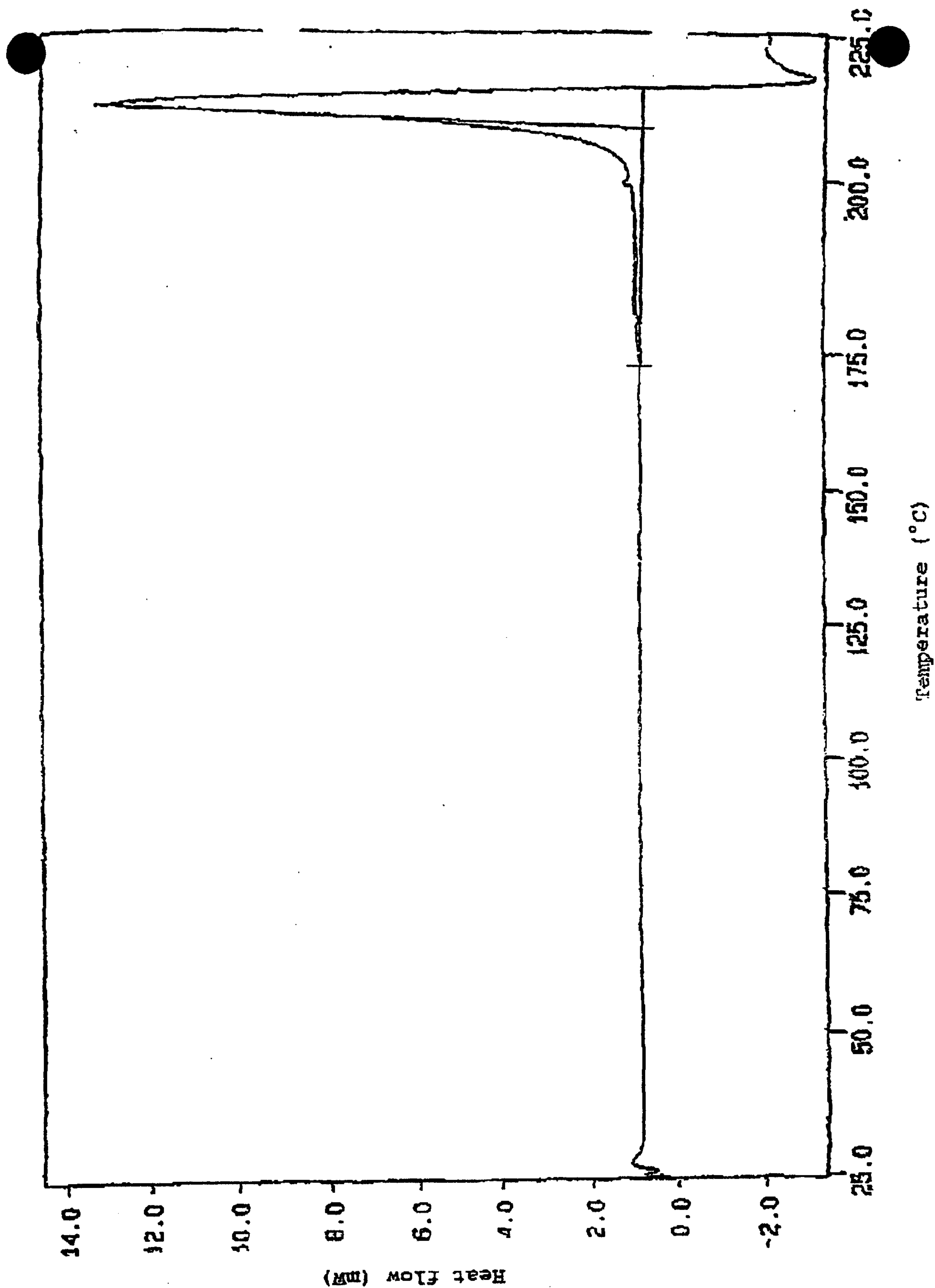


FIGURE 3

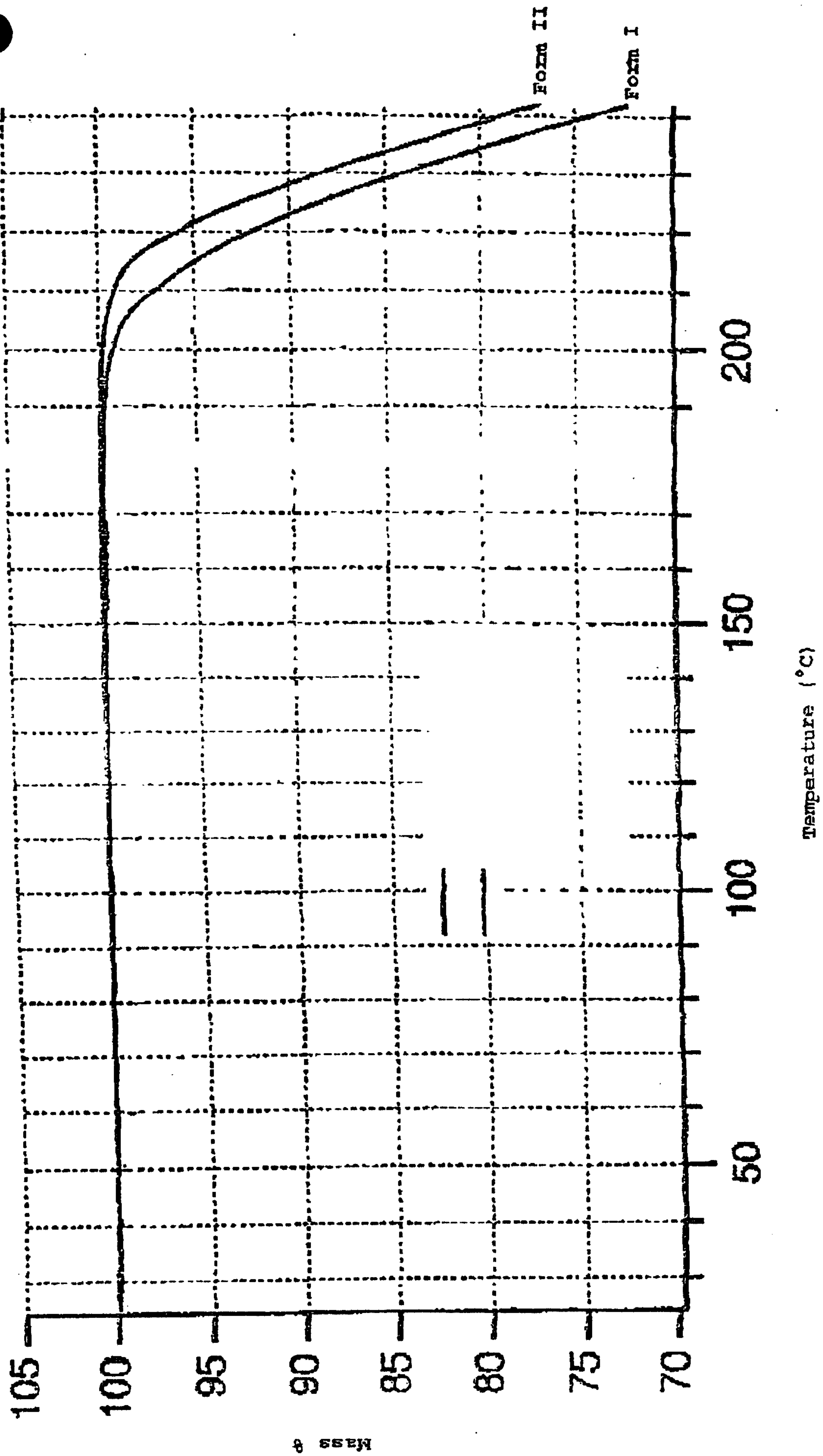


FIGURE 4

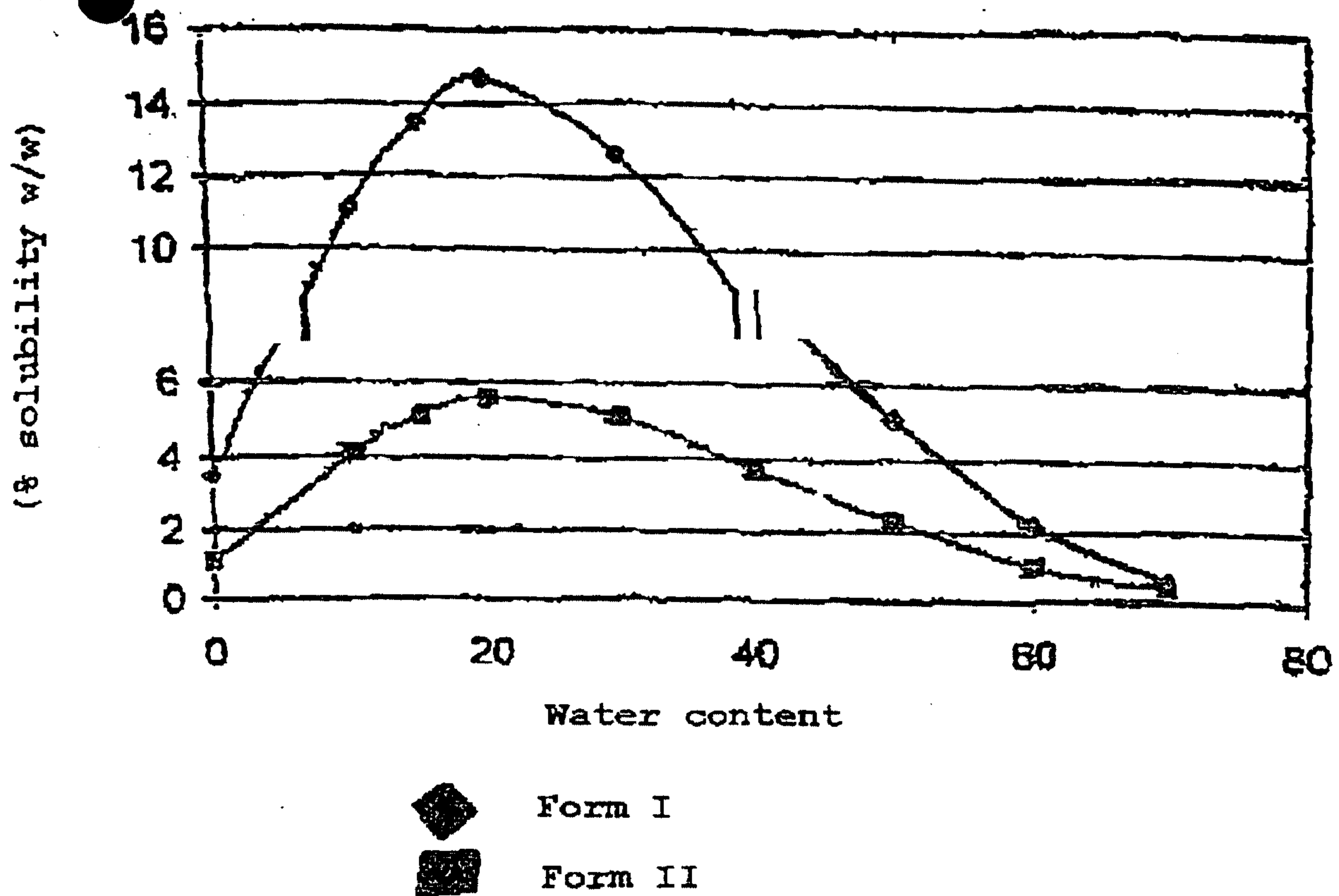


FIGURE 5

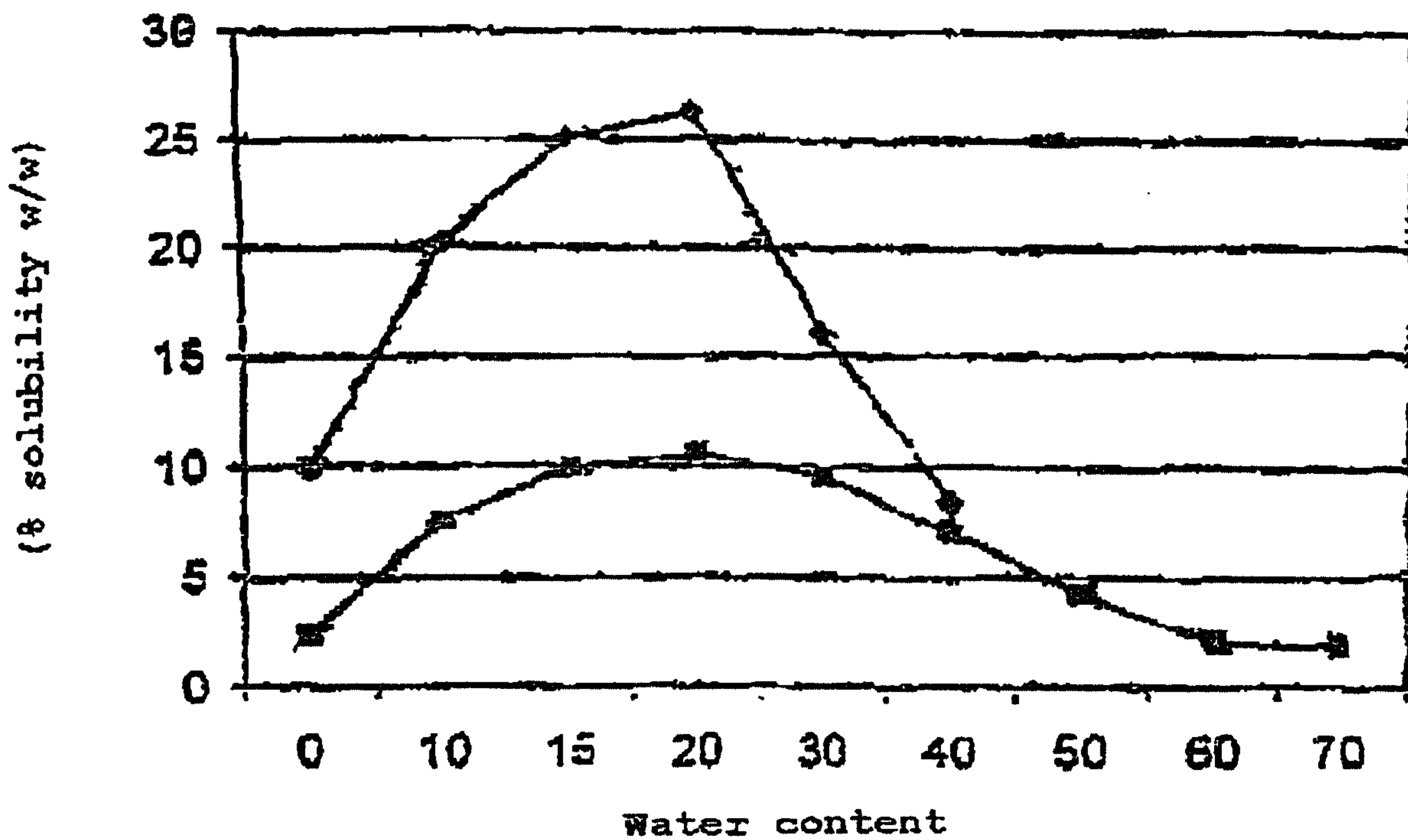


FIGURE 6

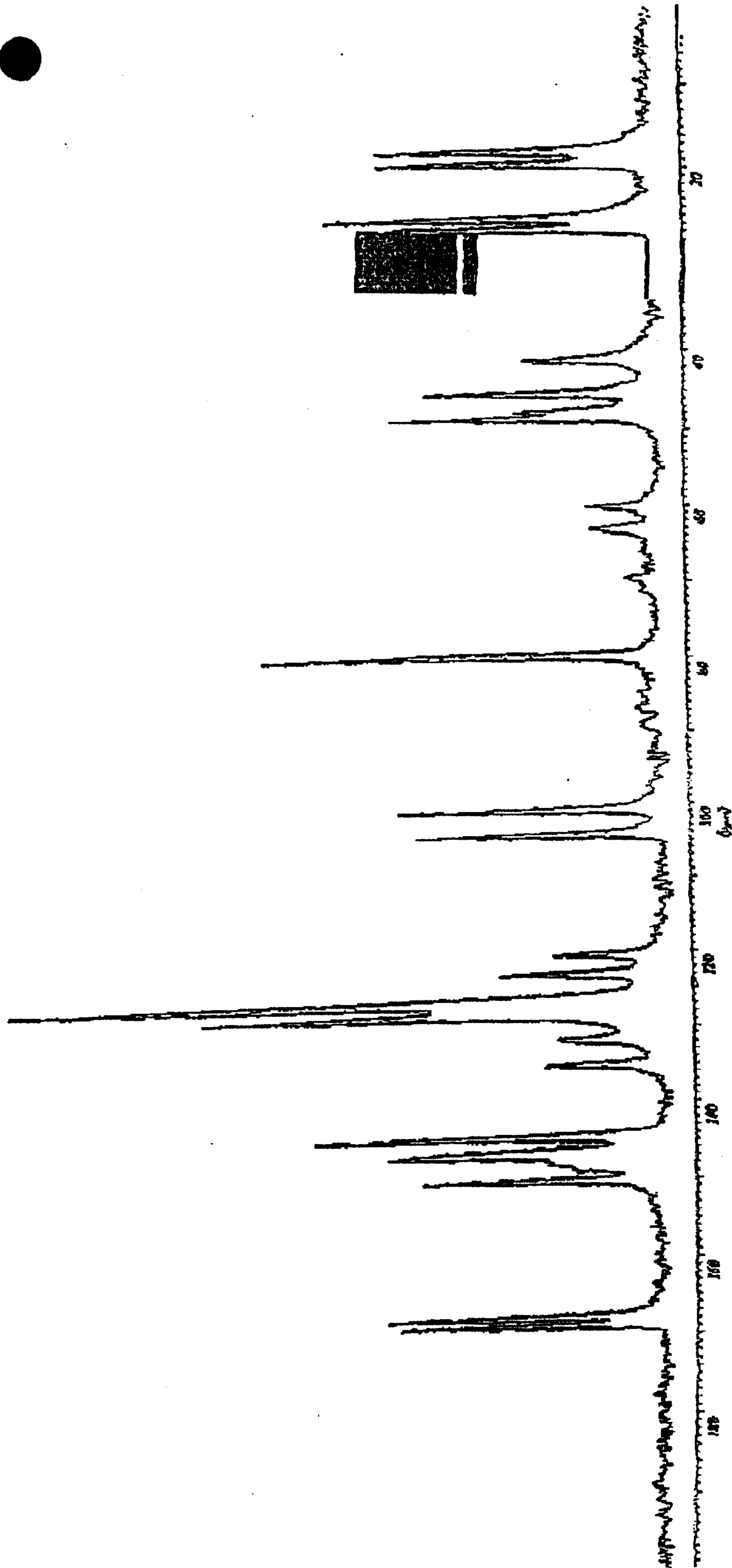
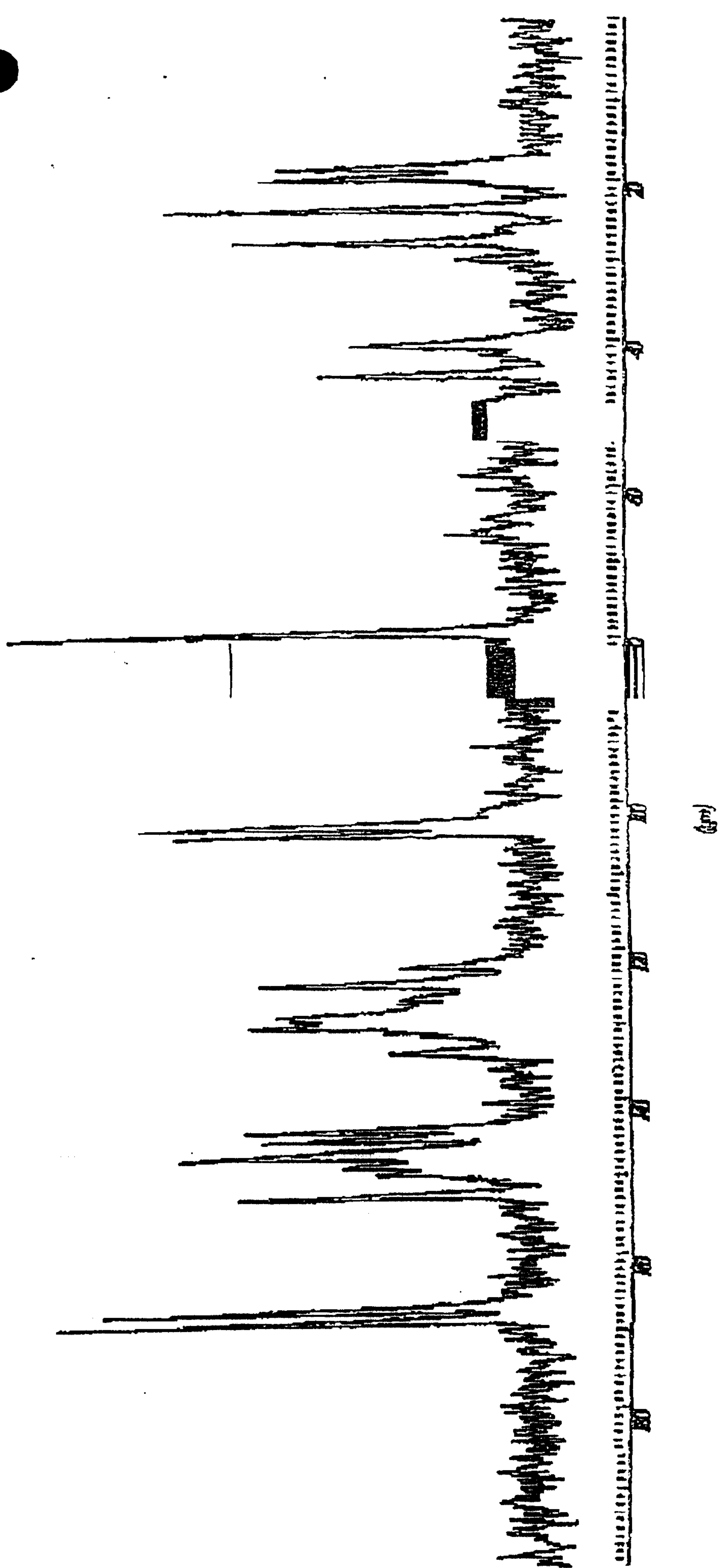


FIGURE 7



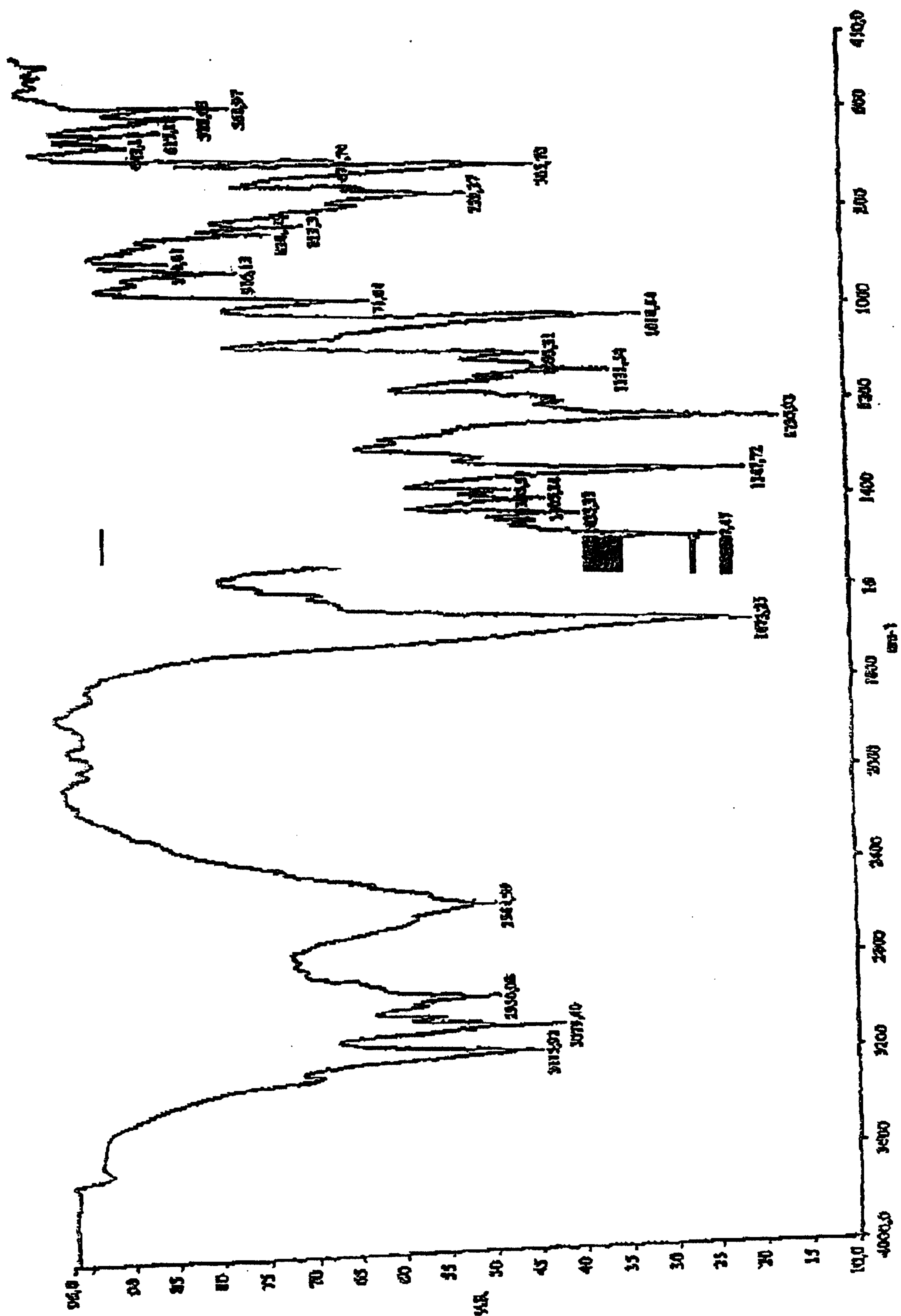


FIGURE 8

FIGURE 9

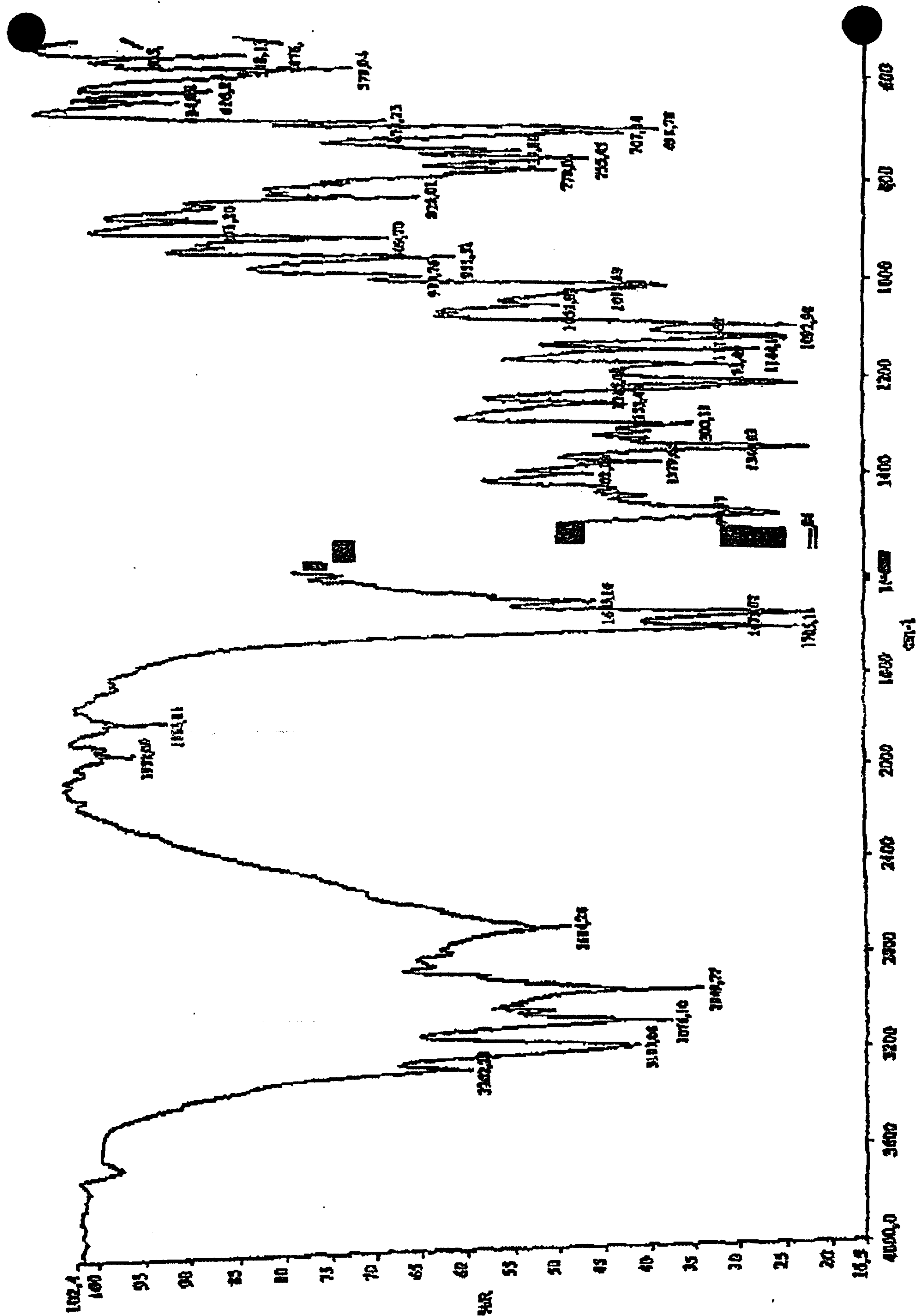


FIGURE 10

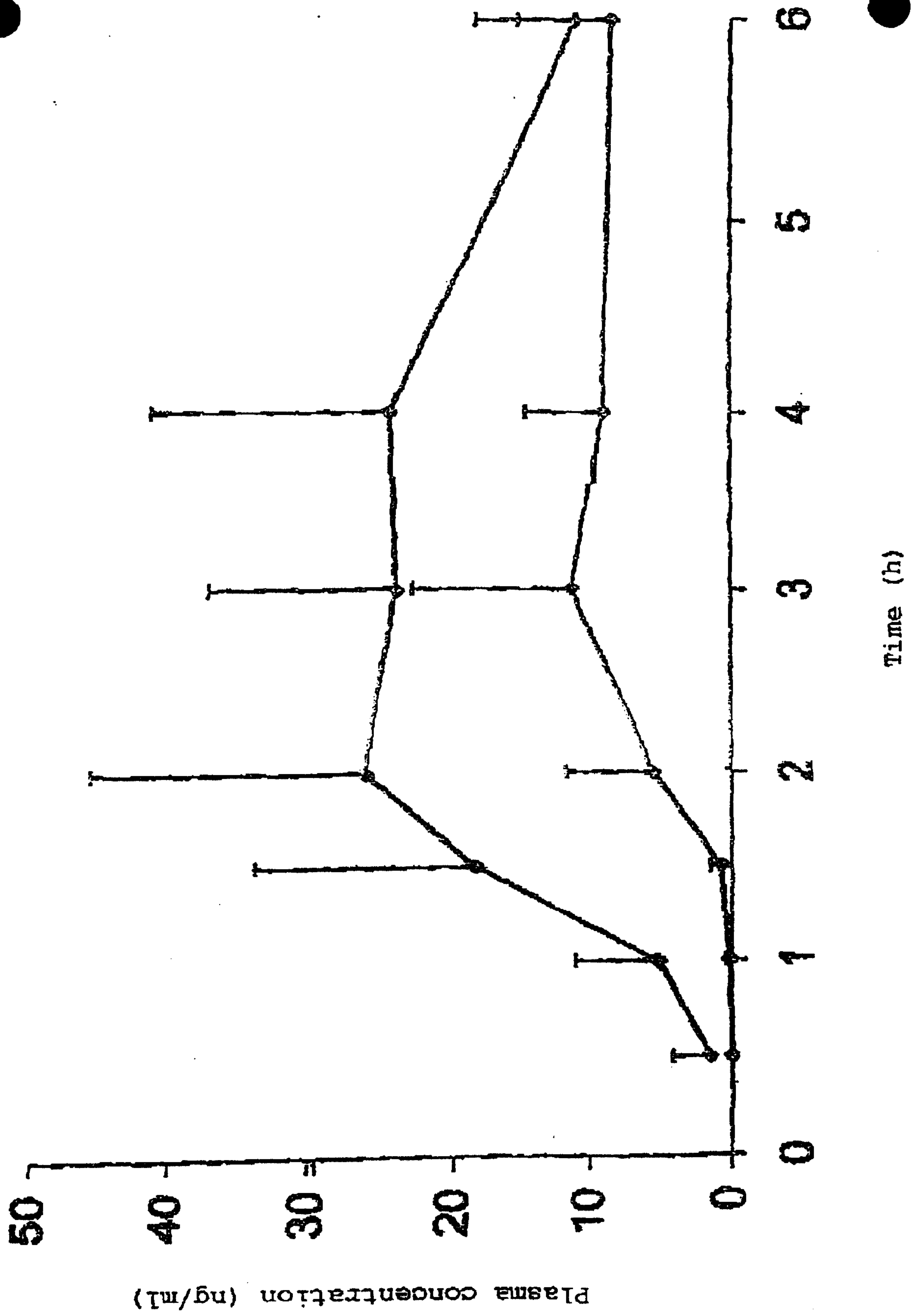


FIGURE 11

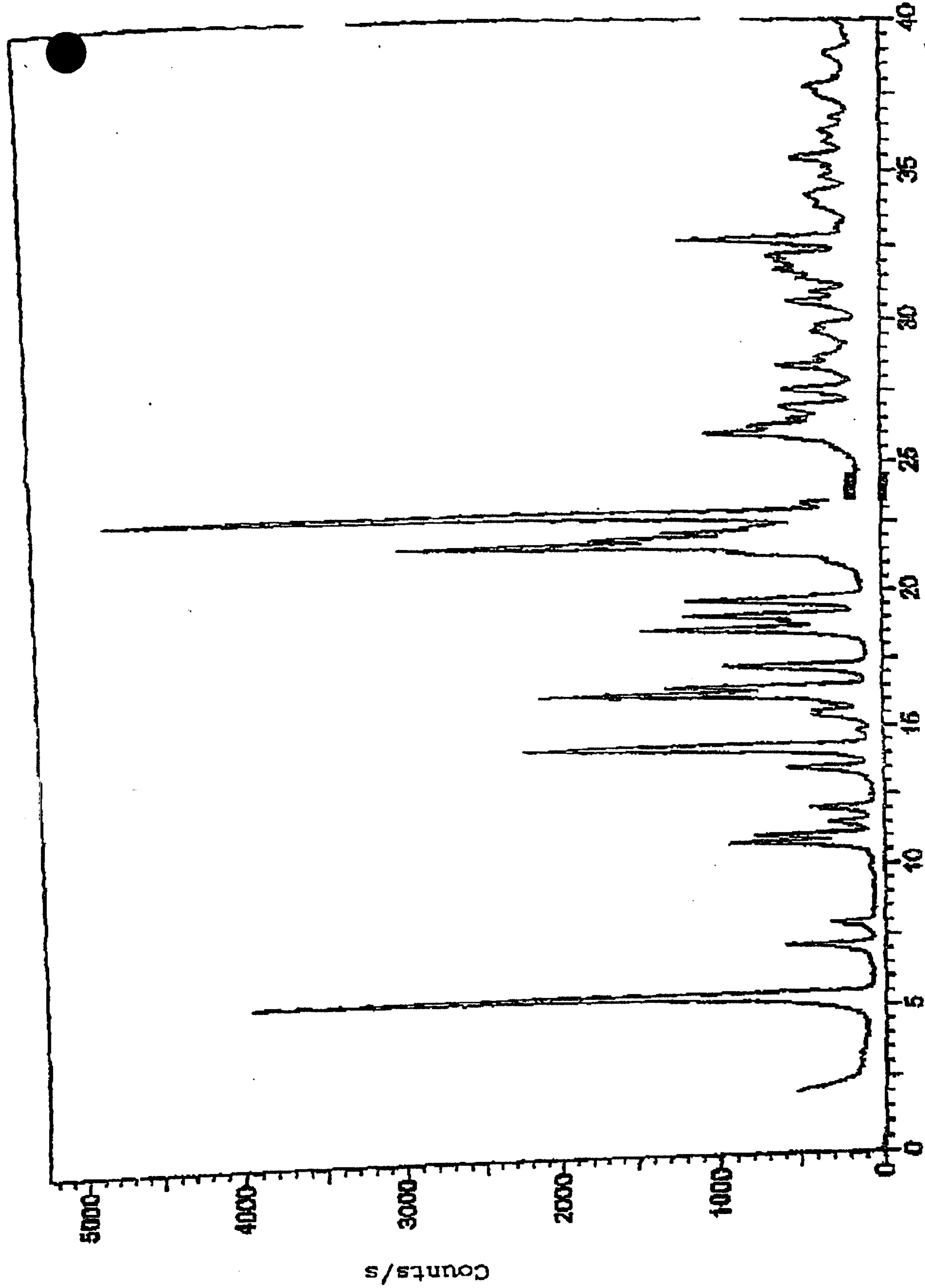


FIGURE 12

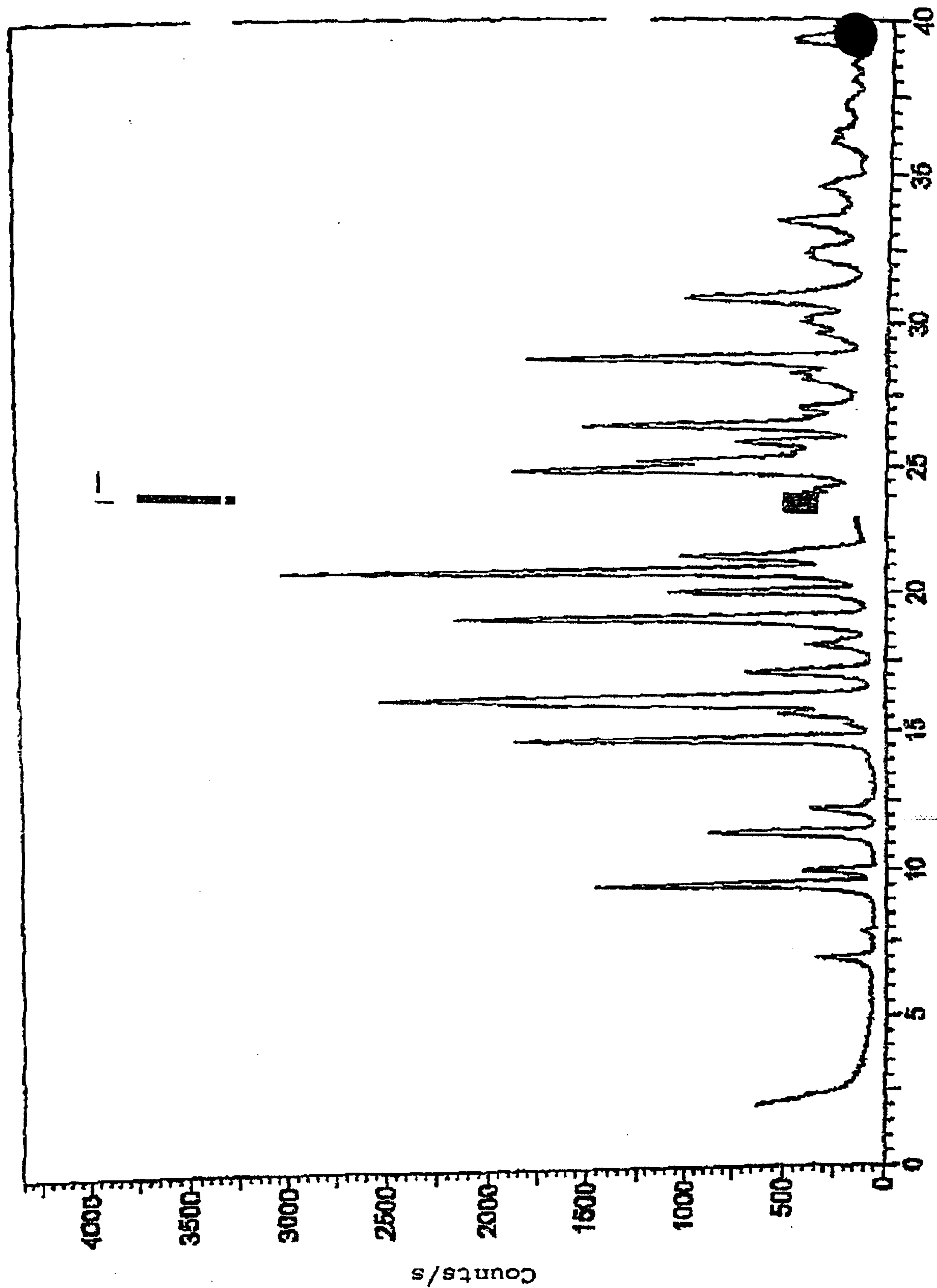


FIGURE 13

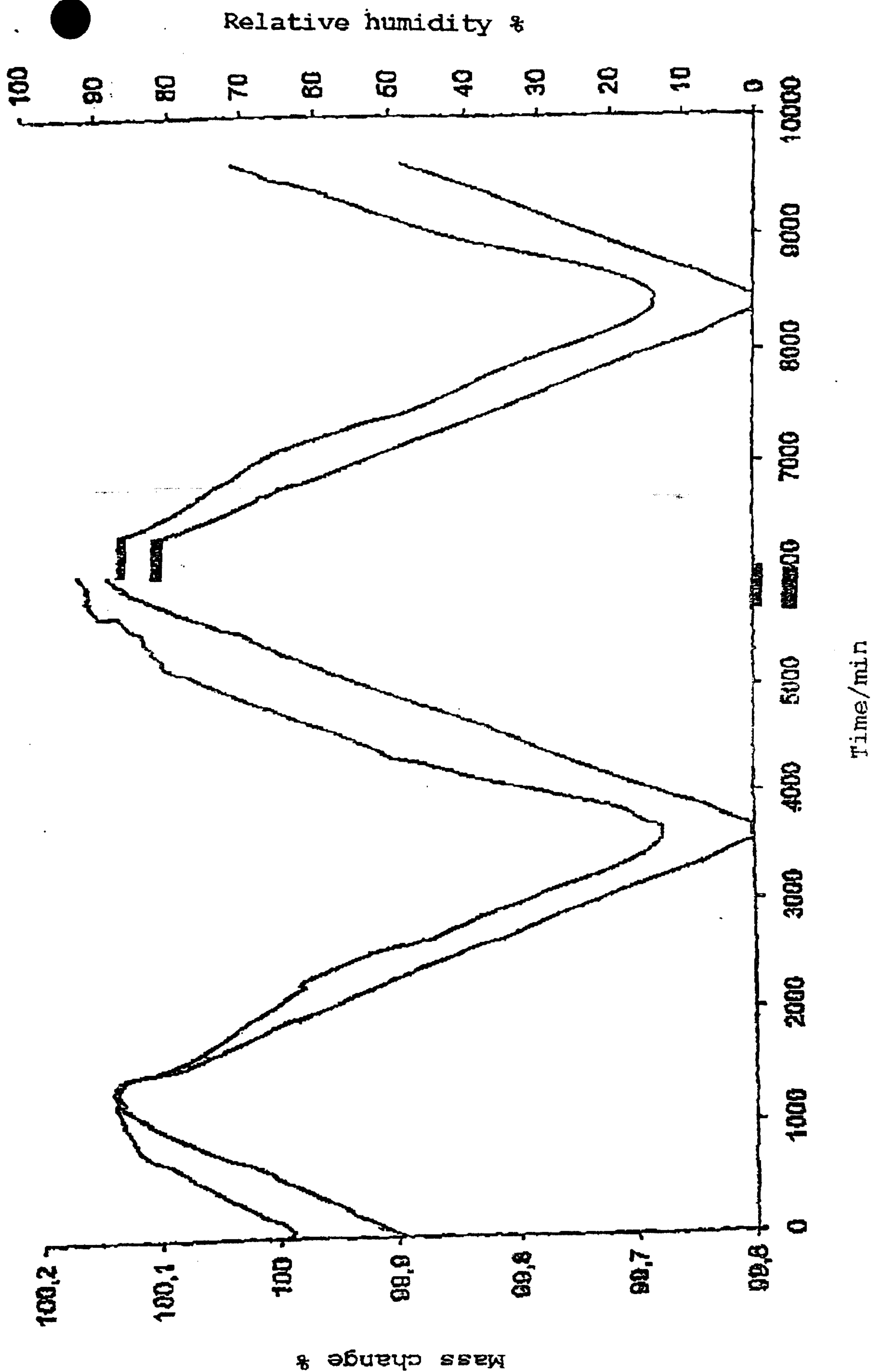


FIGURA 14

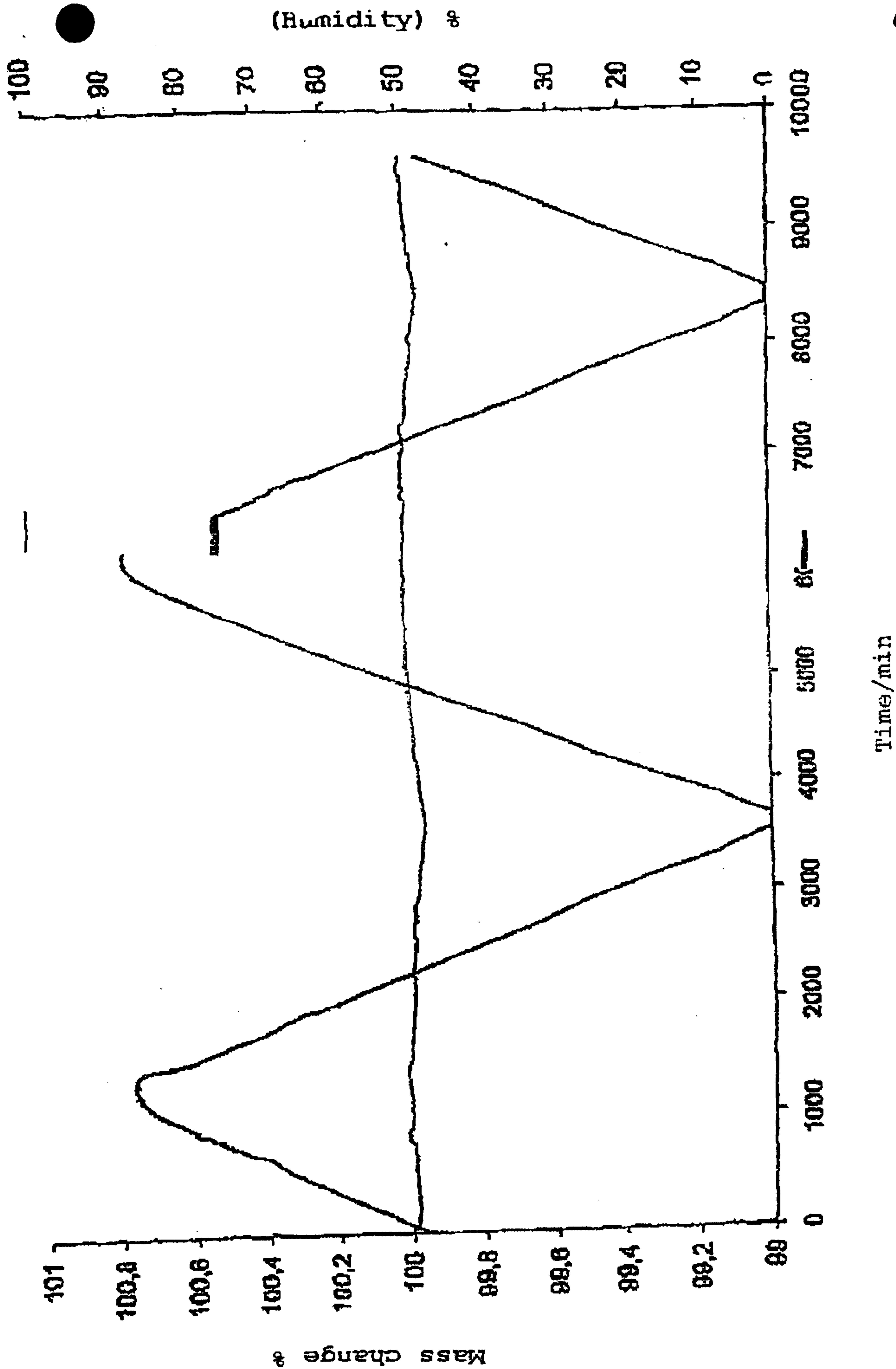


FIGURE 15

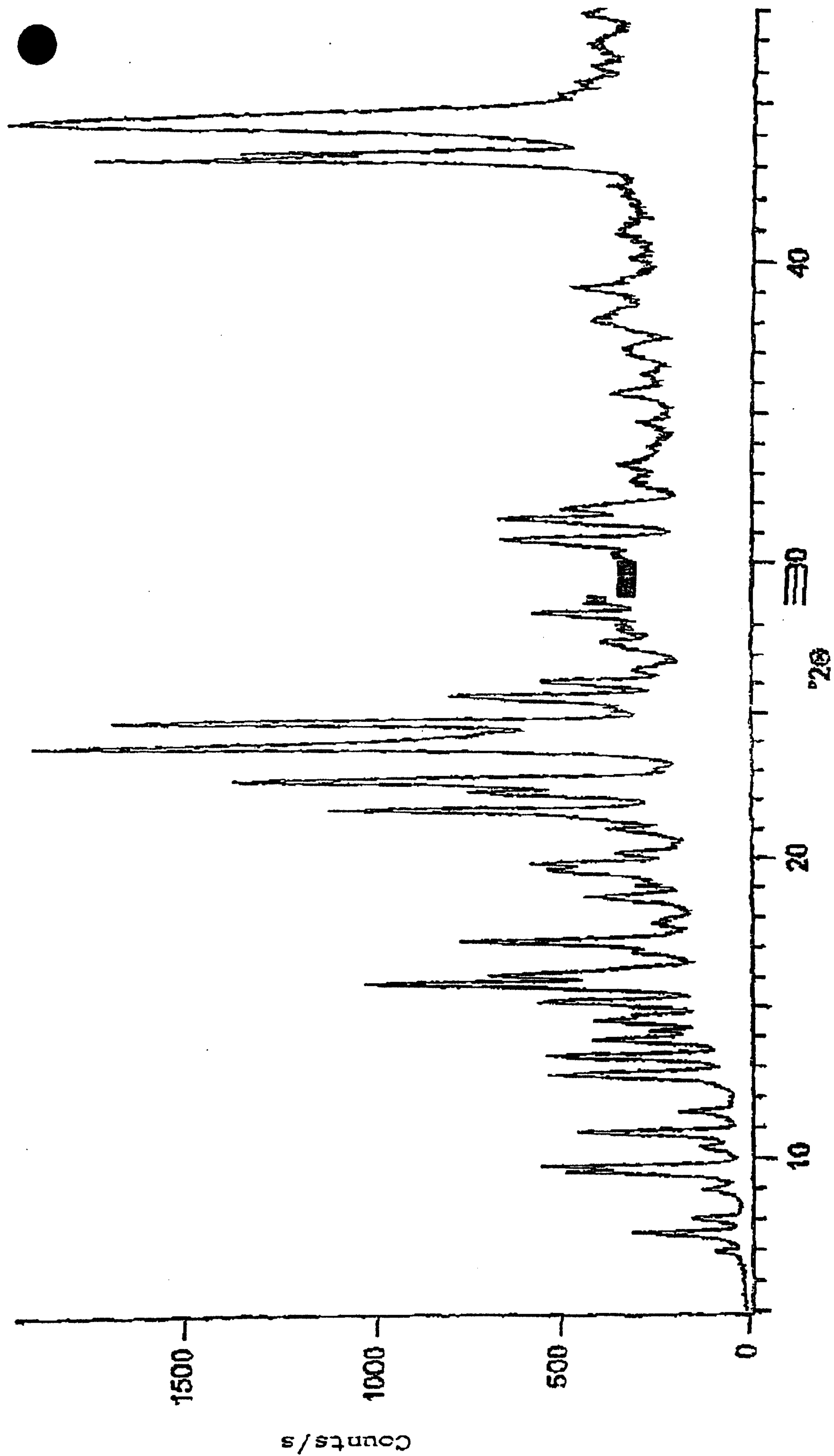


FIGURE 16

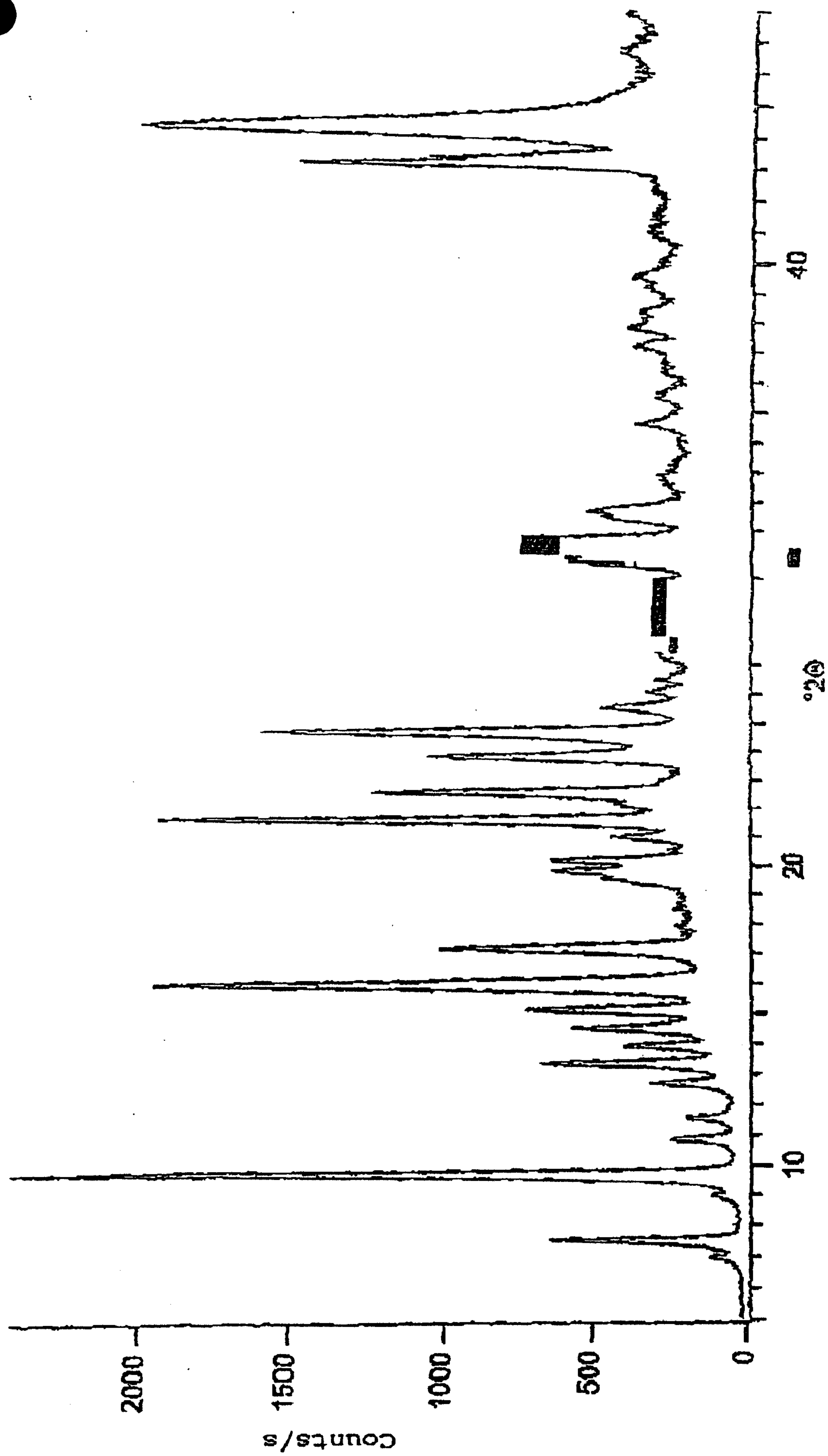


FIGURE 17

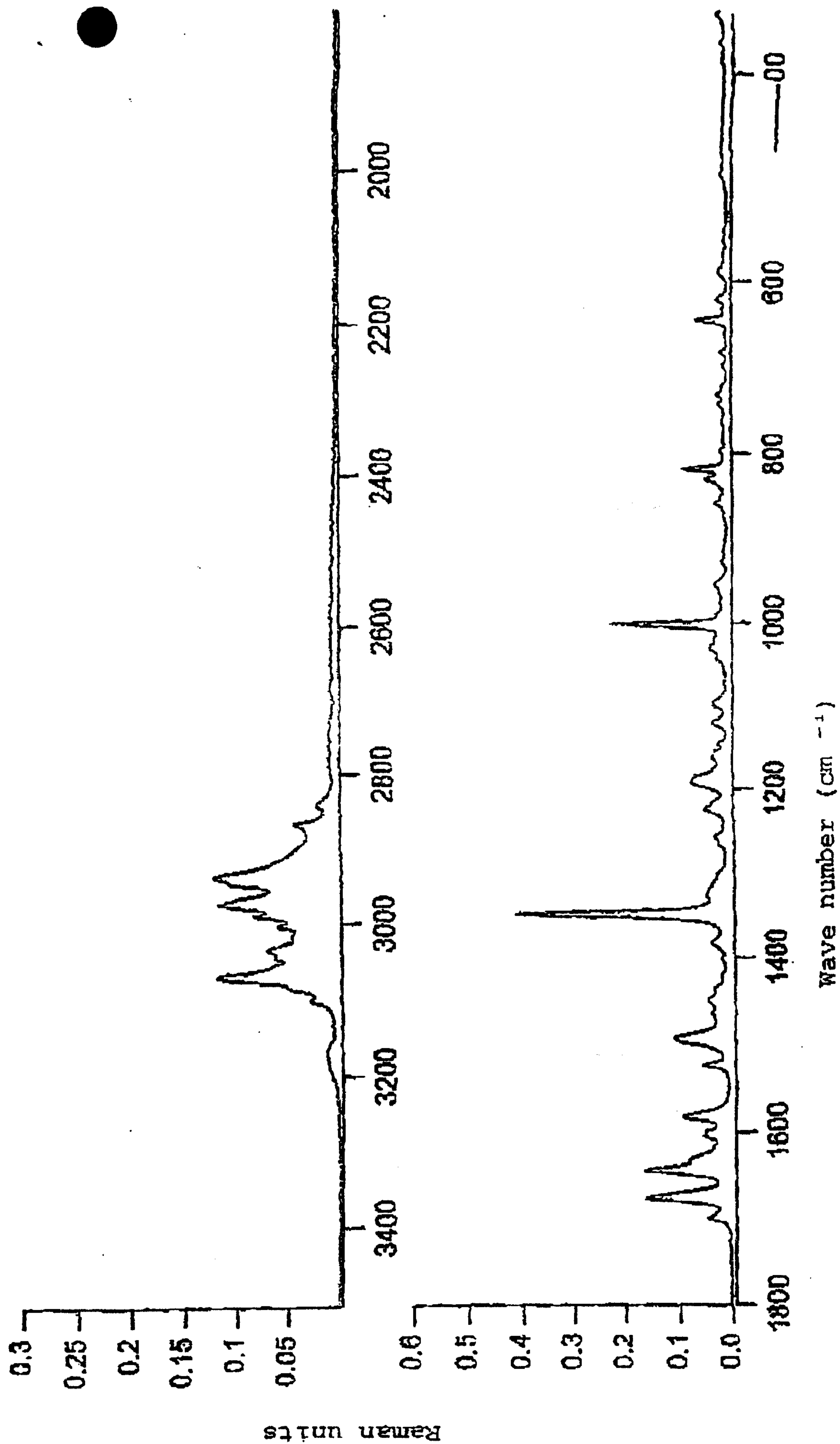


FIGURE 18

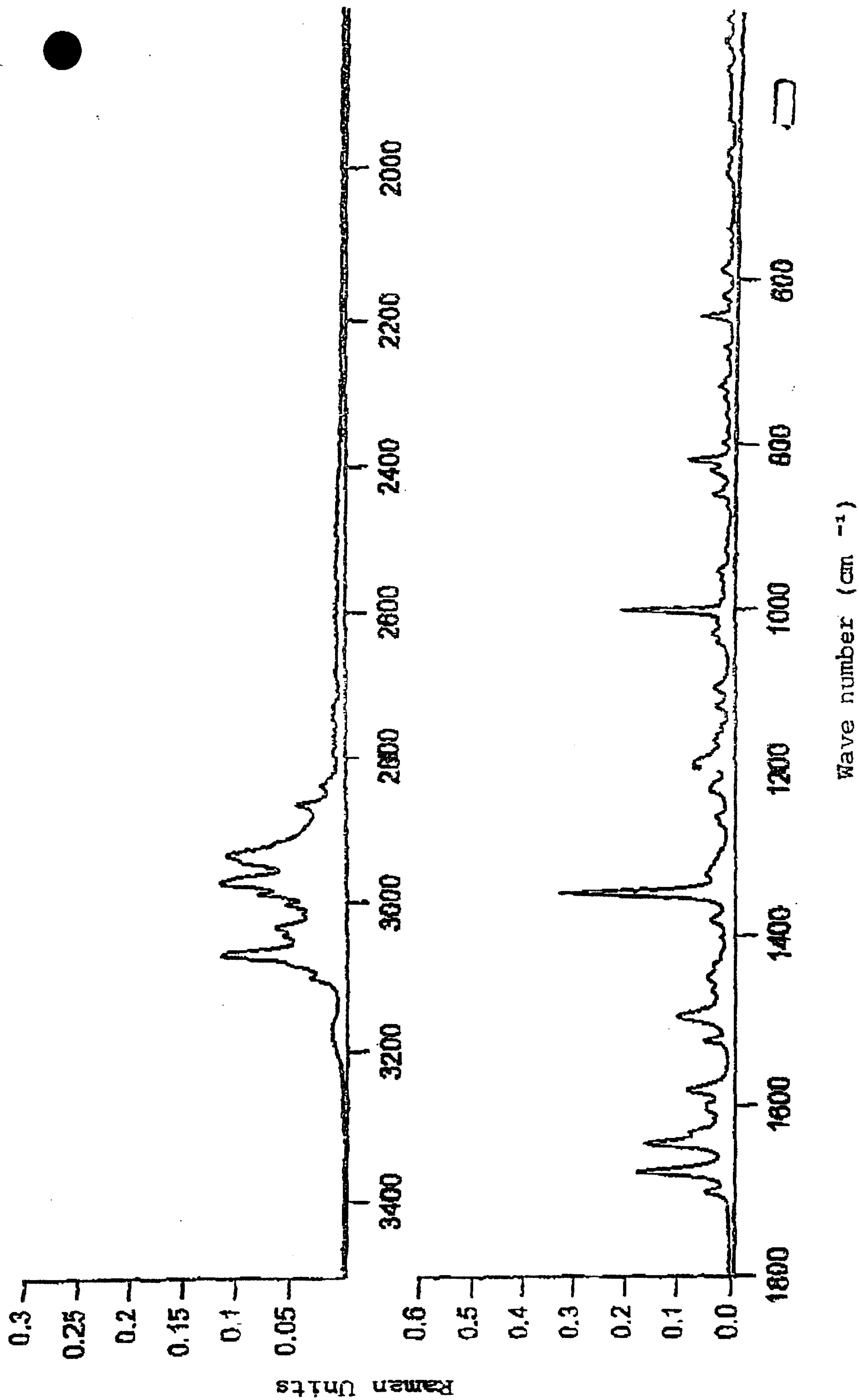
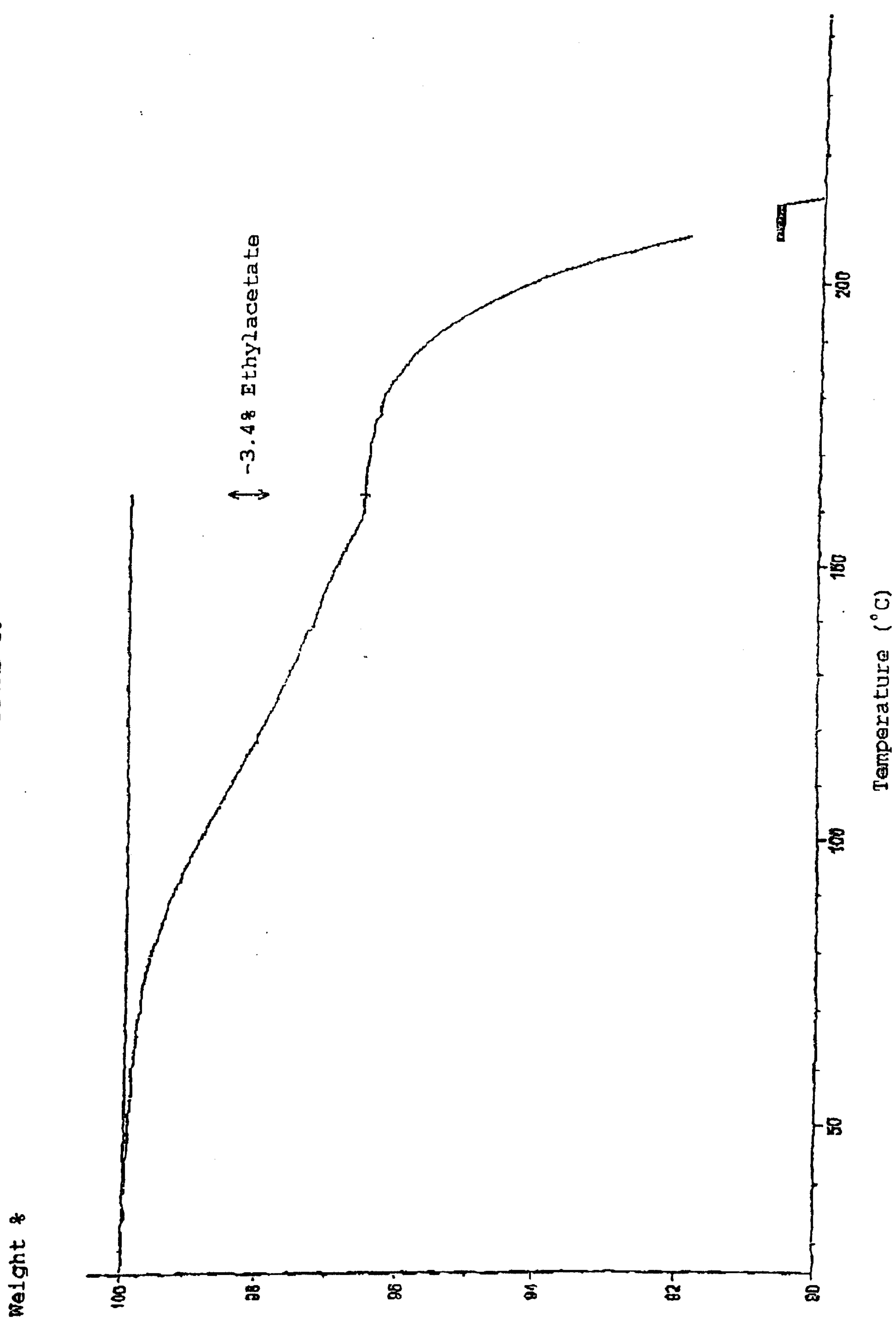


FIGURE 19



Weight %

FIGURE 20

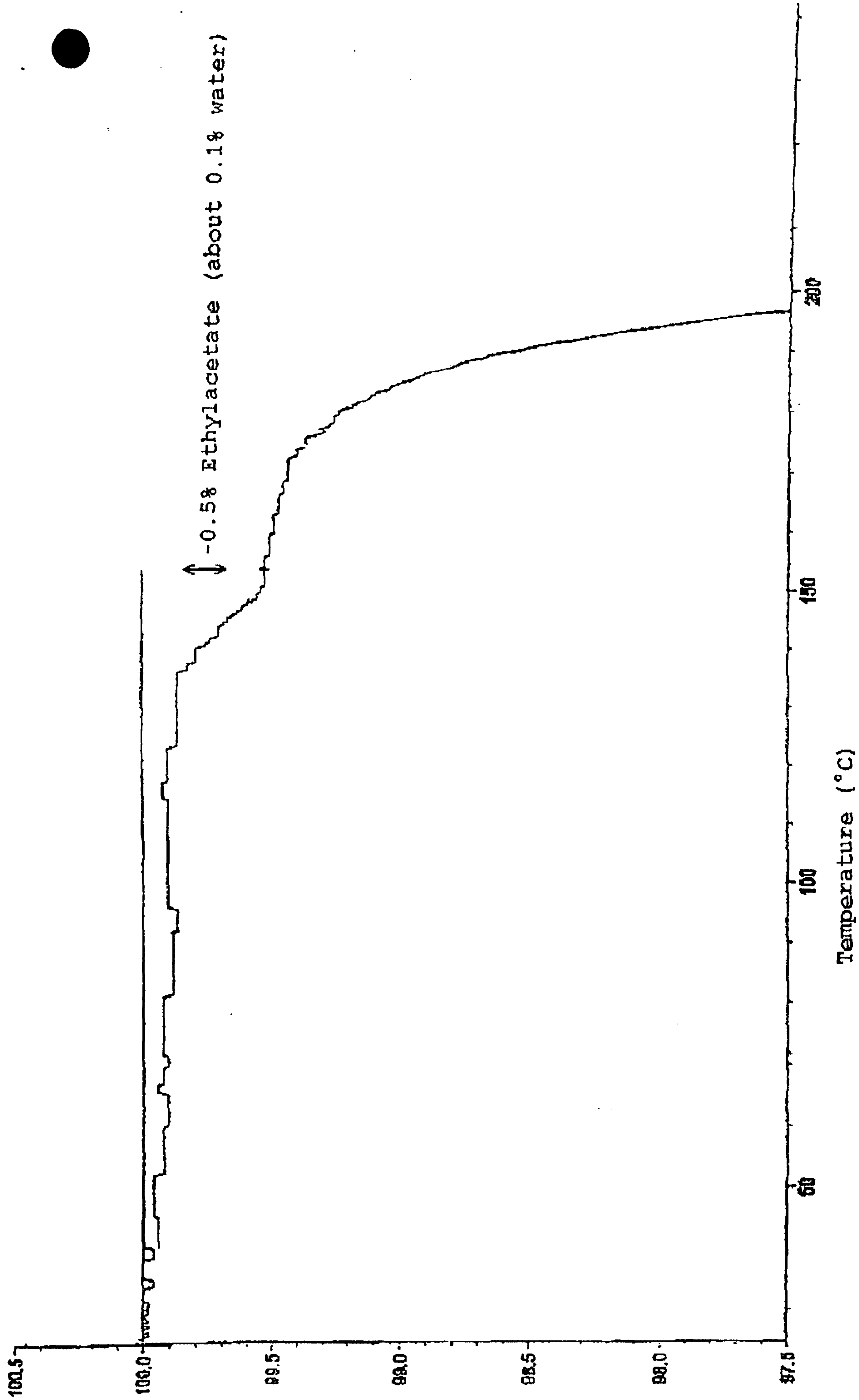


Fig. 21 - LERCANIDIPINE HYDROCHLORIDE/METHYLENE CHLORIDE XRD SPECTRUM

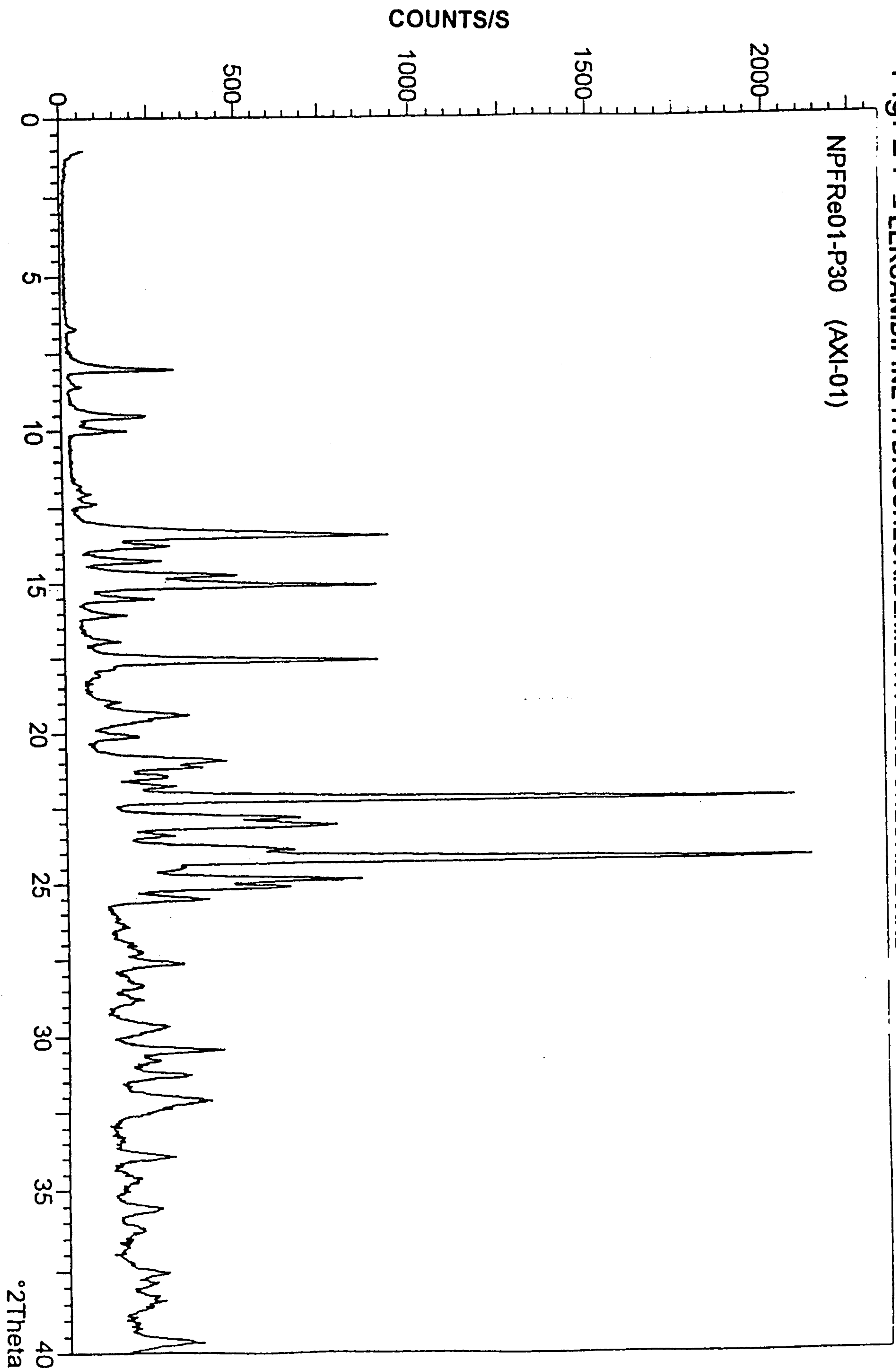


Fig. 22 - LERCANIDIPINE HYDROCHLORIDE FORM (III) XRD SPECTRUM

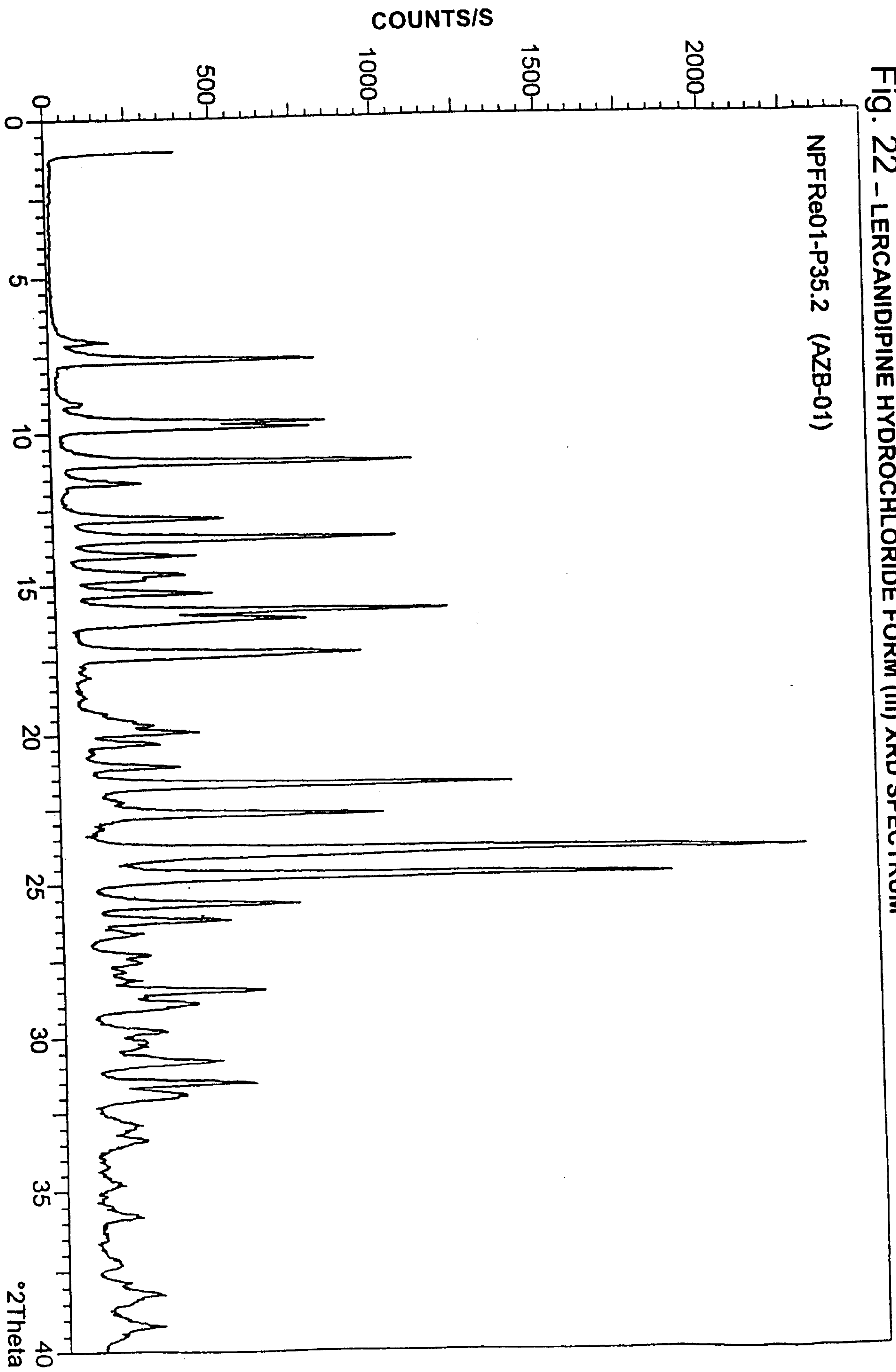


Fig. 23 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/METHYLENE CHLORIDE
THERMOGRAVIMETRIC ANALYSIS

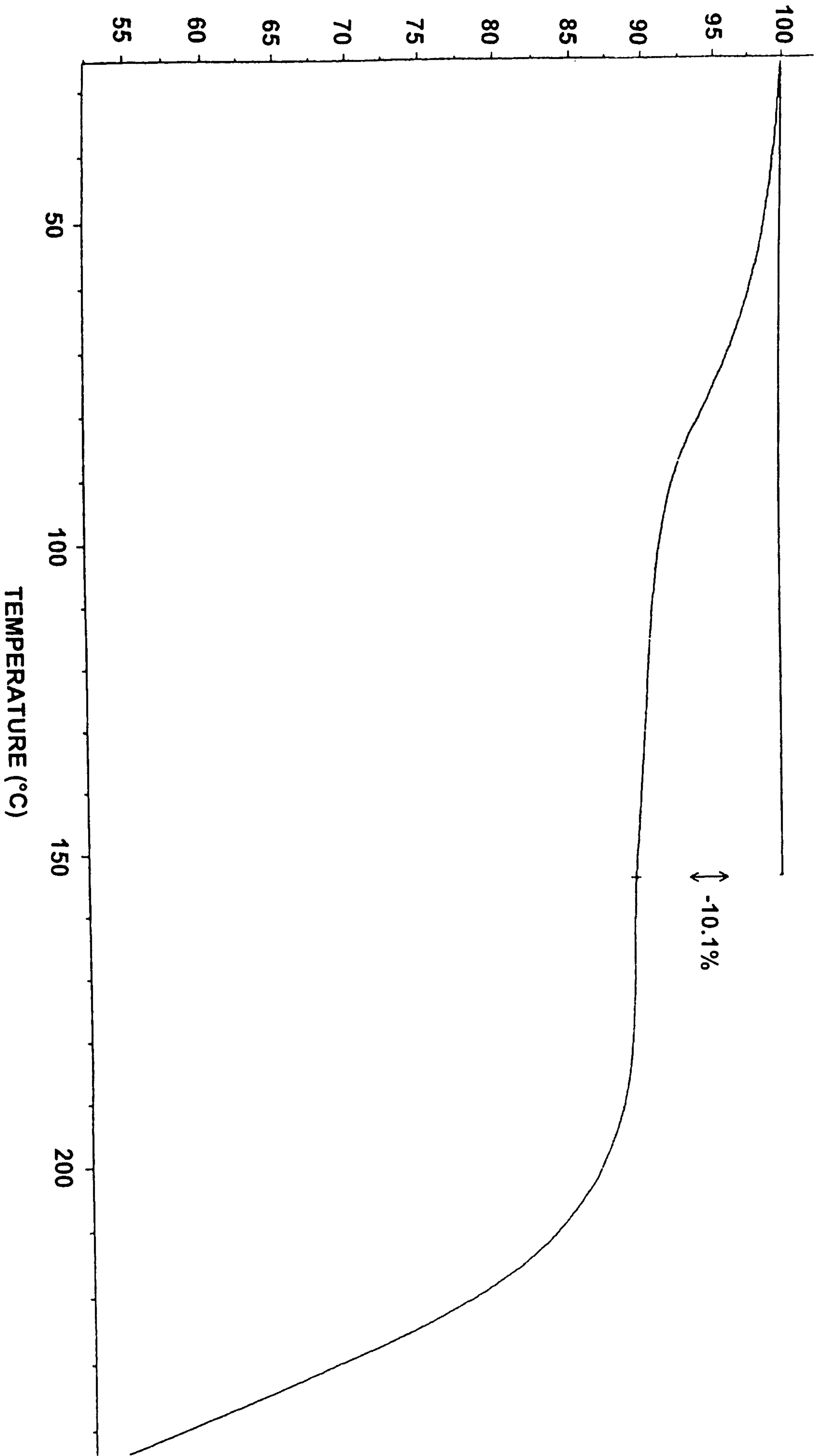


Fig. 24 - LERCANIDIPINE HYDROCHLORIDE FORM (III) THERMOGRAVIMETRIC ANALYSIS

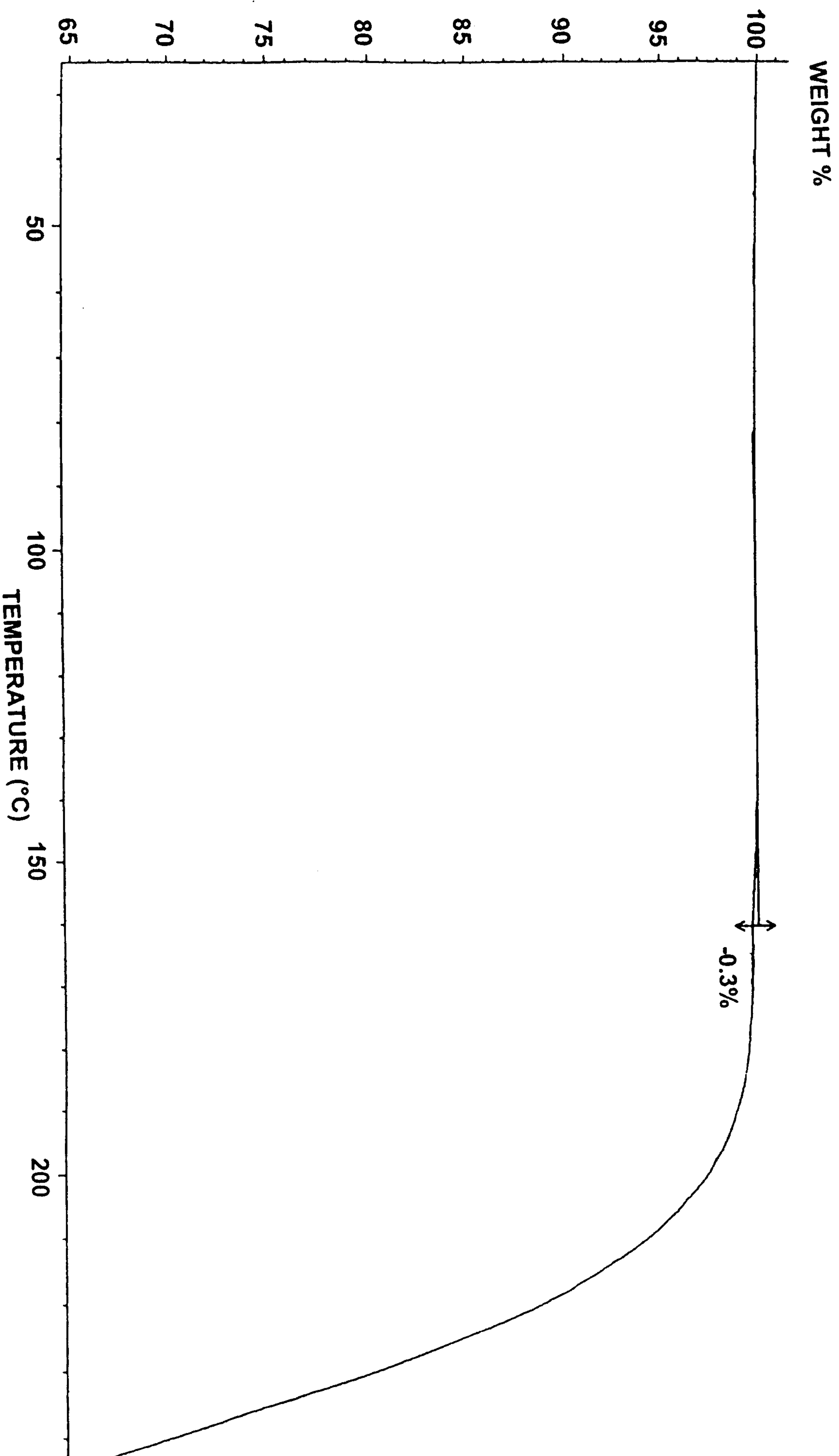


**Fig. 25 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/METHYLENE CHLORIDE
RAMAN SPECTRUM**

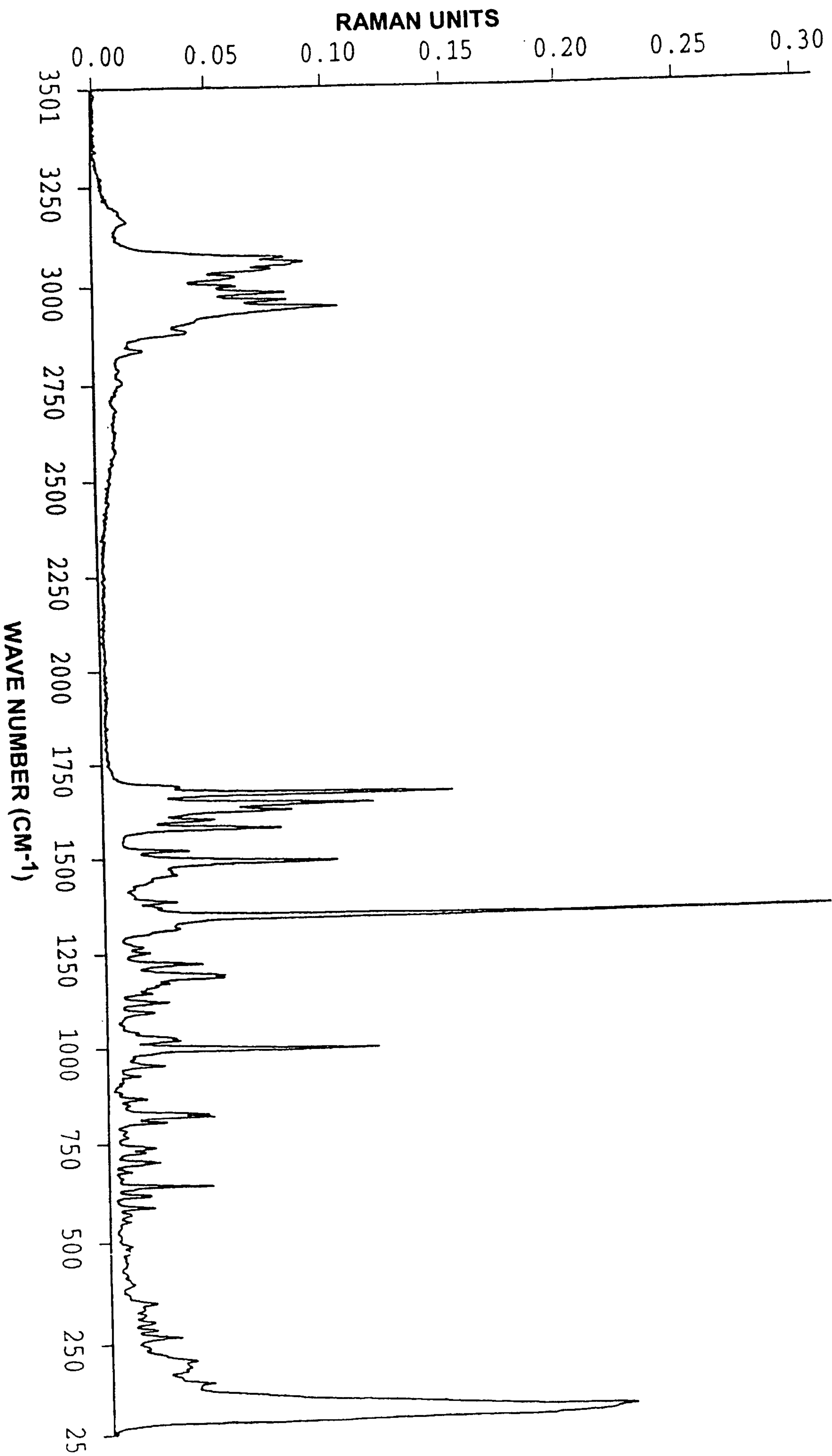
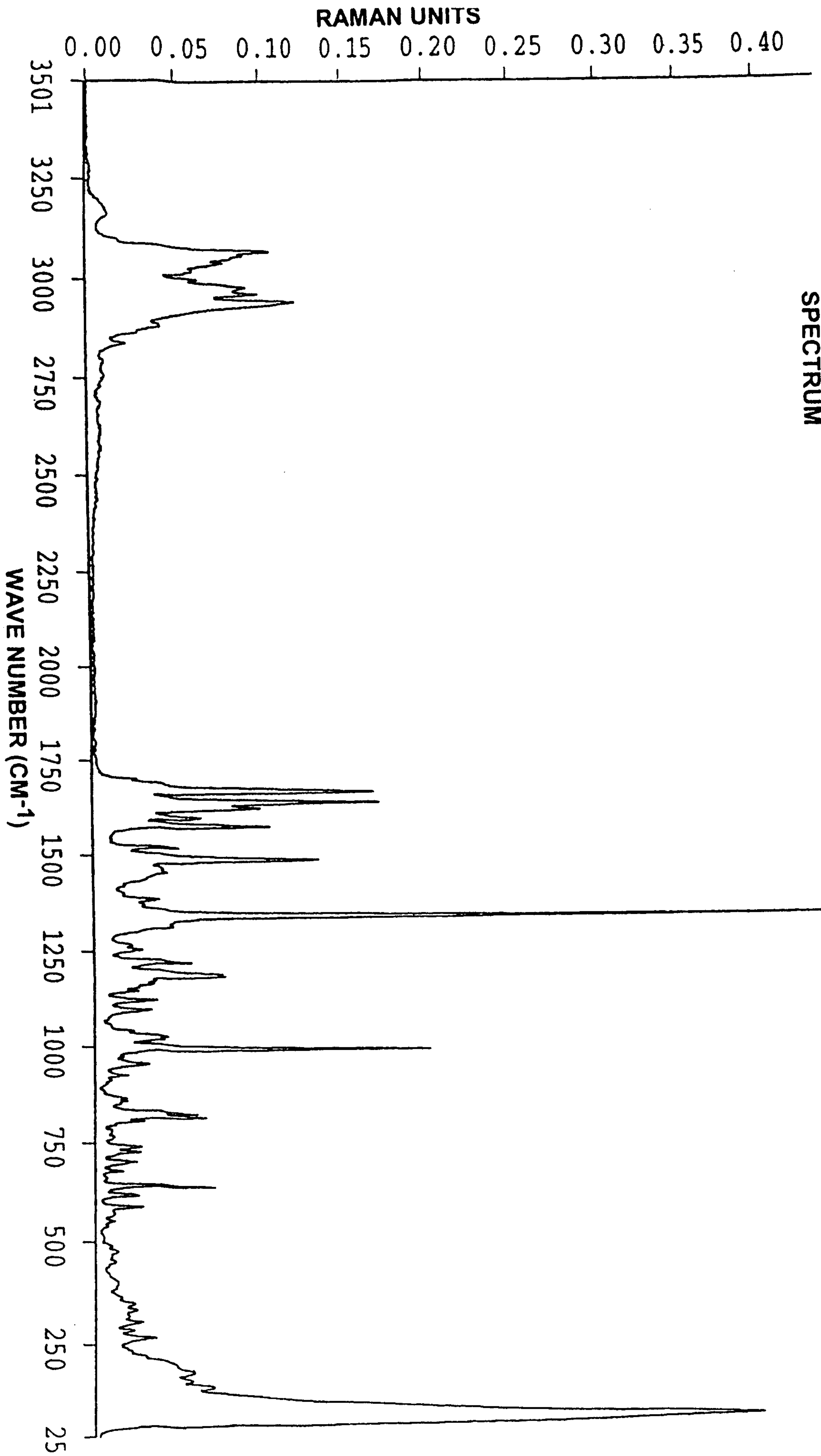


Fig. 26 - LERCANIDIPINE HYDROCHLORIDE CRYSTALLINE FORM (III) RAMAN
SPECTRUM



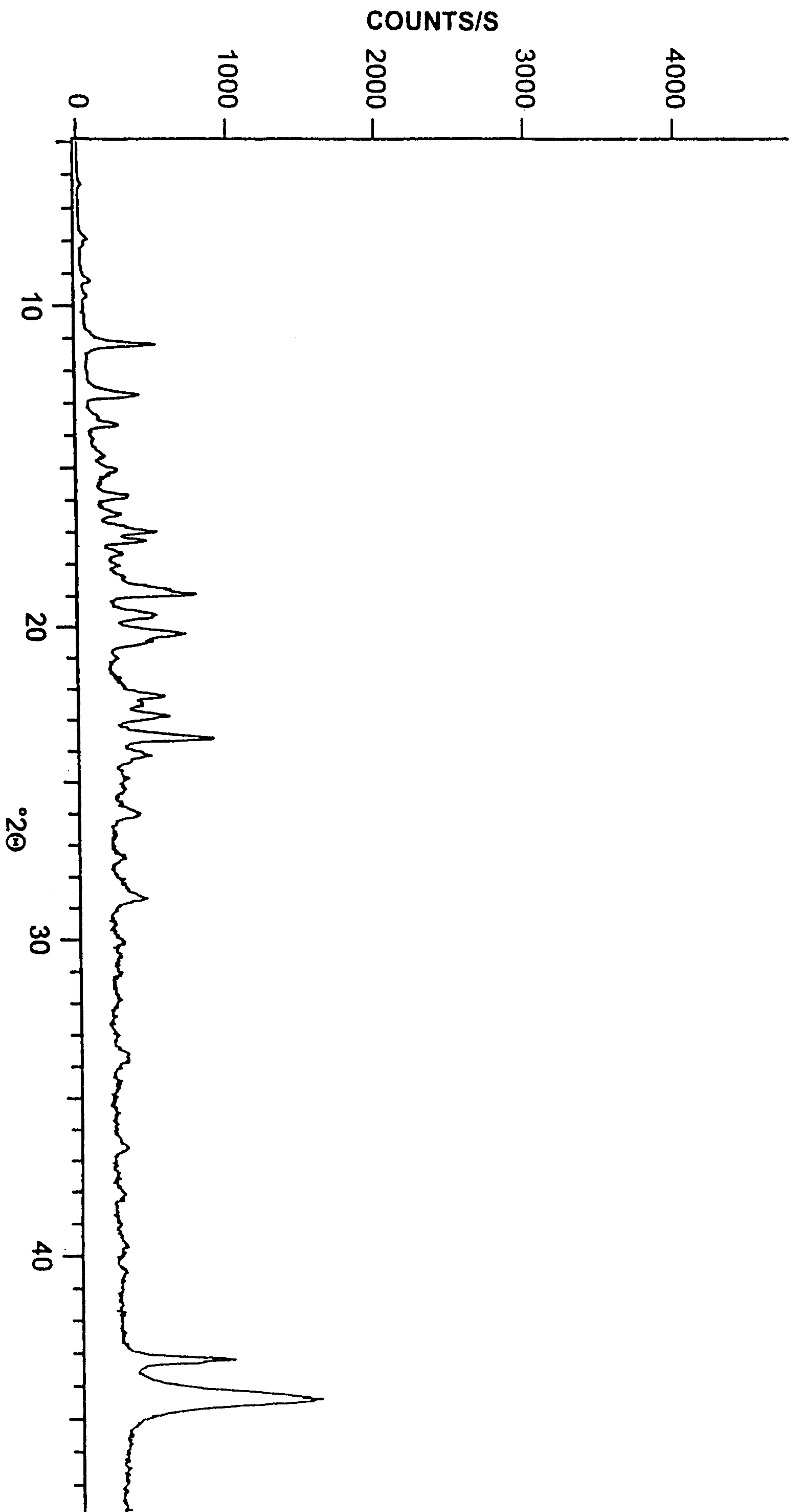


Fig. 27 – LERCANIDIPINE HYDROCHLORIDE FORM IV XRD SPECTRUM

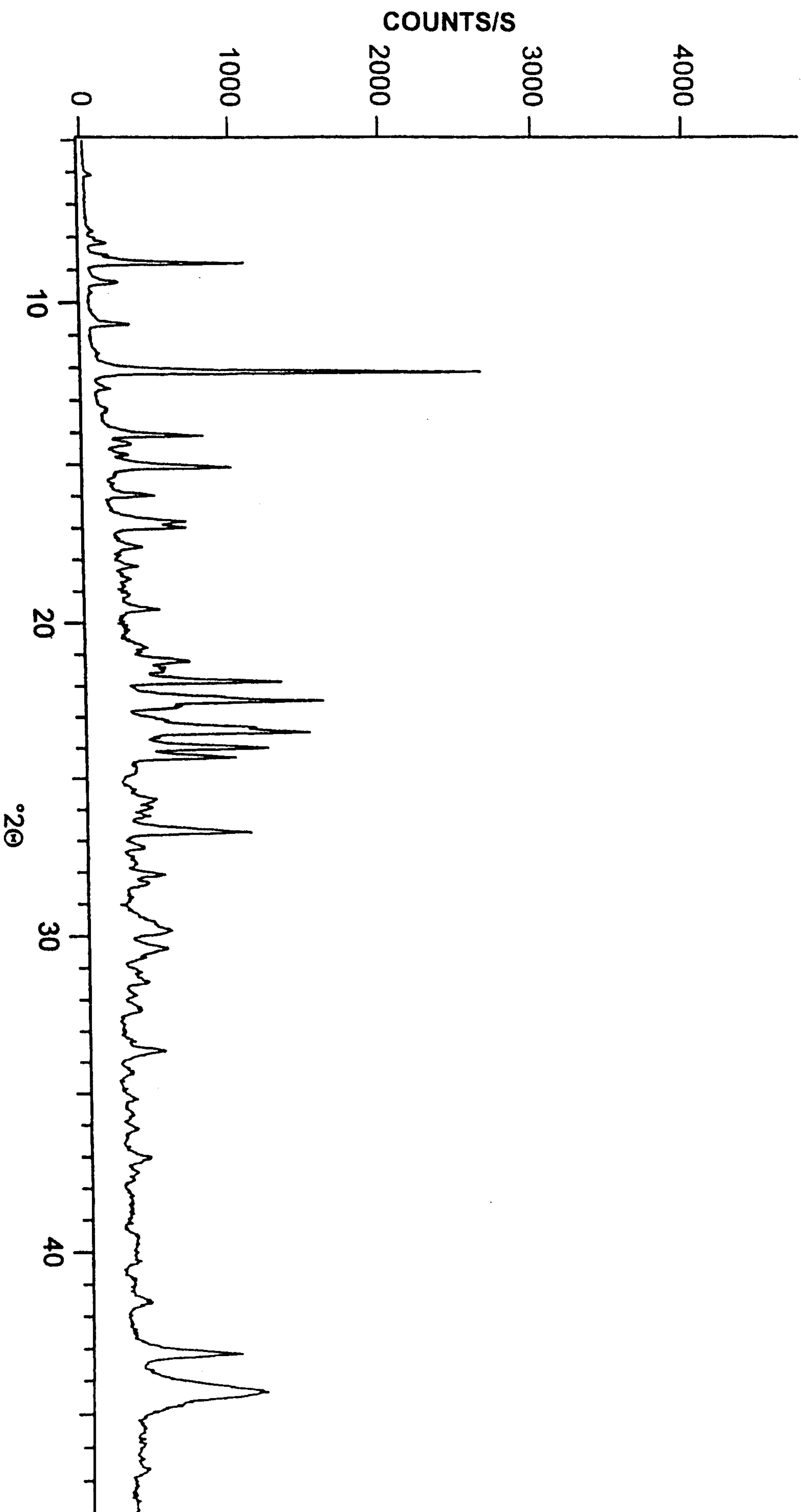
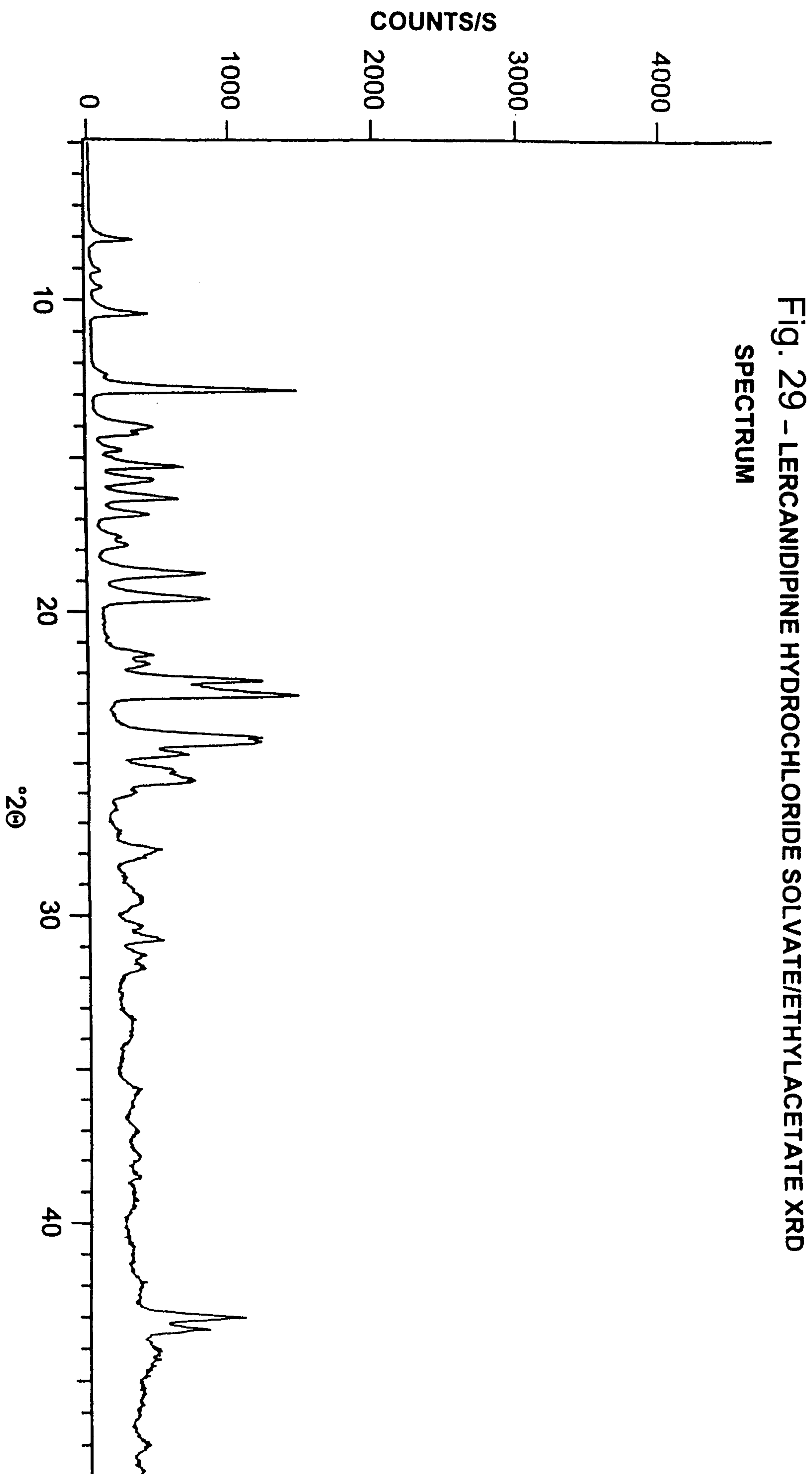


Fig. 28 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/ACETONE XRD SPECTRUM



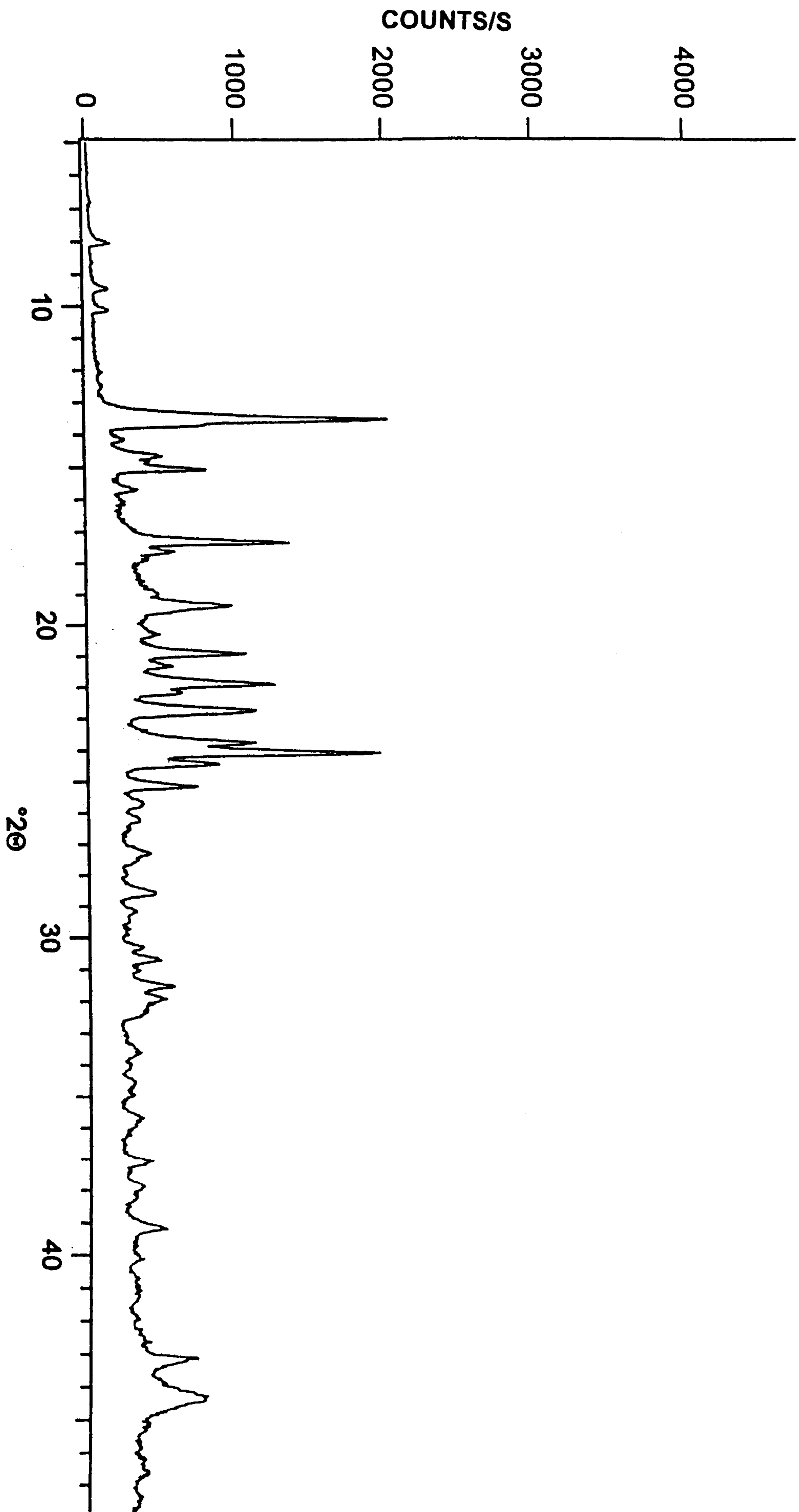


Fig. 30 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/THF XRD SPECTRUM

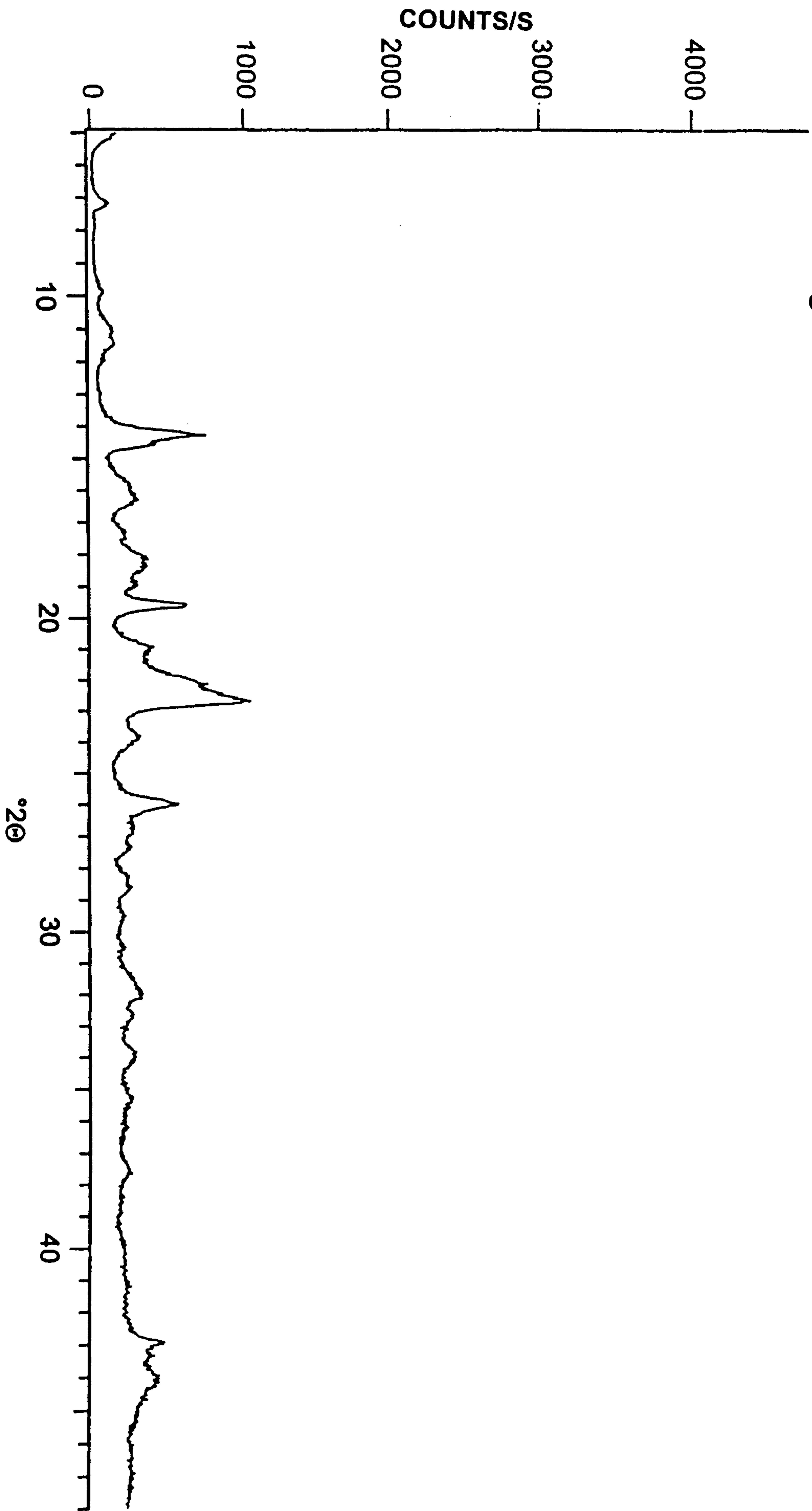


Fig. 31 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/TMBE XRD SPECTRUM

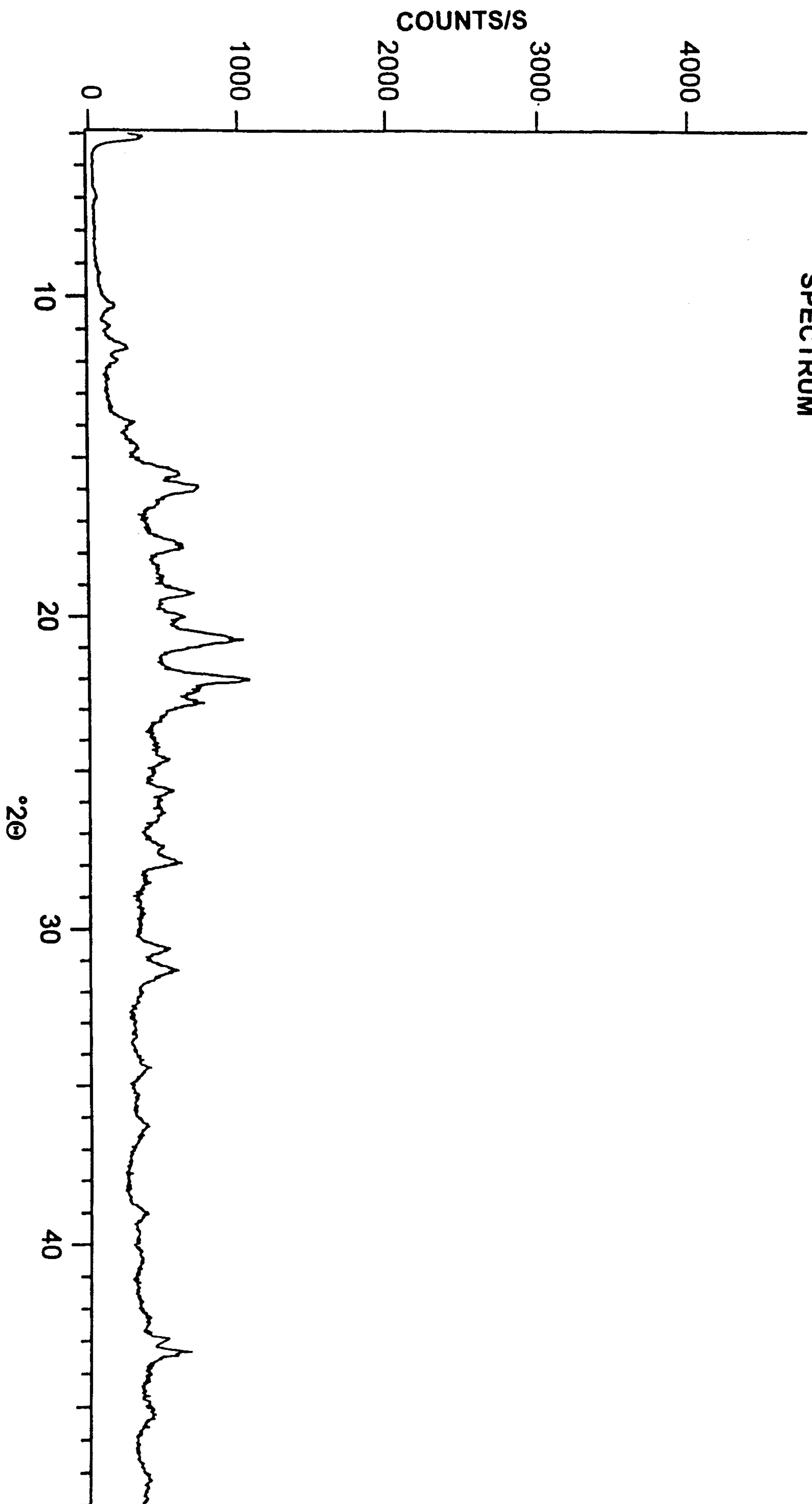
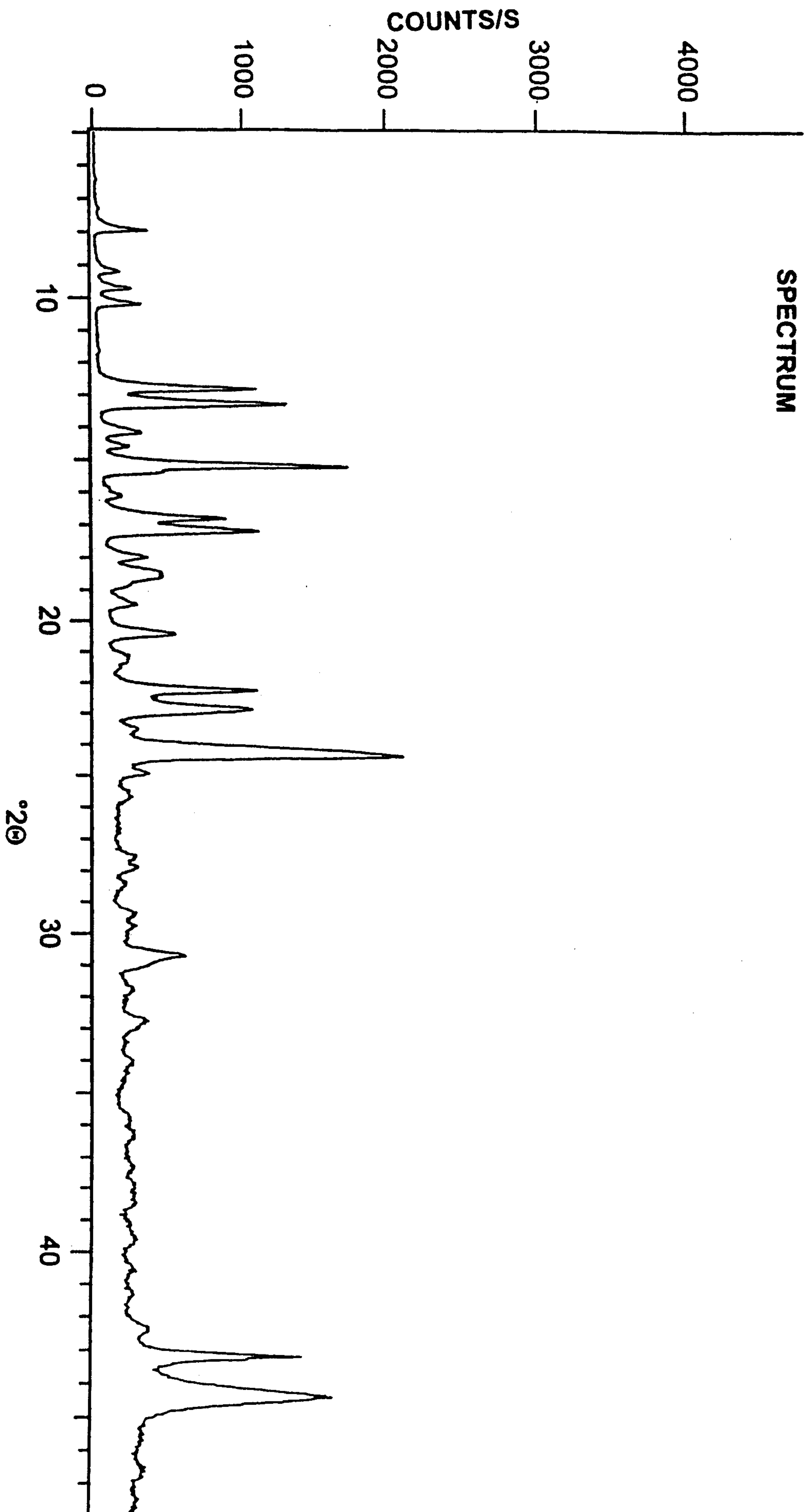


Fig. 32 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/ANISOLE FORM (A) XRD SPECTRUM



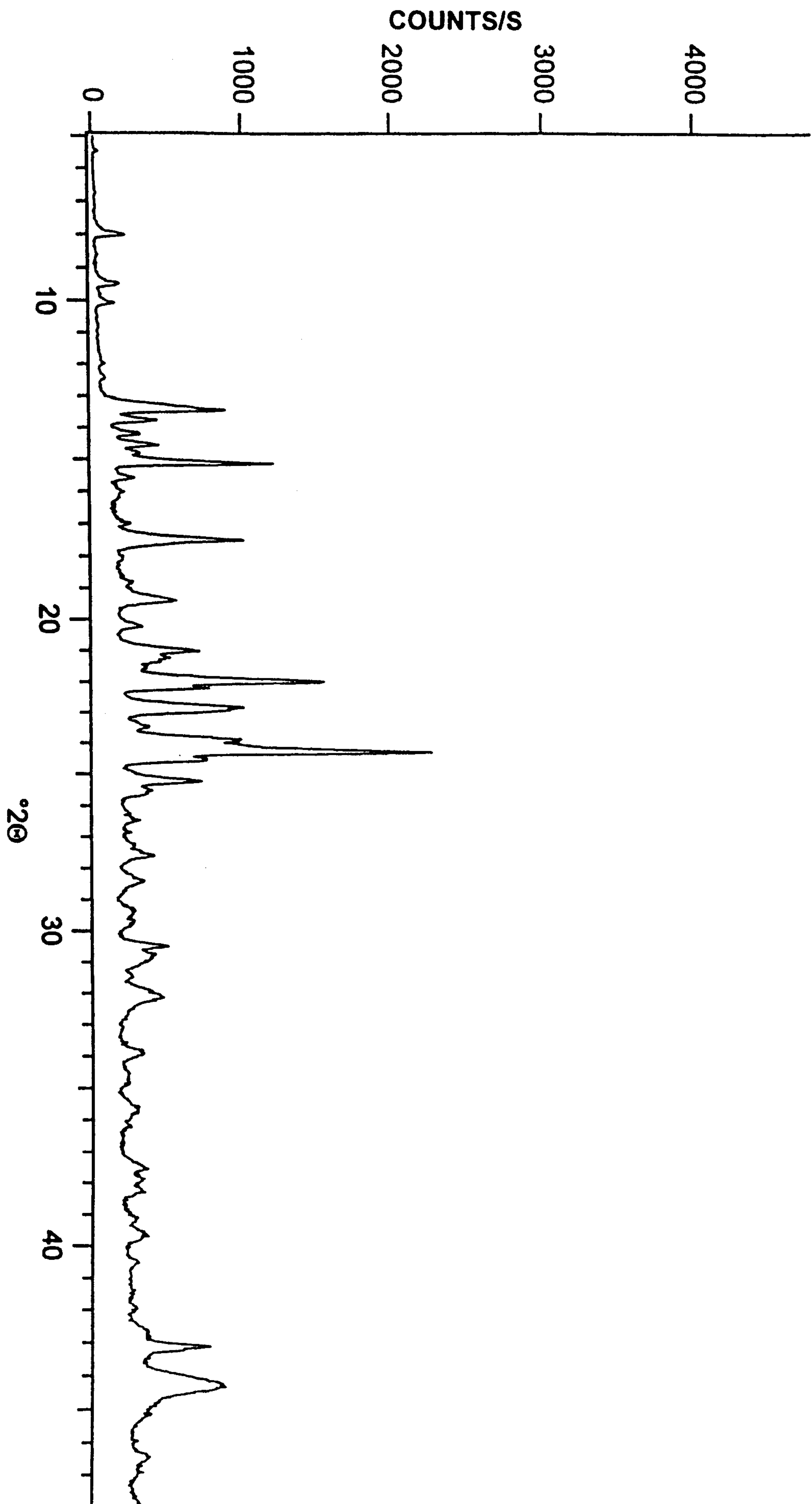


Fig. 34 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/ISOPROPYL ALCOHOL XRD SPECTRUM

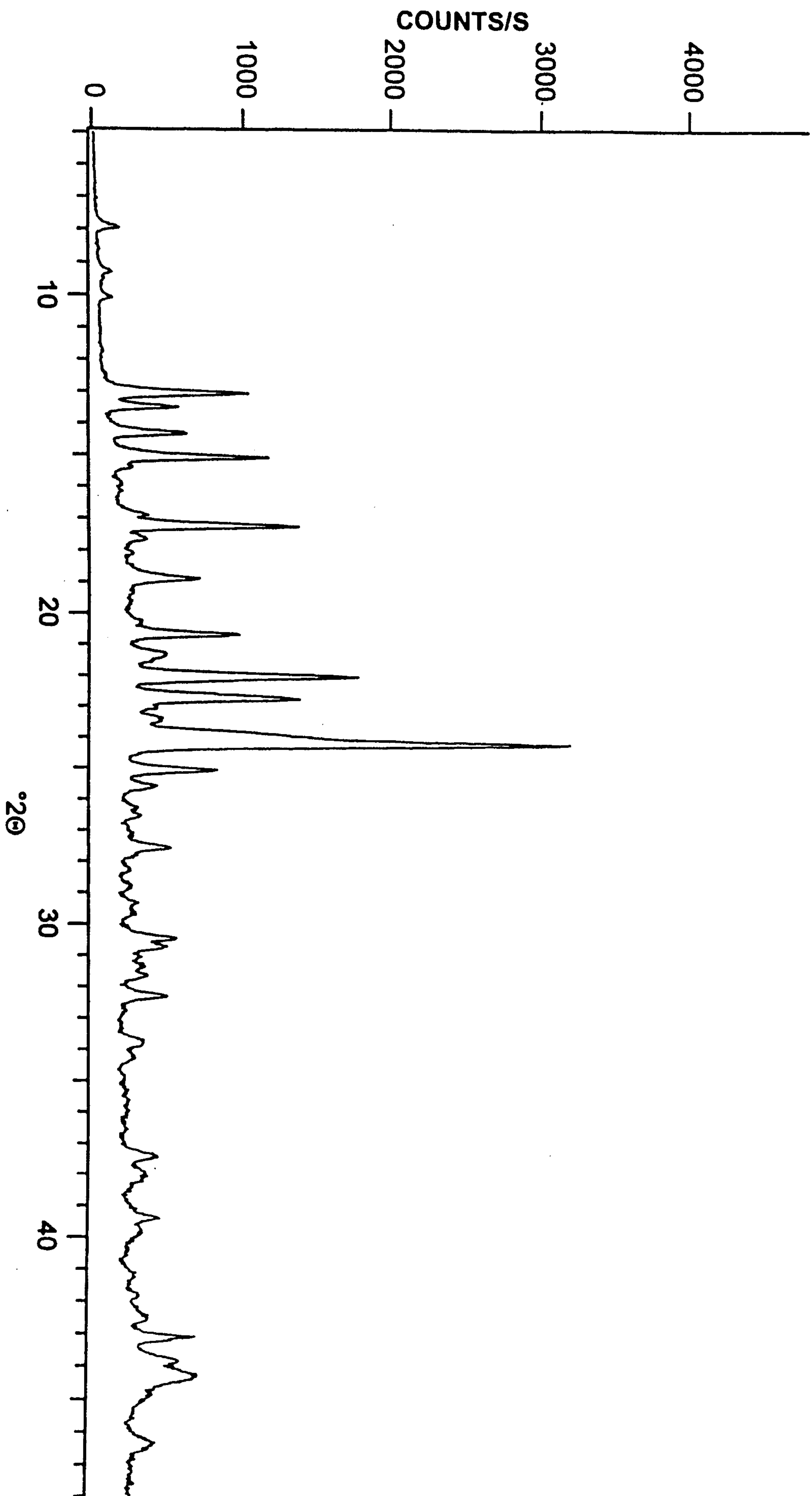


Fig. 35 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/ISOBUTYL ALCOHOL XRD SPECTRUM

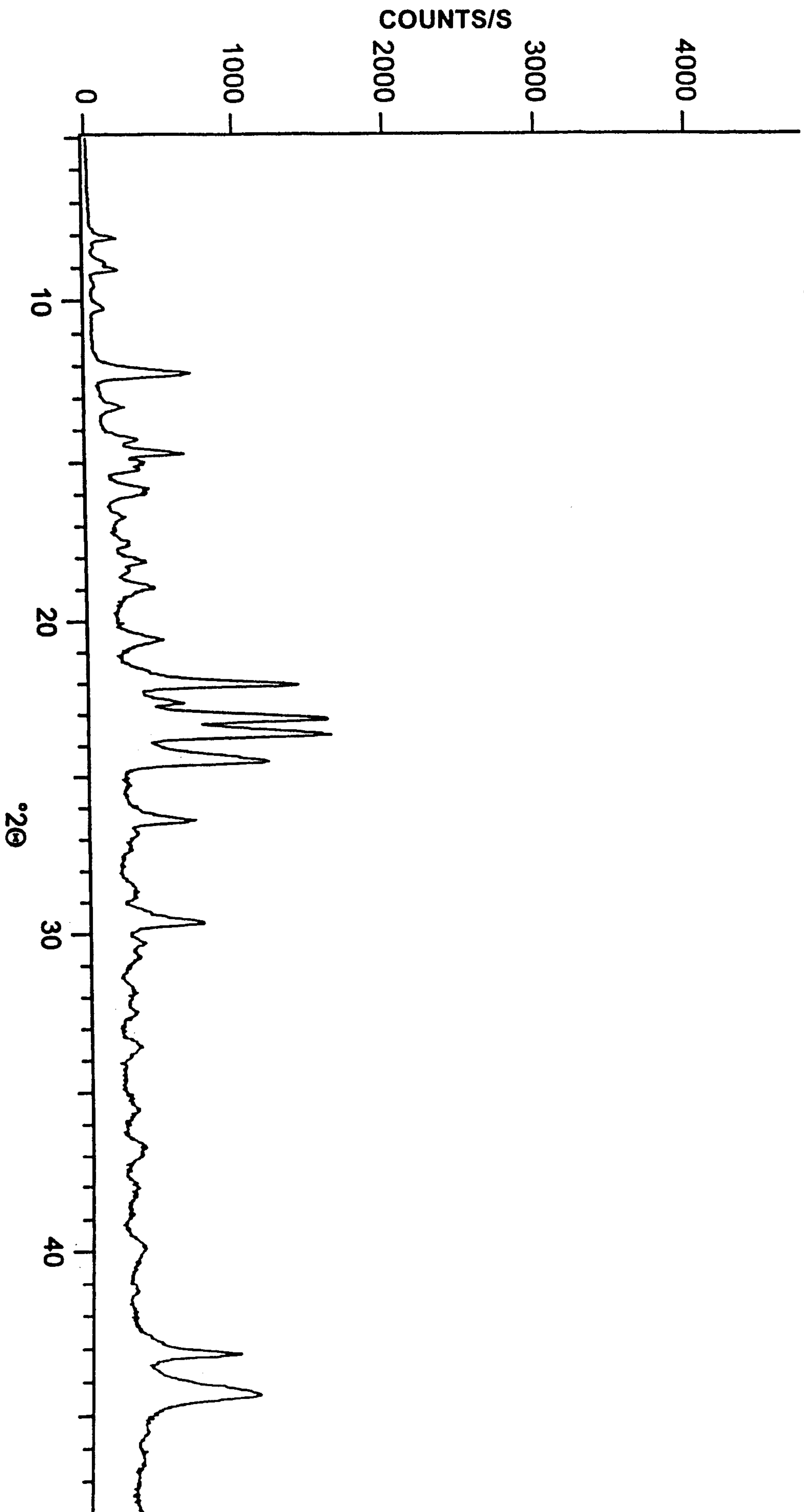


Fig. 36 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/HEPTANE XRD SPECTRUM

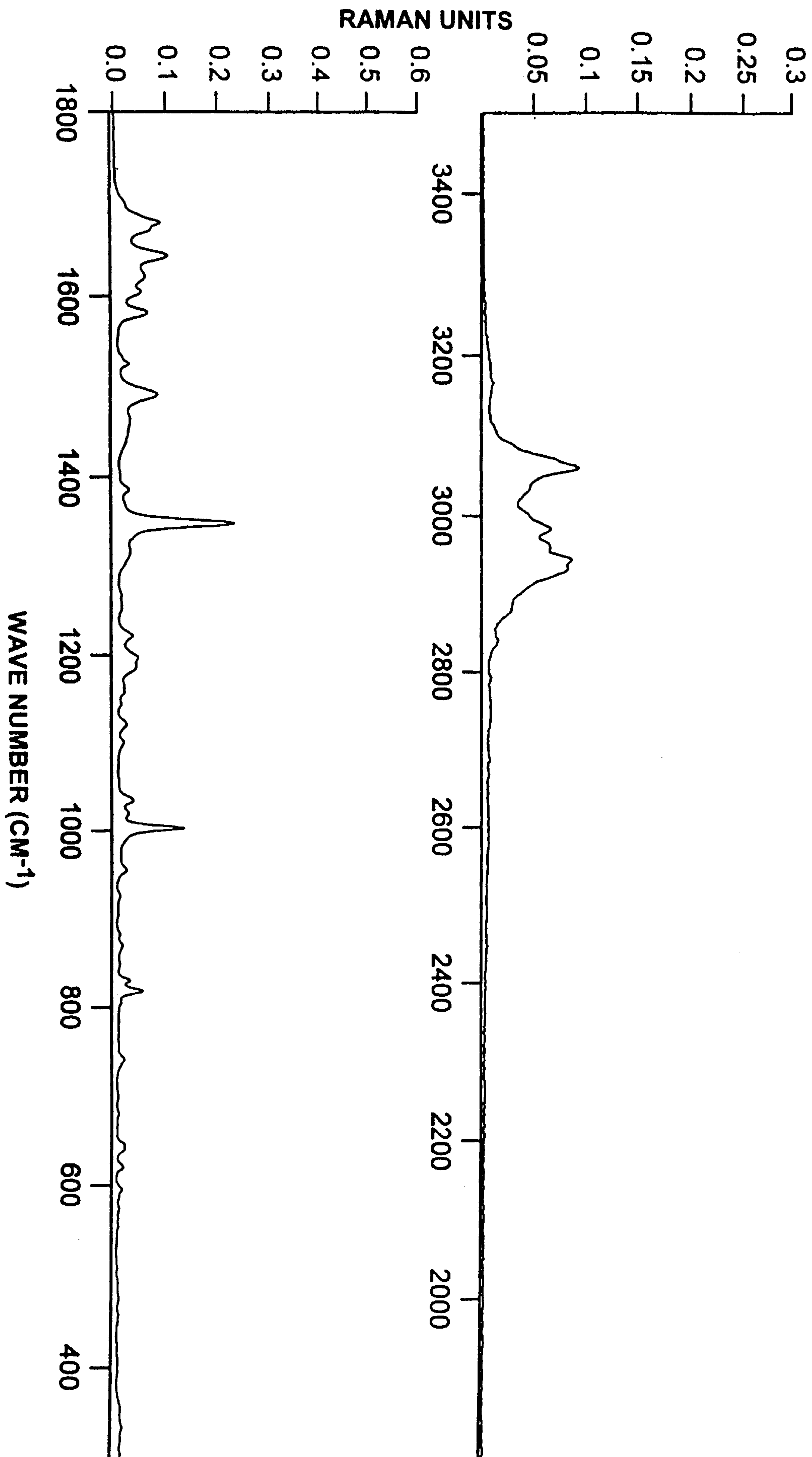
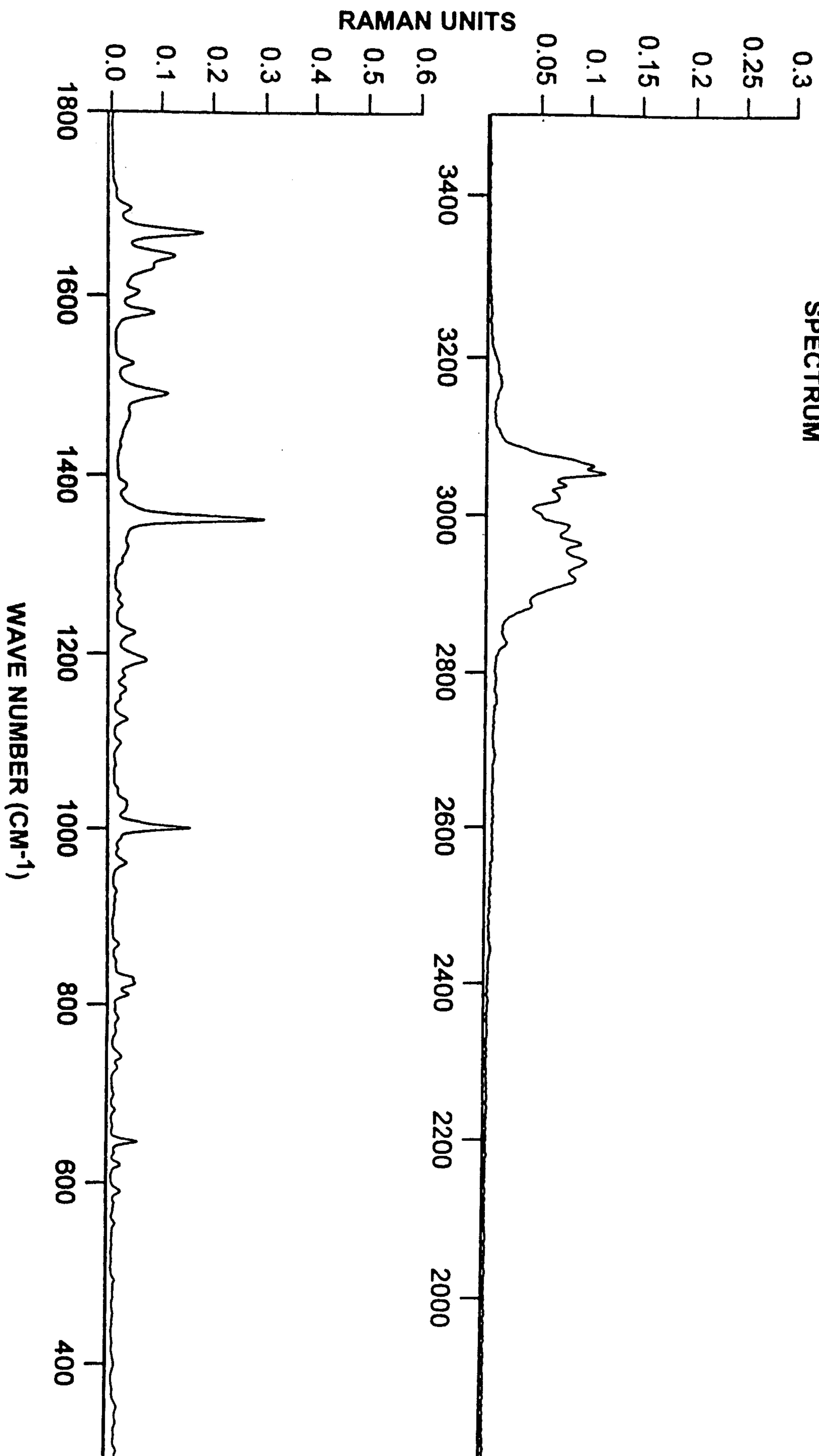


Fig. 38 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/ACETONE RAMAN
SPECTRUM



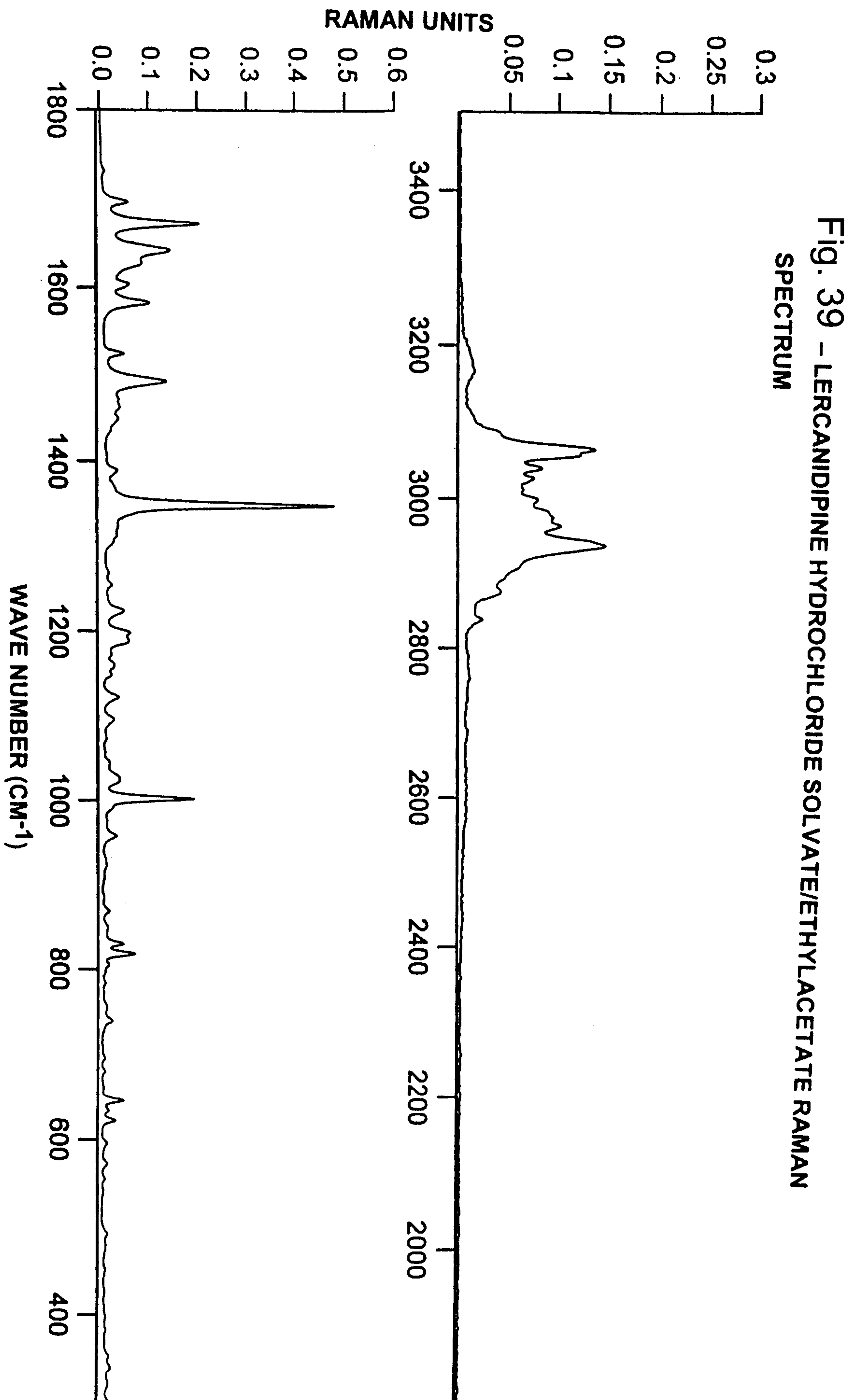
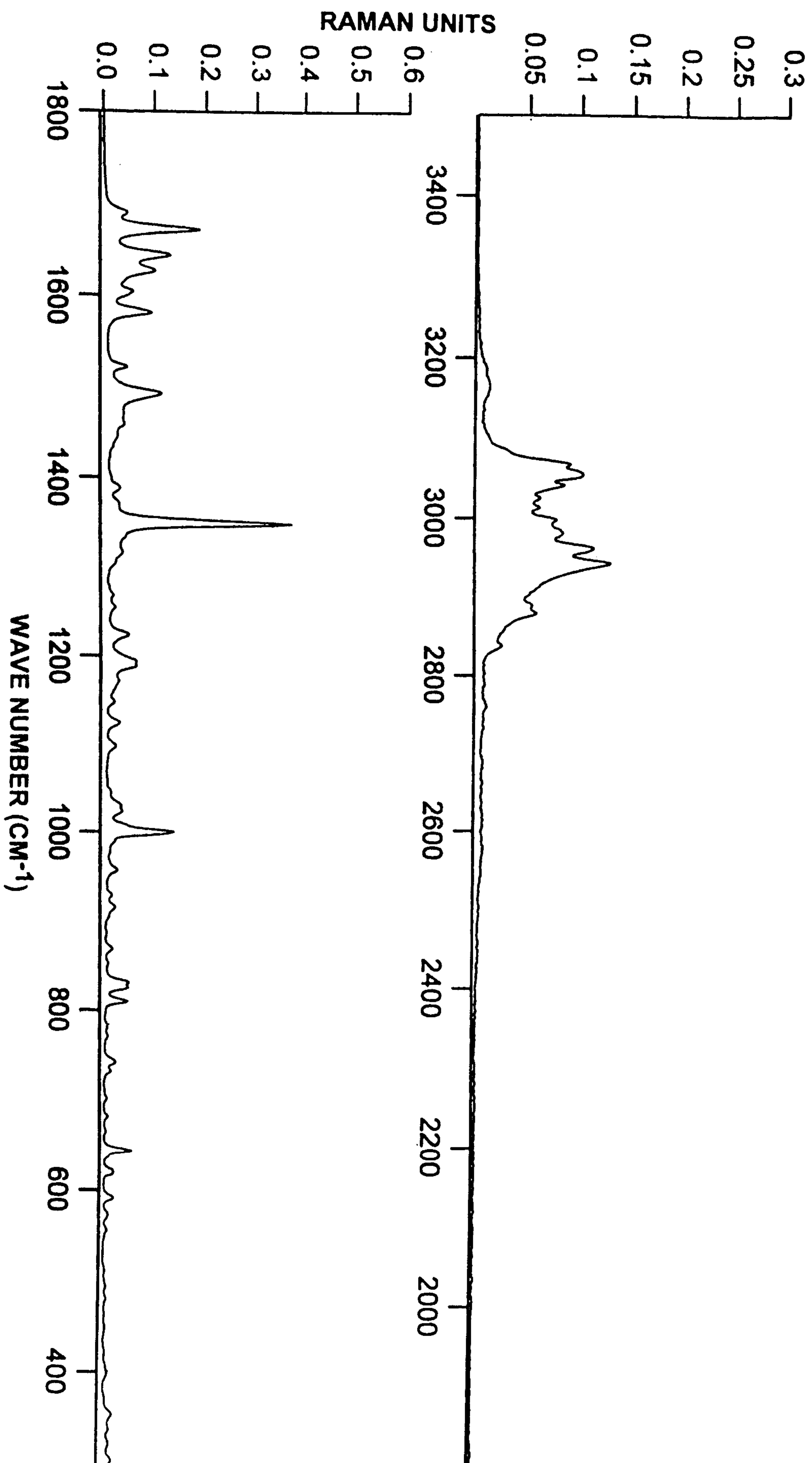


Fig. 40 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/THF RAMAN SPECTRUM



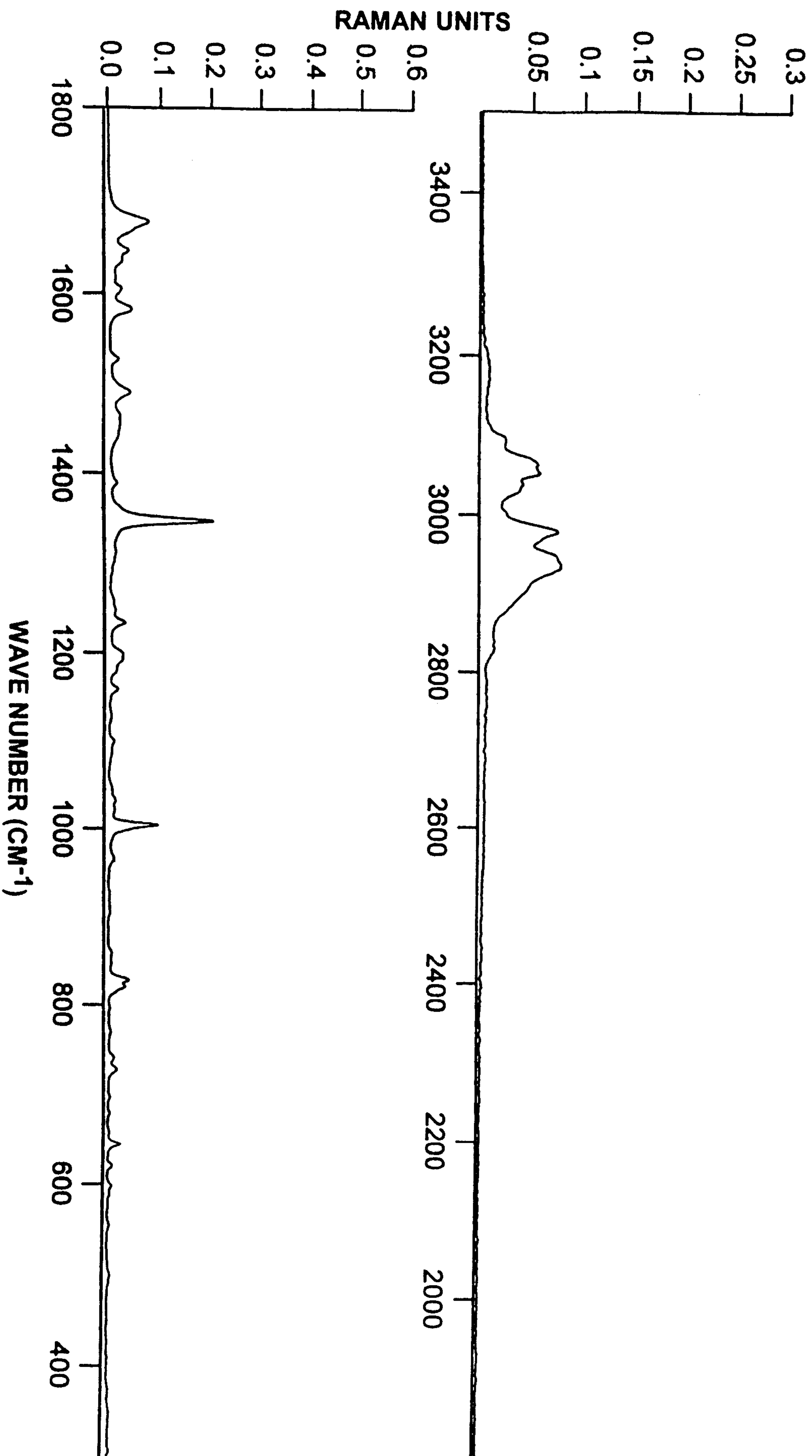
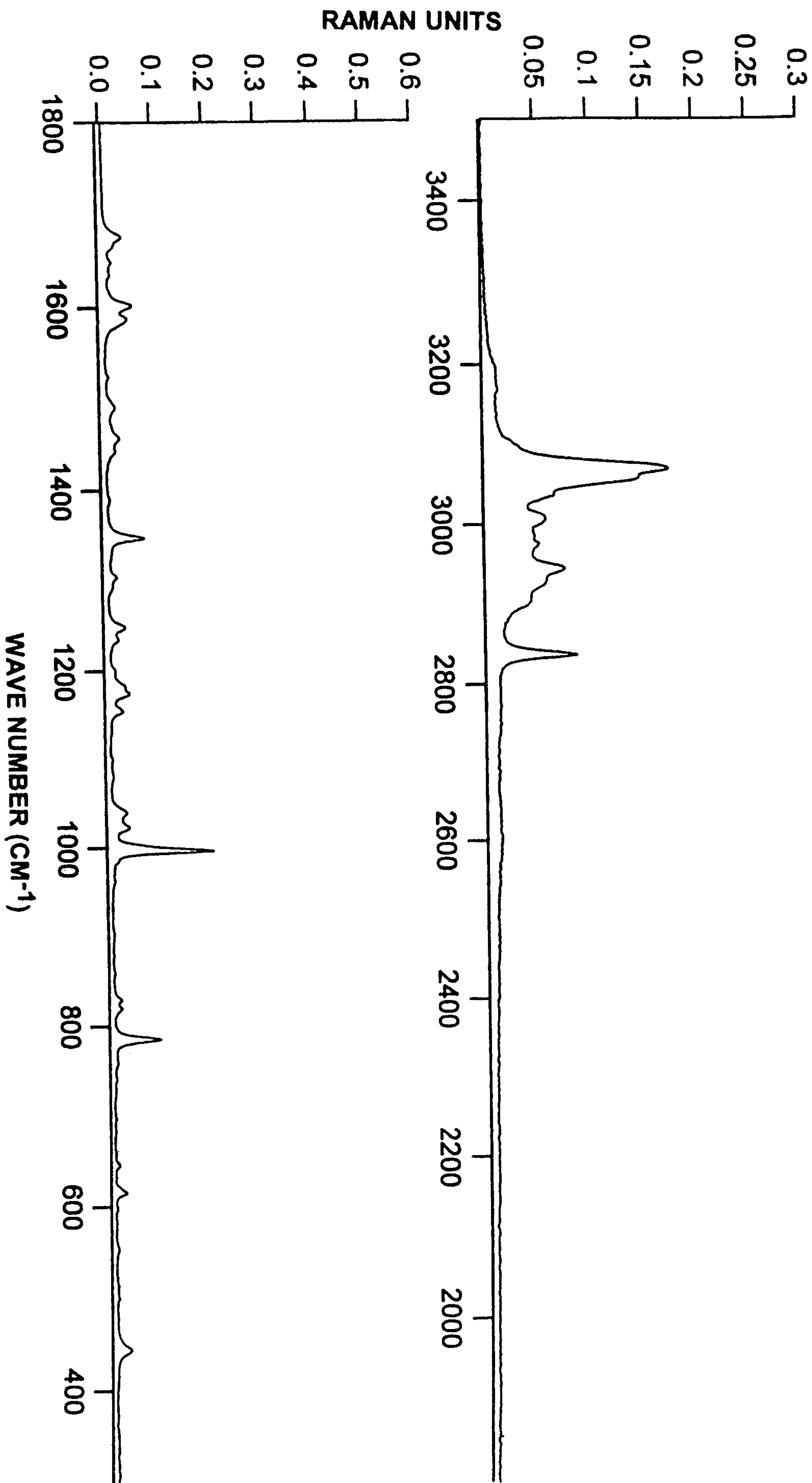


Fig. 41 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/TBME RAMAN SPECTRUM

Fig. 42 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/ANISOLE FORM (A)
RAMAN SPECTRUM



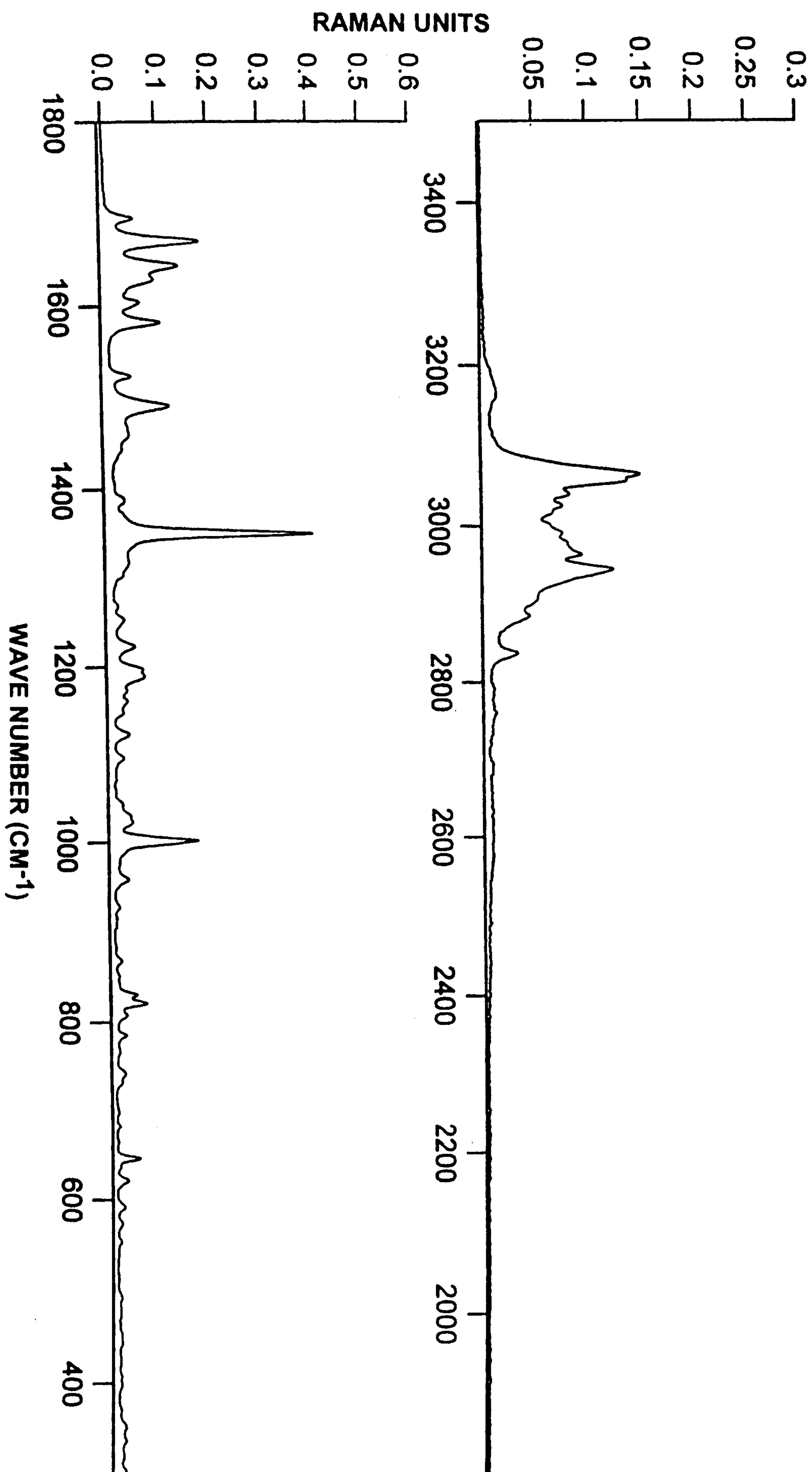


Fig. 44 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/ISOPROPYL ALCOHOL
RAMAN SPECTRUM

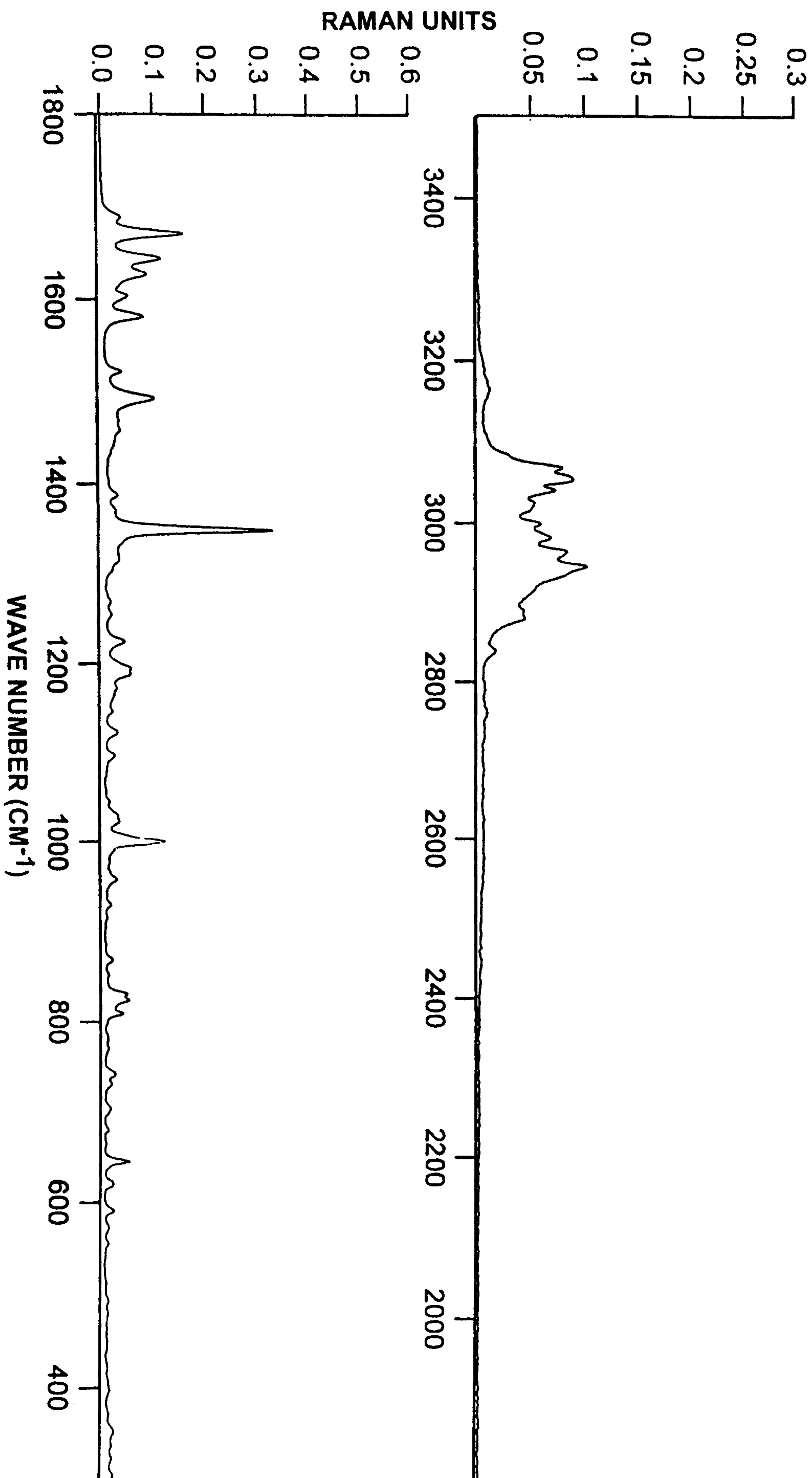


Fig. 45 – LERCANIDIPINE HYDROCHLORIDE SOLVATE/ISOBUTHYL ALCOHOL
RAMAN SPECTRUM

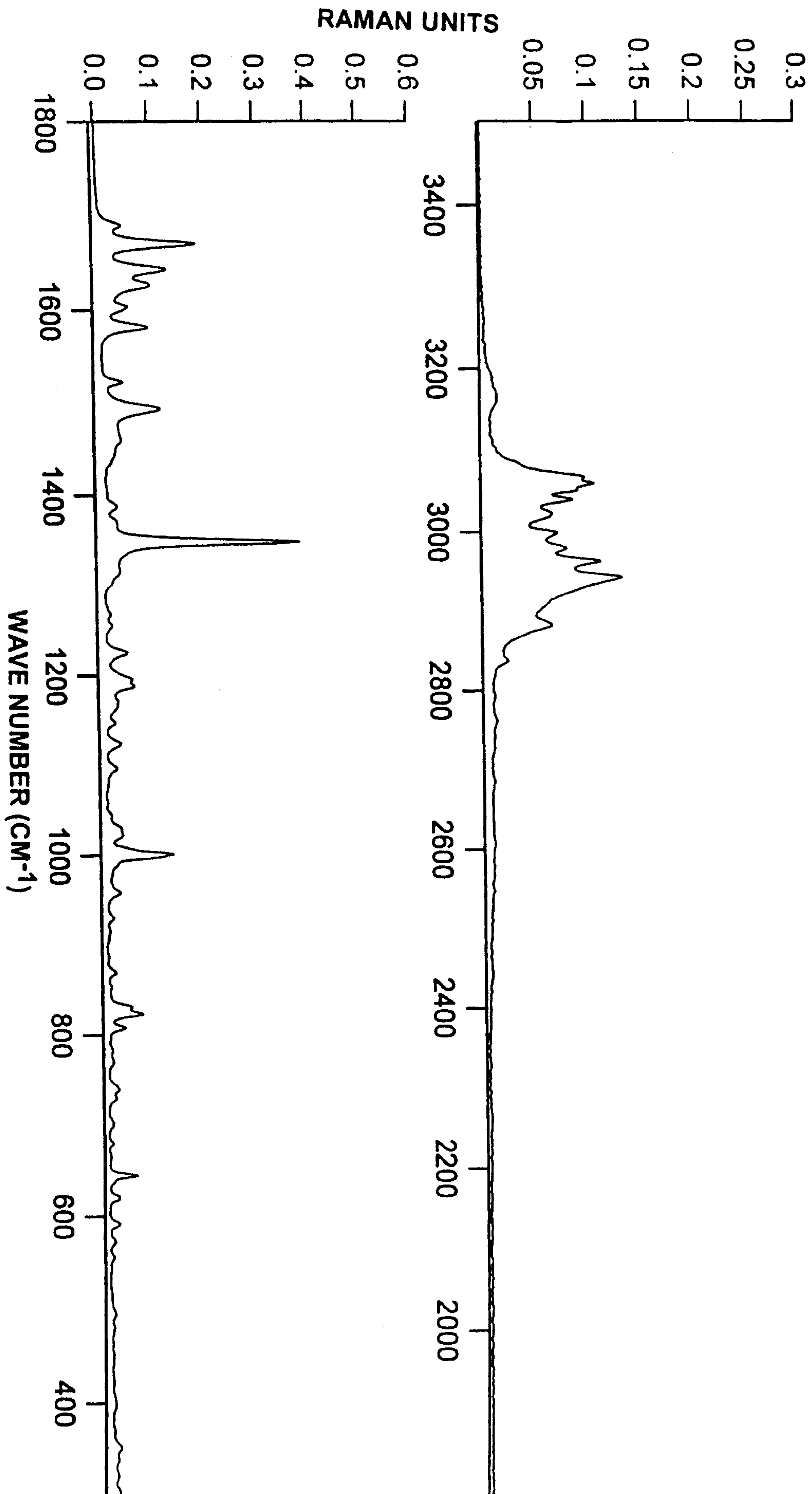


Fig. 46 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/HEPTANE RAMAN
SPECTRUM

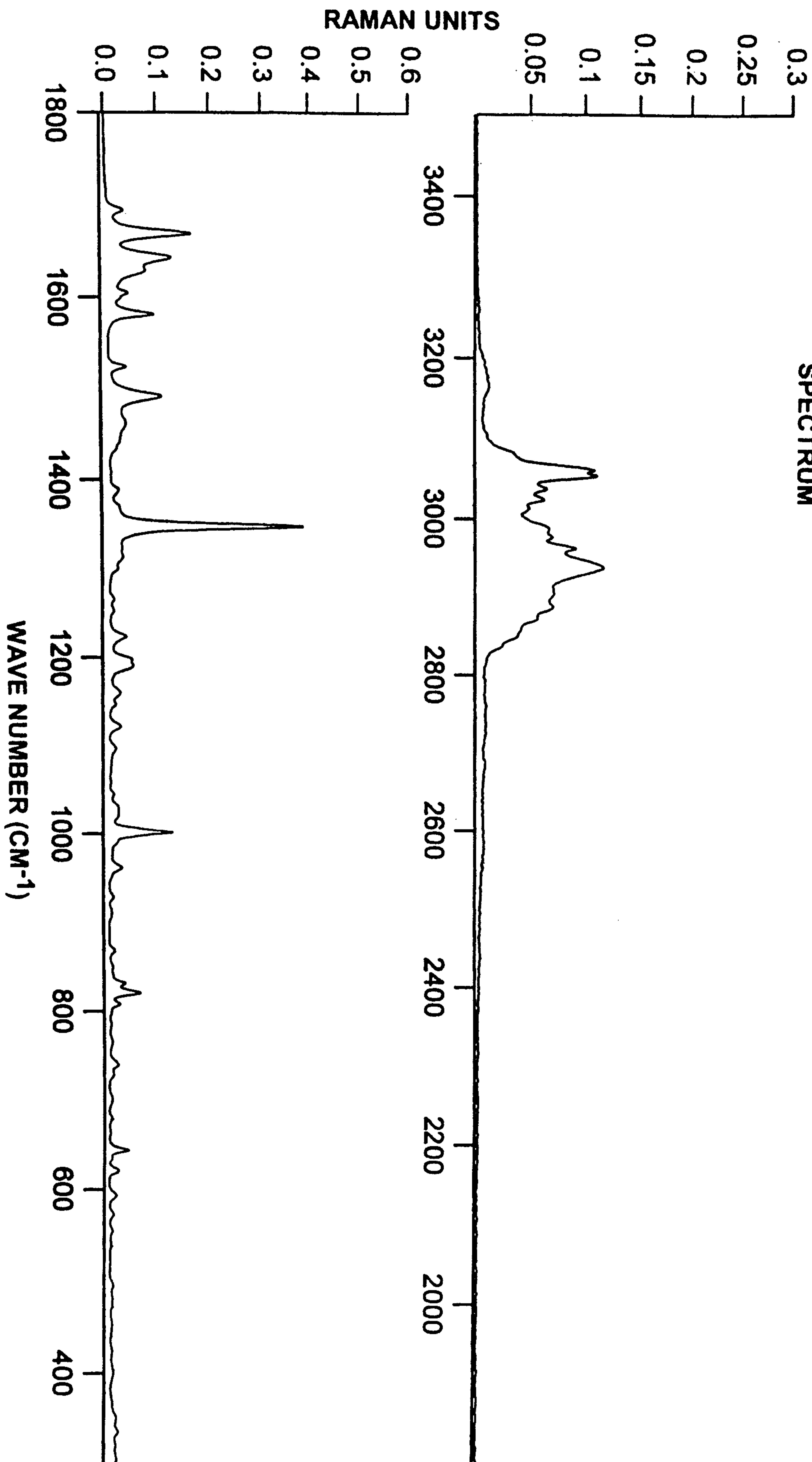


Fig. 47 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/ANISOLE FORM (B)
THERMOGRAVIMETRIC ANALYSIS

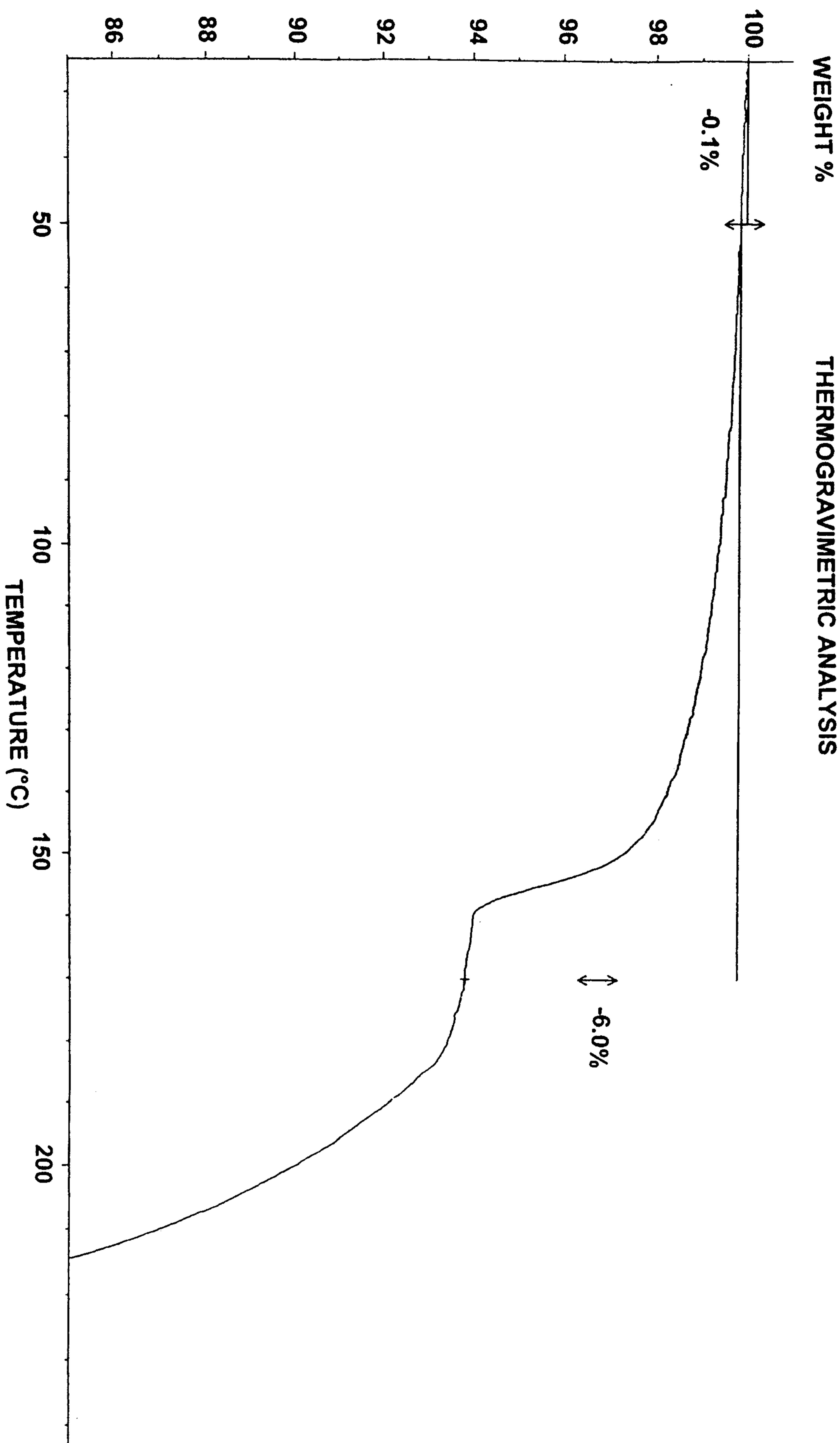
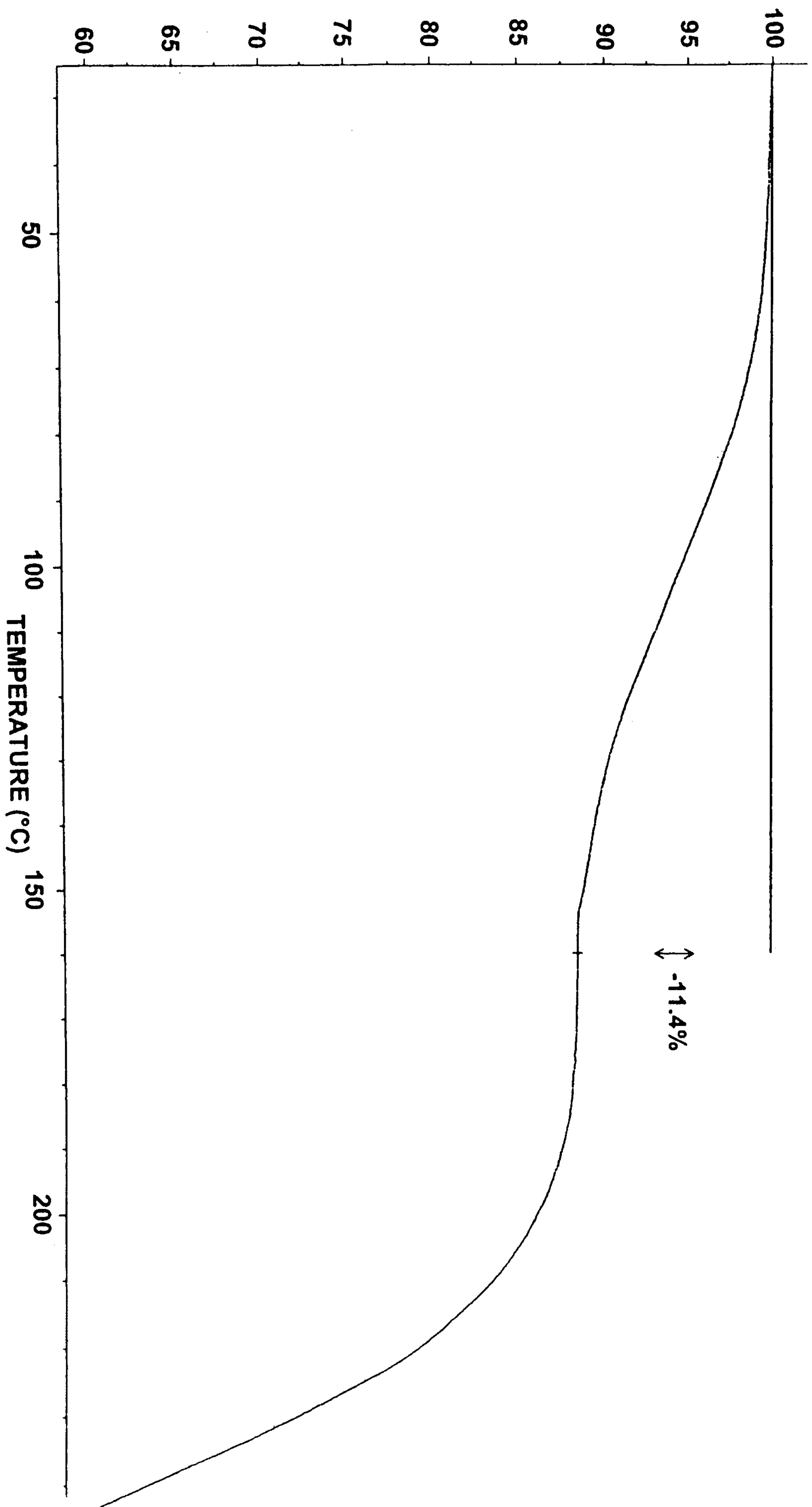


Fig. 48 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/ETHYLACETATE
THERMOGRAVIMETRIC ANALYSIS



WEIGHT %

Fig. 49 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/ACETONE THERMOGRAVIMETRIC ANALYSIS

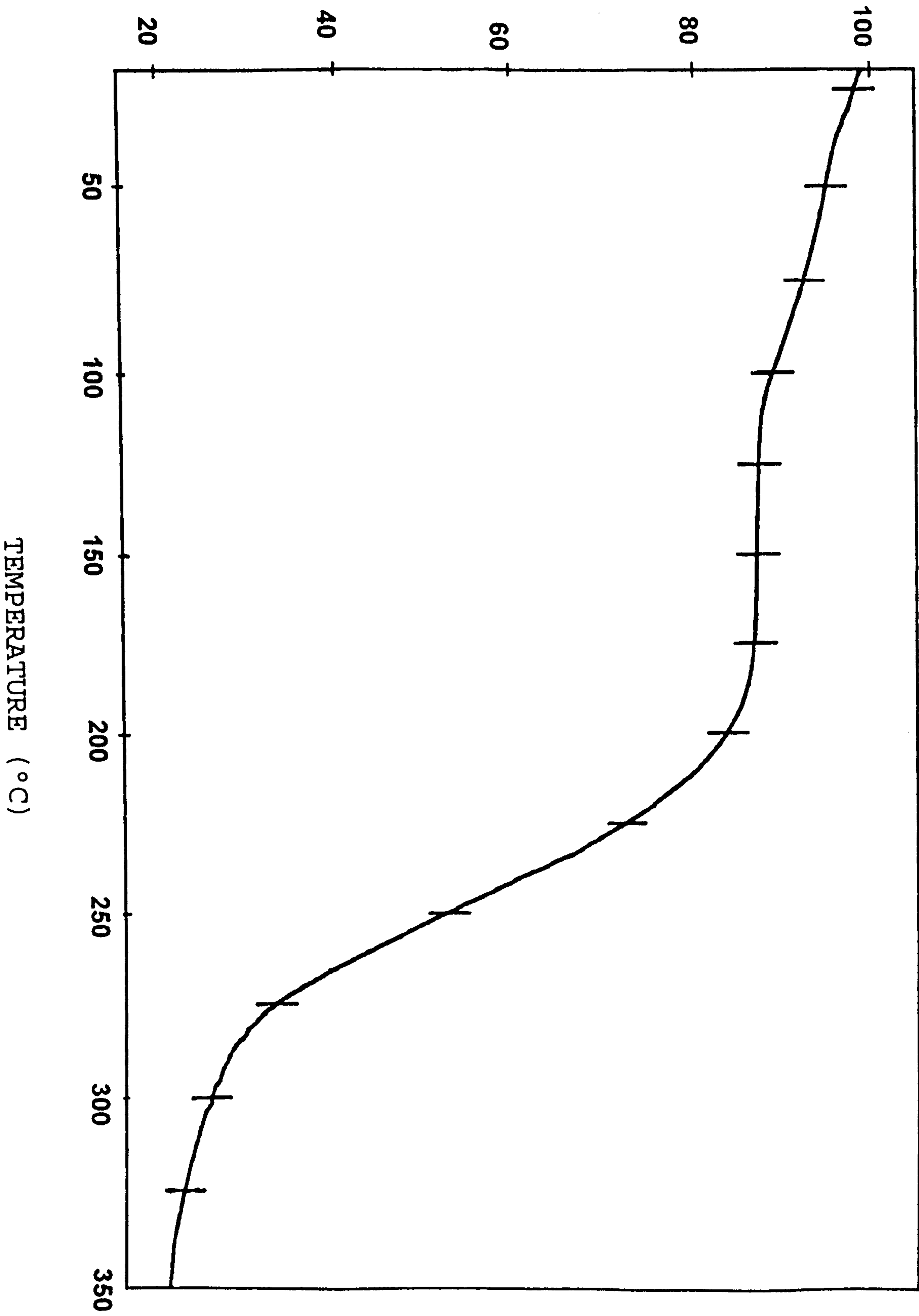


Fig. 50 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/THF
THERMOGRAVIMETRIC ANALYSIS

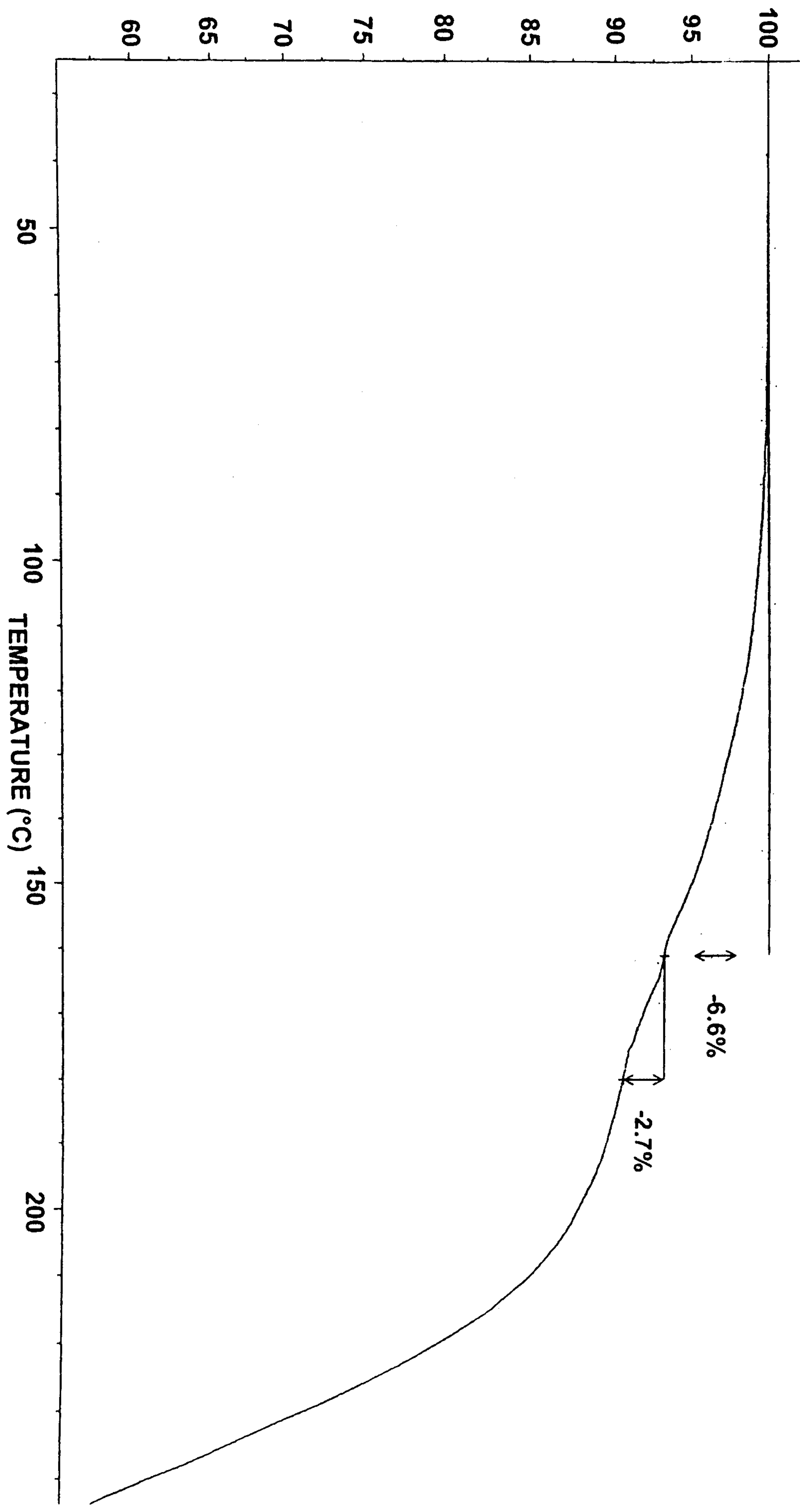


Fig. 51 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/ANISOLE FORM (A) THERMOGRAVIMETRIC ANALYSIS

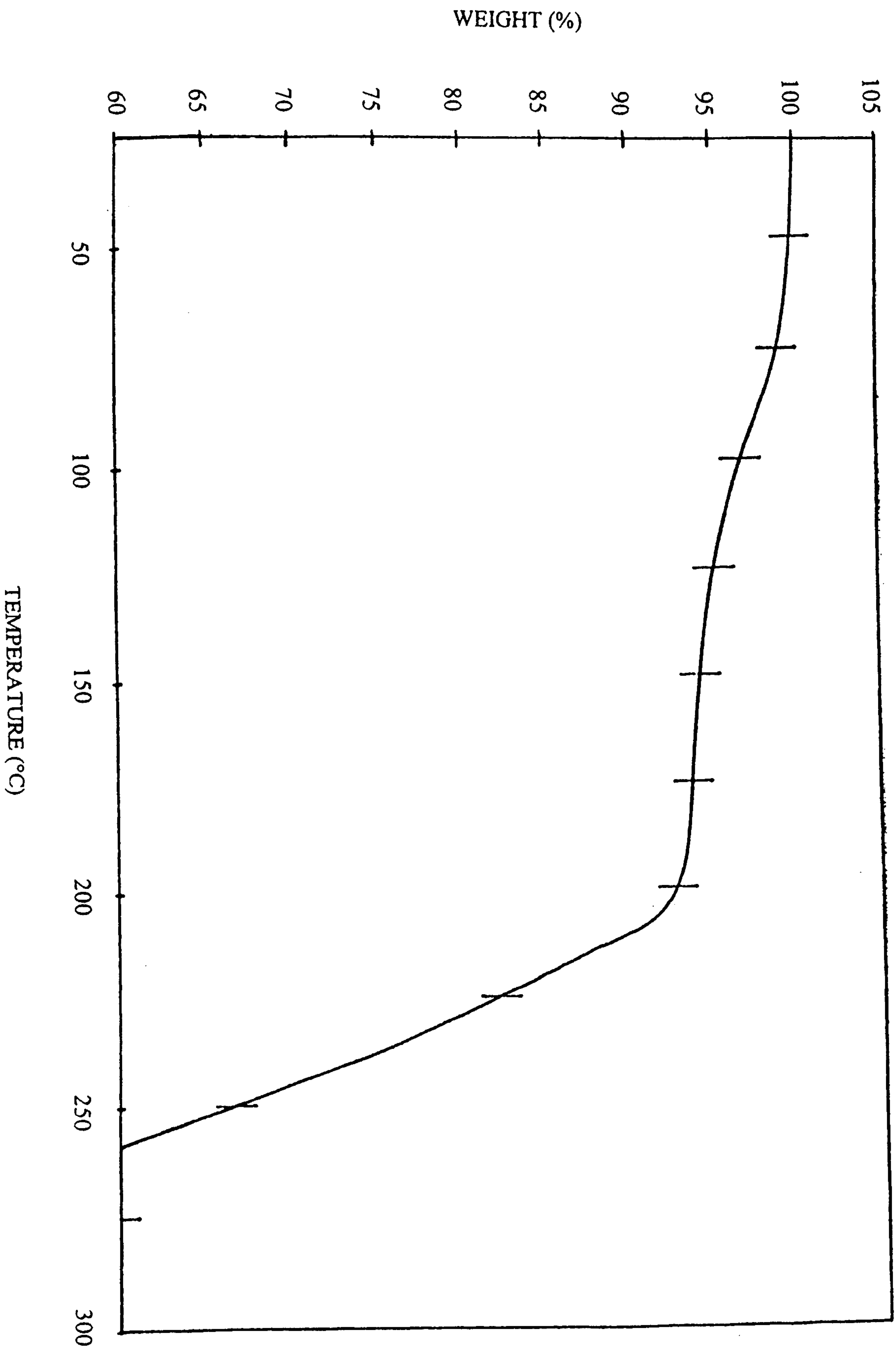


Fig. 52 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/TBME
THERMOGRAVIMETRIC ANALYSIS

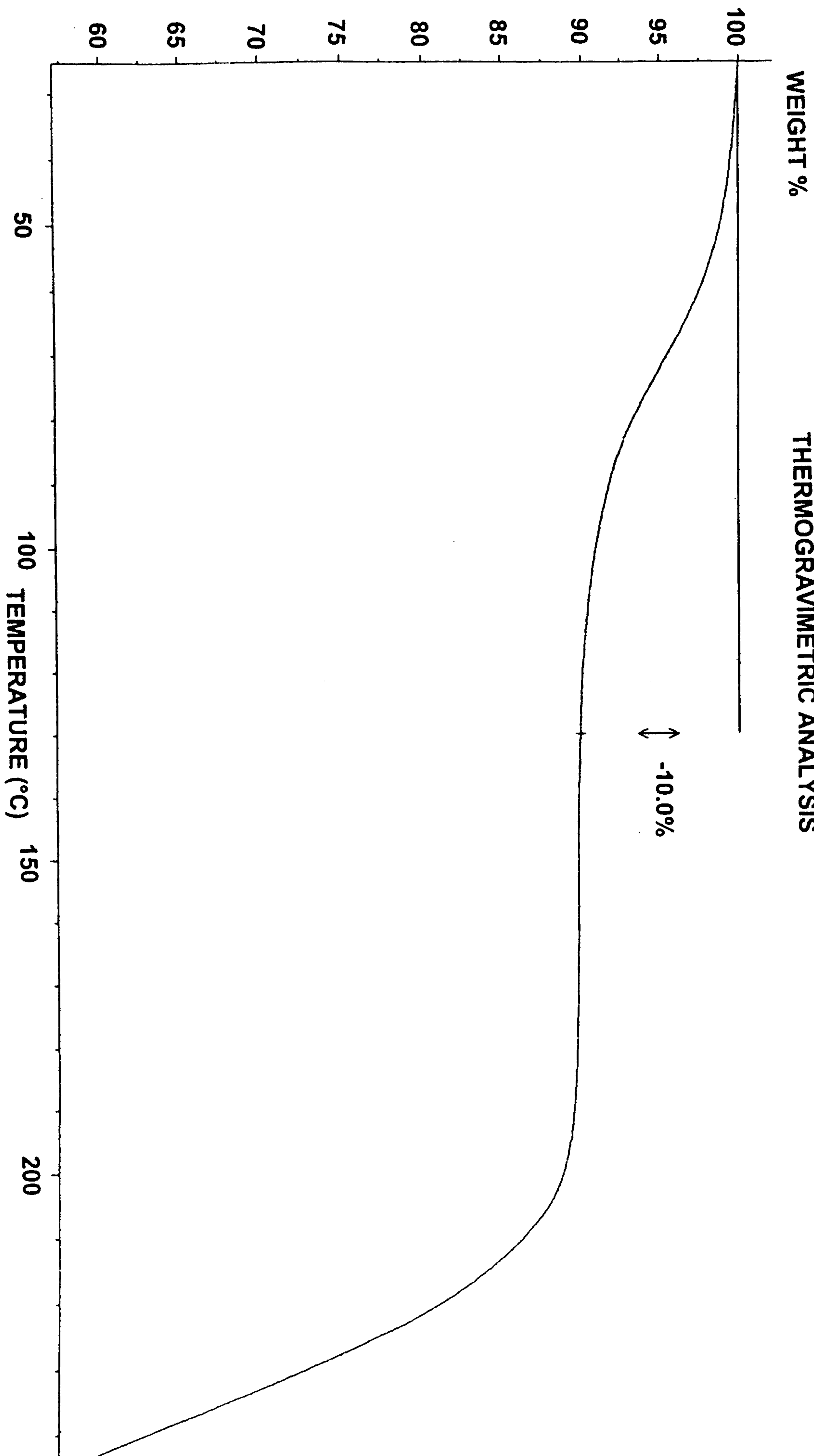


Fig. 53 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/ISOPROPYL ALCOHOL
THERMOGRAVIMETRIC ANALYSIS

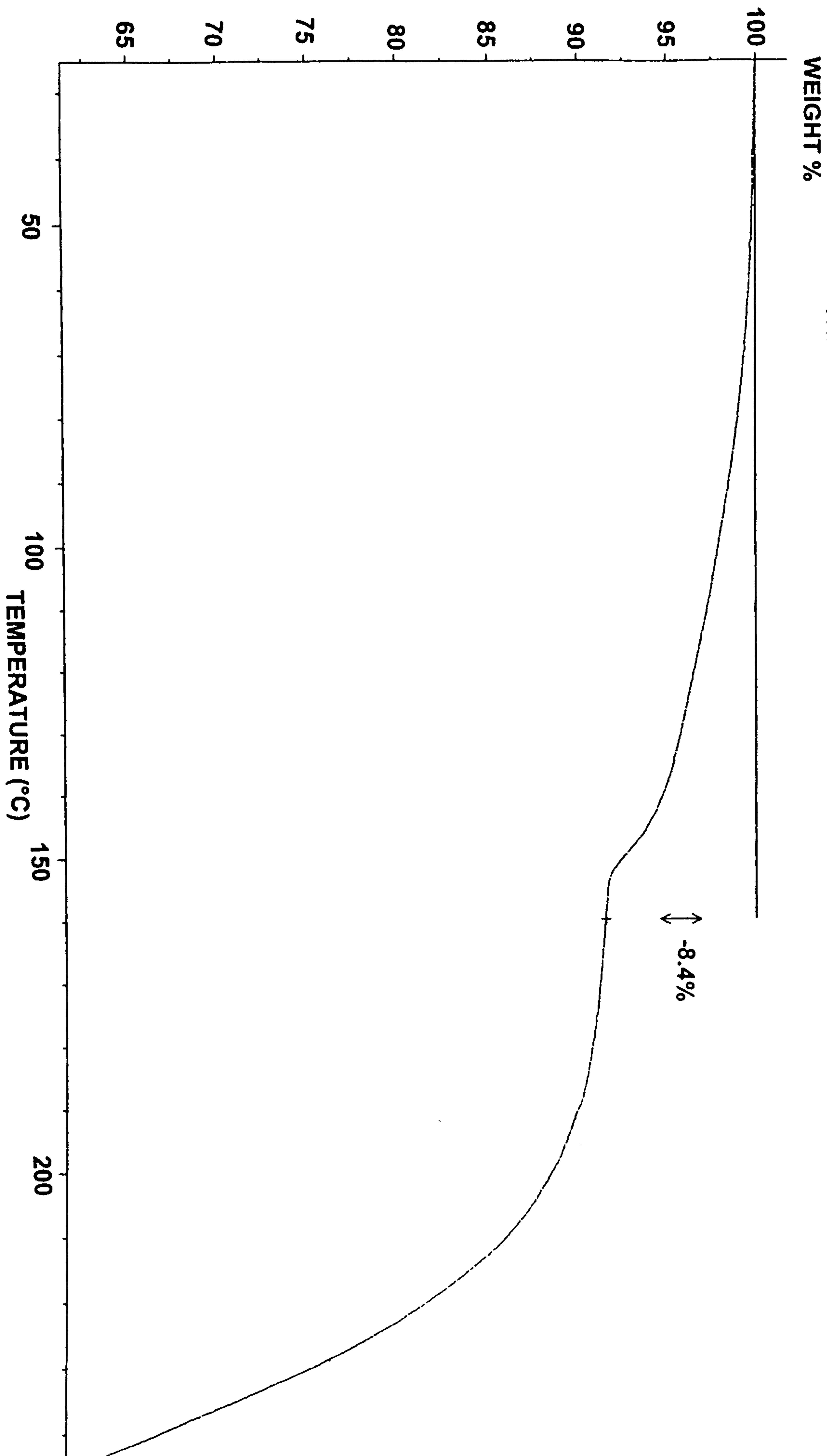


Fig. 54 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/ISOBUTYL ALCOHOL
THERMOGRAVIMETRIC ANALYSIS

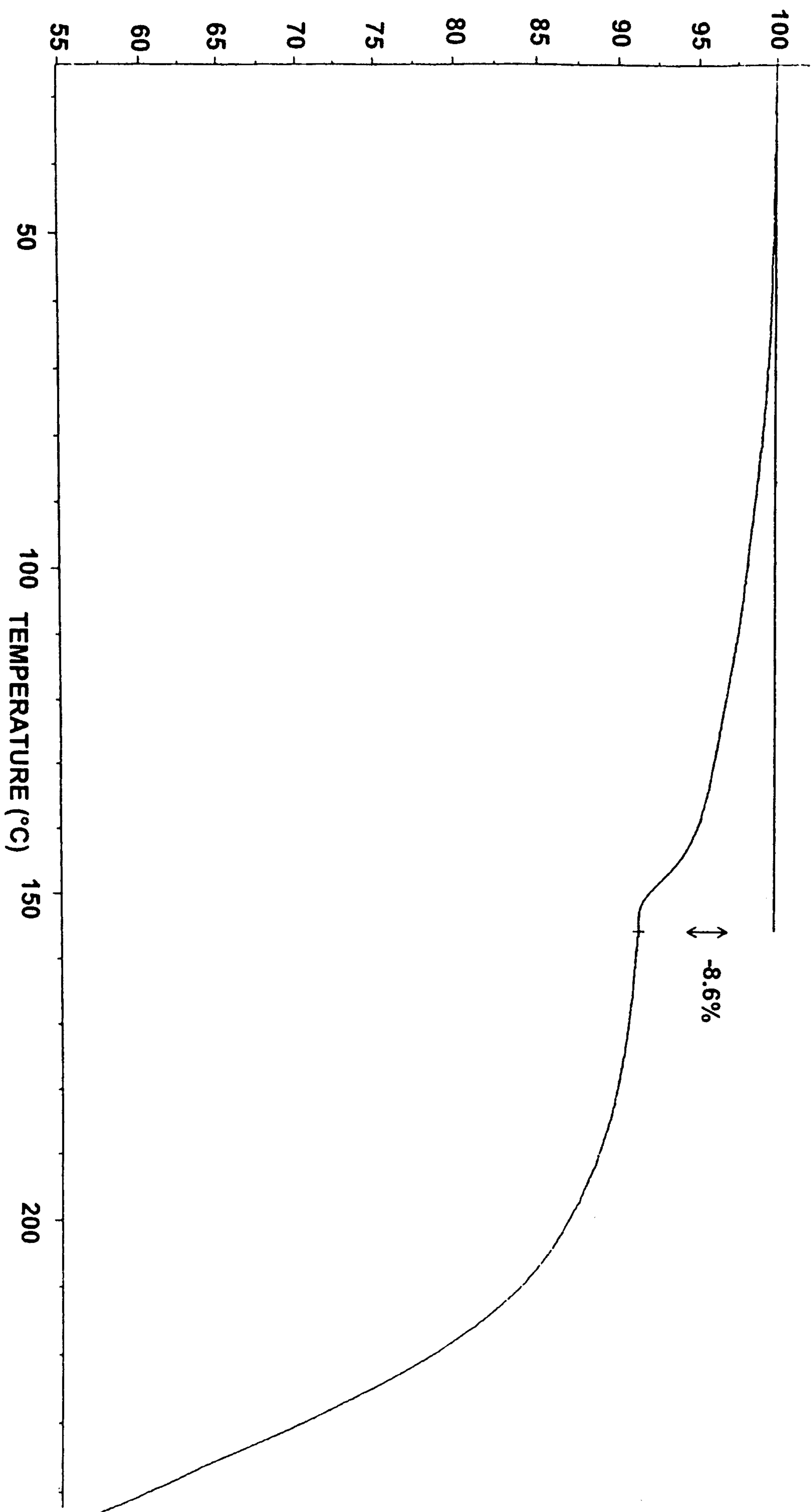
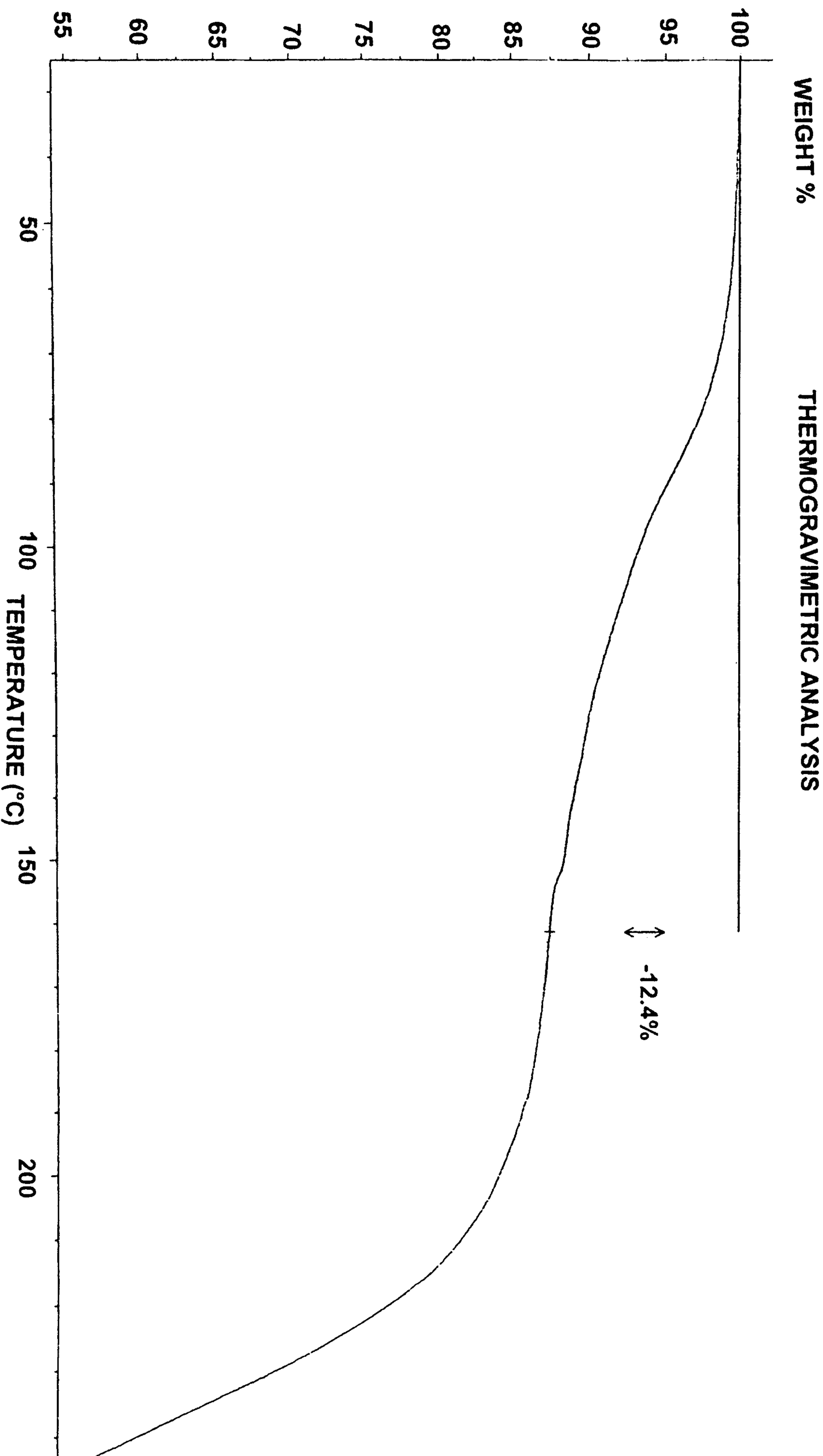


Fig. 55 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/HEPTANE
THERMOGRAVIMETRIC ANALYSIS



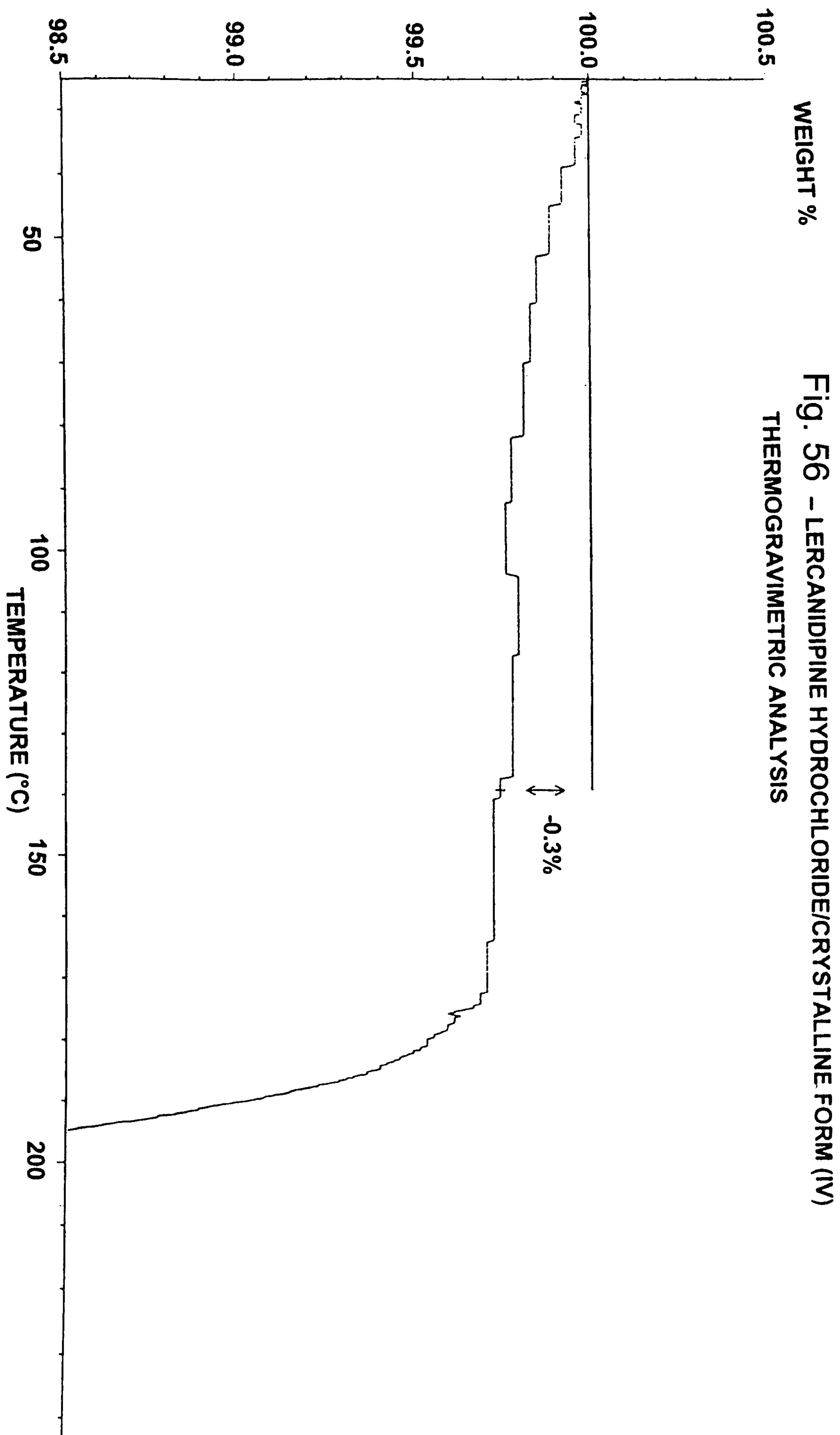
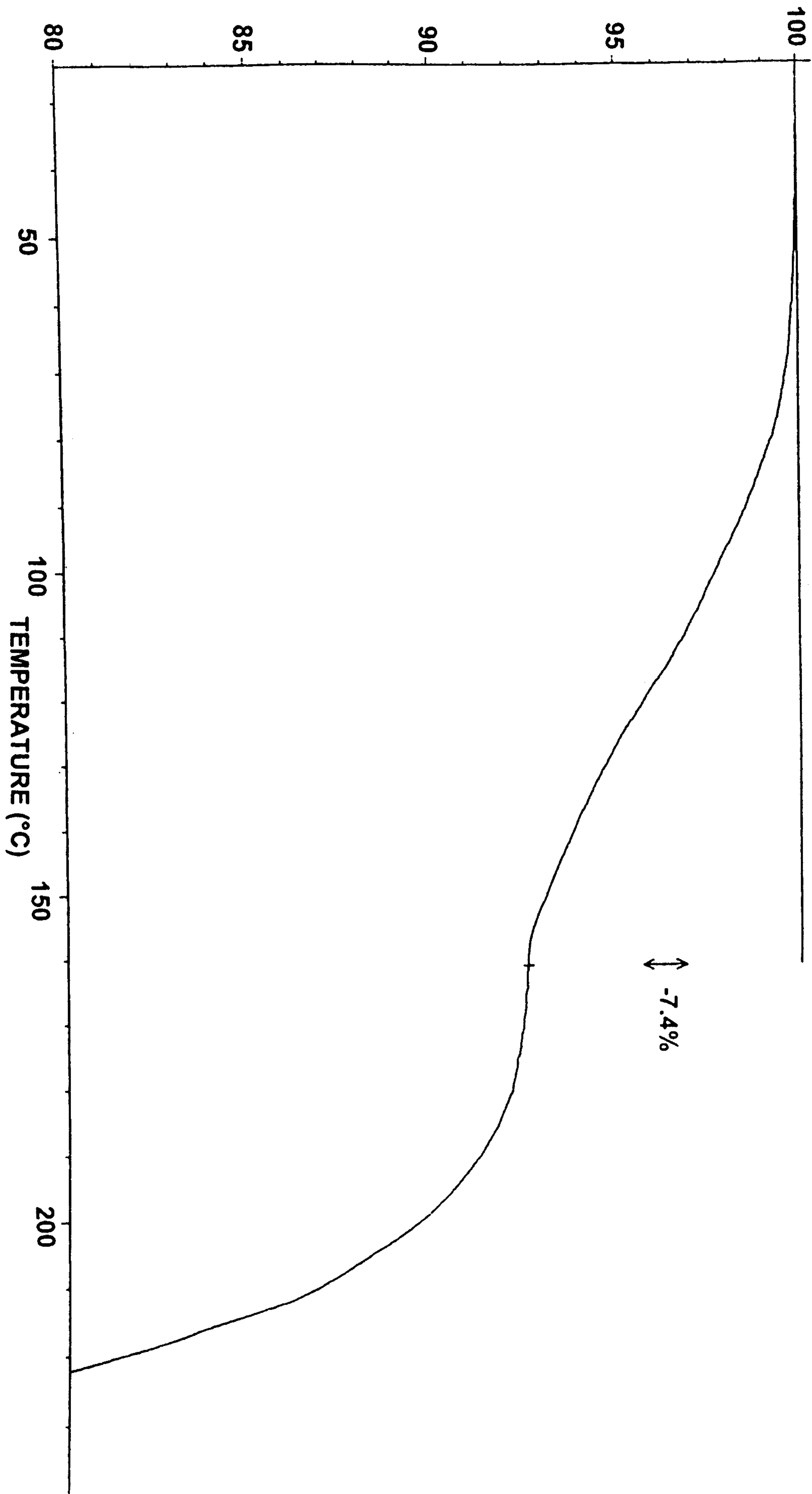


Fig. 57 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/METHYL ETHYL KETONE
THERMOGRAVIMETRIC ANALYSIS



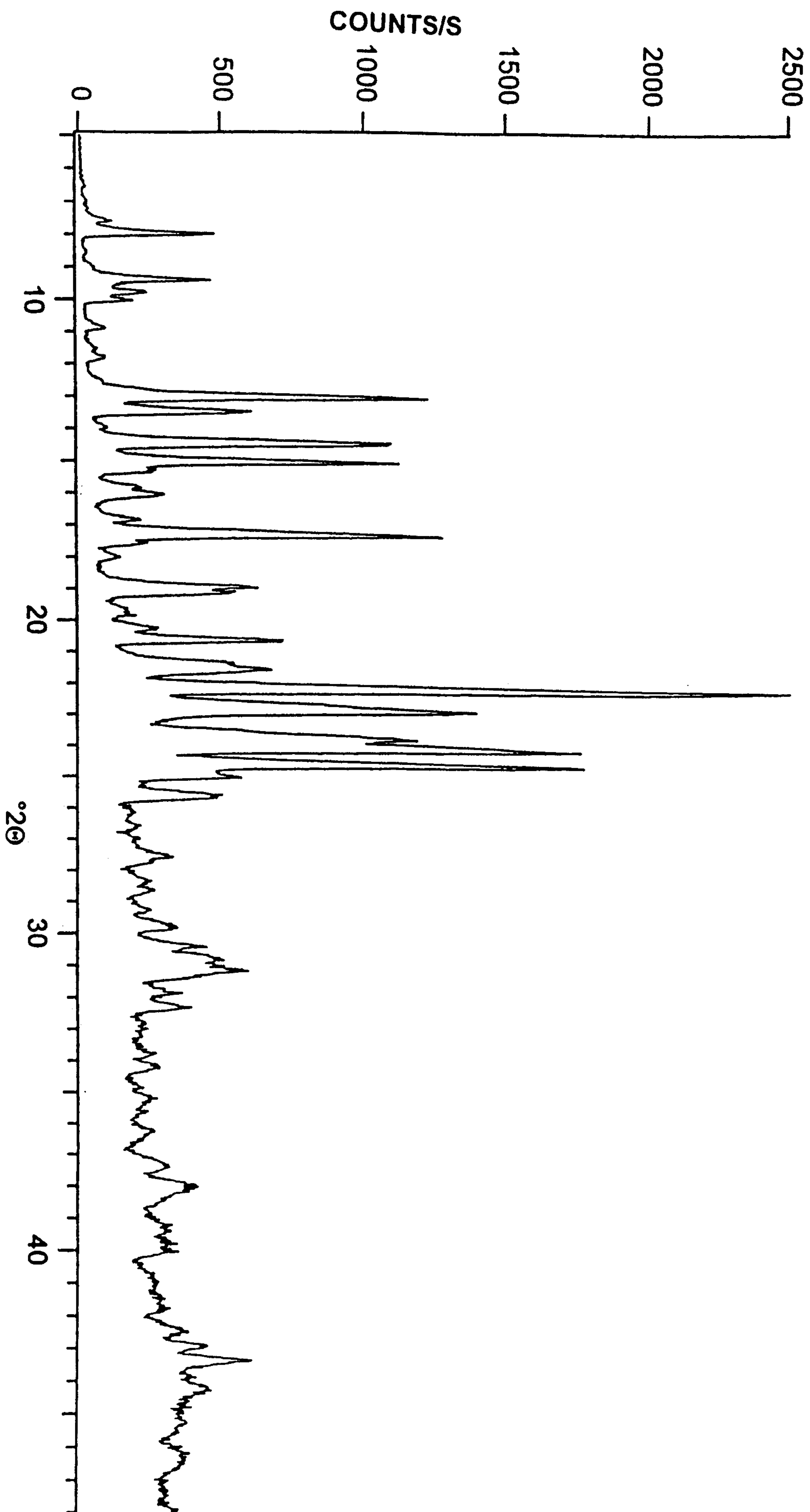


Fig. 58 - LERCANIDIPINE HYDROCHLORIDE SOLVATE/METHYL ETHYL KETONE
XRD SPECTRUM

