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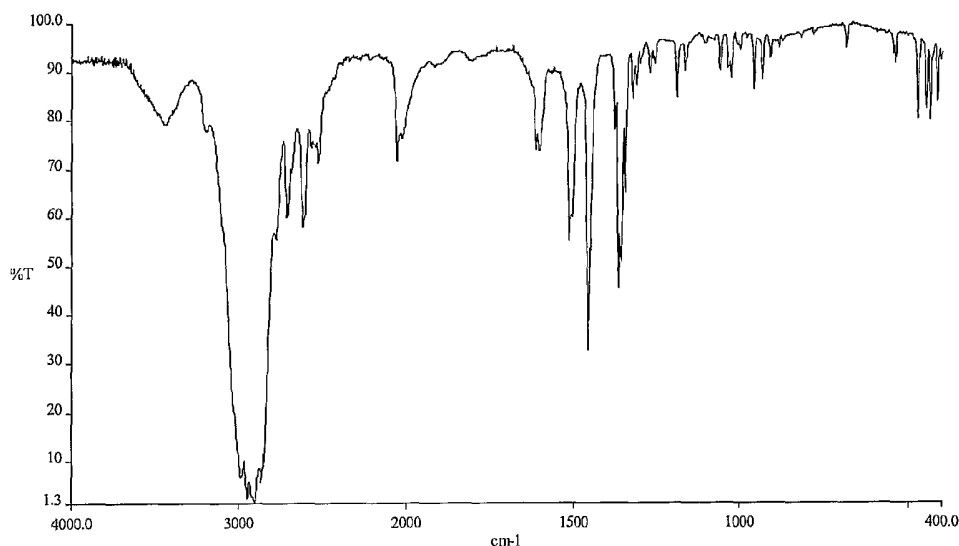
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[Continued on next page]

(54) Title: CRYSTAL FORM II OF MEMANTINE HYDROCHLORIDE



IR SPECTRA OF FORM II

(57) Abstract: Crystalline memantine hydrochloride with improved properties.

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**Declarations under Rule 4.17:**

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CRYSTAL FORM II OF MEMANTINE HYDROCHLORIDE

FIELD OF THE INVENTION

- 5 The present invention relates to crystalline form II of memantine hydrochloride. Memantine hydrochloride is used in the treatment of Alzheimer's & Parkinson's disease.

BACKGROUND OF THE INVENTION

United States Patent No. 3,391,142 (Assigned to Eli Lilly and Company) discloses
10 memantine hydrochloride, the process for its preparation and recrystallization of the product from a mixture of alcohol and ether. This patent however does not disclose different crystal forms of memantine hydrochloride. The disadvantage of this process is the use of alkanol : ether mixtures on large scale in terms of cost and eco-friendliness. The ether solvent easily forms peroxides and can cause potential hazards in terms of storage, handling and product
15 degradation. Due to the volatile nature of ether at ambient temperatures of 25 to 30°C the feasibility of recovery and reuse of mixture of solvents is unviable. Yet another hazard potential of ether is its highly inflammable nature which prevents the use of ether as a solvent in large scale operations.

20 When we recrystallized memantine hydrochloride using alcohol and ether solvent mixtures or neat solvents, for e.g. methanol : ether, ethanol : ether, isopropanol : ether, we obtained memantine hydrochloride in a crystalline form which is spongy and fluffy in nature. This crystalline form is referred to herein as form I. Form I being fluffy is difficult to handle during processing of formulation.

25

OBJECT OF THE INVENTION:

The object of the present invention is to provide crystalline form II of memantine hydrochloride with improved properties.

- 5 Yet another object is to provide process for the preparation of crystalline form II of memantine hydrochloride.

SUMMARY OF THE INVENTION

10

Crystalline memantine hydrochloride that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2 theta at about 12.50, 14.1, 16.5, 18.8.

15 **DETAILED DESCRIPTION OF THE INVENTION:**

In our attempt to improve the crystalline properties of memantine hydrochloride so as to furnish material with better handling properties we obtained an improved crystalline form referred to herein as Form II.

20

The present invention provides novel crystalline form II of memantine hydrochloride.

25

The novel crystalline form II of memantine hydrochloride of the present invention exhibits a different x-ray powder diffraction pattern compared to Form I. The x-ray diffraction pattern of form I is depicted in figure 1 and form II is depicted in figure 2. The Differential Scanning Calorimetry (DSC) profile of form II and Infra red spectra of form II are depicted in Figures 3 and 4 respectively.

According to the present invention crystalline memantine hydrochloride exhibits X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2 theta of about 12.50, 14.1, 16.5, 18.8. Particularly, crystalline memantine hydrochloride exhibits X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2 theta of about
5 6.28, 10.84, 12.50, 14.18, 16.56, 18.76, 21.21, 21.77, 24.39, 27.42, 30.29, 31.47, 32.80, 34.04.

Typically, crystalline memantine hydrochloride exhibiting the X-ray diffraction pattern as given below:

°2 theta values	Relative Intensity %
6.28	11.99
10.84	6.11
12.50	54.64
14.18	61.59
16.56	31.48
18.76	100
21.21	12.73
21.77	22.21
22.61	9.53
22.98	2.89
24.39	17.28
25.10	3.79
25.49	2.88
25.97	6.01
27.42	12.81
28.17	7.10
30.29	15.24
31.47	13.08
32.21	3.4
32.80	14.57
33.54	6.56
34.04	10.00
35.42	5.16
36.99	6.88
37.55	9.90
38.60	9.39
39.15	4.89

10 The novel crystalline form II of memantine hydrochloride of the present invention exhibits physical properties like bulk density, average aspect ratio and particle size which are distinct when compared to Form I.

As referred to herein the term "bulk density untapped" is the weight of the sample divided by its non packed volume and the term "bulk density tapped" is the weight of the sample divided by its packed volume. The units of bulk density are grams (g) per cubic centimeter (cc) or grams per milliliter. A powder having low bulk density will be lightweight and have greater surface area. A powder with high density will be much more compact and dense, exist as harder particles and will result in a more flowable product compared to powder with low bulk density.

As referred to herein the term "aspect ratio" refers to the length of the particle divided by its breadth, the length being defined as longest distance on one axis and breadth being shortest distance on other axis. Generally, crystals with large aspect ratios for e.g. needle-shaped crystals, have poor flow properties.

In preferred embodiments the crystalline form II of memantine hydrochloride has an average aspect ratio less than 6.

Preferably, the crystalline memantine hydrochloride has bulk density greater than about 0.4g/ml particularly about 0.4 to 0.7 g/ml.

In preferred embodiments the crystalline memantine hydrochloride has particle size such that 75% of particles are equal to or less than 25 μ . Particularly 50% of particles of crystal form II of memantine hydrochloride are greater than or equal to 12.0 μ and 75% of particles are less than or equal to 25 μ .

More preferably, the crystalline memantine hydrochloride of the present invention has lower average aspect ratio, greater particle size and higher bulk density as compared to Form I. The comparative data of the same is depicted in table I. The crystalline form II of the present invention has better handling properties, as it is free flowing, making it useful in formulation work. Also crystalline Form II is stable under ambient conditions of storage as depicted in table II.

According to process of the present invention the crystalline memantine hydrochloride may be prepared by a process comprising dissolving memantine hydrochloride in solvent(s) followed by crystallizing memantine hydrochloride from solvent(s). Crystallization may be achieved by dissolving memantine hydrochloride in a solvent followed by cooling or addition of non-solvent or by removing solvent in the presence or absence of vacuum. The process of crystallization may be carried out with or without the presence of seed crystals.

The dissolution of memantine hydrochloride in solvent(s) may be carried out by stirring at ambient or at elevated temperatures.

The solvent(s) may be selected from the group consisting of aliphatic or aromatic or cyclic hydrocarbon such as n-pentane, n-hexane, n-octane, cyclohexane, toluene and the like; halogenated aliphatic or aromatic hydrocarbons such as dichloromethane, chlorobenzene and the like; alcohols such as methanol, ethanol, t-butanol, isopropanol, cyclohexanol and the like; ethers such as diethylether, tetrahydrofuran, dioxane and the like; ketones such as acetone, methylethylketone, cyclohexanone and the like; nitriles such as acetonitrile; amides such as

dimethylformamide, dimethylacetamide and the like; esters such as ethylacetate, butylacetate ;
sulfoxides such as dimethylsulfoxide and the like; water and mixtures thereof.

Crystallization of memantine hydrochloride from the solution may be carried out at ambient
5 or lower temperatures. Crystallization may be allowed to occur by chilling or seeding or
scratching the glass of the reaction vessel or cooling and other such common techniques.

Isolation of the novel polymorphic form may be achieved by using standard techniques known
to those skilled in the art such as filtration/centrifugation and drying. Filtration may be carried
10 out in the presence or absence of vacuum. Drying may be carried out at ambient or elevated
temperature in the presence or absence of vacuum. Spray or freeze-drying may be used.

For instance crystalline memantine hydrochloride of the present invention may be prepared
by dissolving memantine hydrochloride in water or aqueous alcoholic mixture. The
15 dissolution may be carried out by stirring at ambient or higher temperature. This is followed
by cooling and stirring at lower temperatures and distilling out the alcoholic solvent to
crystallize memantine hydrochloride within about 3 hours at ambient or lower temperature,
preferably -10 to 30°C and isolating the product by filtration.

The crystalline form of the present invention may be mixed with pharmaceutically acceptable
20 excipients and converted to pharmaceutical compositions and dosage forms. Particularly, a
pharmaceutical composition comprising crystalline memantine hydrochloride and
pharmaceutically acceptable carrier.

The invention is further illustrated but not restricted by the description in the following
25 examples.

EXAMPLES

A) Preparation of Form I of Memantine hydrochloride:

5 Comparative example 1:

120 gm Memantine free base is dissolved in 600 ml IPA at room temperature and 150 ml IPA-HCl is added at 20-25⁰C for 30 minutes to adjust the pH to ~2.0. The reaction mixture is stirred for 1.0 hour at room temperature. 200 ml of IPA is added and heated to 60-65⁰C and stirring continued till reaction mixture becomes clear solution. Charcoalise with 5.0 gm
10 charcoal. The IPA is distilled with vacuum to an extent that the reaction mixture contains some trace amounts of IPA. 600 ml diethyl ether is added and the contents stirred for 1.0 hour at room temperature. Cool to 0-5⁰C and further maintain at 0-5⁰C for 1 hour. The material is filtered and washed with chilled diethyl ether and dried at 40-50⁰C to yield form I.

15 Comparative example 2:

30 gm Memantine free base oil is dissolved in 140 ml methanol at room temperature and methanolic-HCl is added at 20-25⁰C for 30 minutes to adjust the pH to ~2.0. Charcoalise with 1.7 gm charcoal and methanol distilled and degassed with vacuum. 140 ml acetone is added and the contents stirred for 30 min at room temperature. Cool to 0-5⁰C and further maintain at
20 0-5⁰C for 30 minutes. The material is filtered and washed with chilled acetone and dried at 50-60⁰C to yield form I.

The x-ray powder diffraction pattern of form I is represented in fig. 1.

Physical properties of Form I are tabulated in Table I

(B) Preparation of Form II of Memantine hydrochloride:**Example 1:**

5.0 gm Memantine hydrochloride is dissolved in 40 ml water at 80-85°C and gradually cooled to room temperature in 1 hour time and further maintained at room temperature for 1 hour. The material is filtered and washed with 10 ml of DM water and dried at 40-50°C to yield crystal form II of memantine hydrochloride.

Example 2:

5.0 gm Memantine hydrochloride is dissolved in 30 ml of water + ethanol mixture (5% water in ethanol) at 50°C and gradually cooled to room temperature in 1 hour time and further maintained at room temperature for 3 hours and cooled to 0-5°C. The solvent is distilled under vacuum and degassed to yield crystal form II of memantine hydrochloride.

Example 3:

To memantine hydrochloride is added acetone at room temperature. Stir for 10 min at 25-35°C. Distill out the acetone and degas. To the crude product so generated is added acetone and the contents of the flask are heated at 40-45°C and stirred for 1 hour at that temperature. Cool the contents gradually to 0-5°C over the period of 2-3 hours. Stir the contents for 1 hour at 0-5°C. Filter the product and wash with chilled acetone.

20

Crystal Form II exhibits x-ray powder diffraction pattern as represented in fig. 2.
Physical properties of Form II are tabulated in Table I

A comparison of the physical properties of Form I and Form II is given in Table I and stability study data for form II after storing under ambient conditions for 330 days is given in Table II.

(C) Measurement of physical properties

(a) The Bulk density is calculated as per USP '26.

(b) The Aspect ratio is calculated with suitable optical microscope with Magnifications:

400X. To 10-20 mg of the sample add 1-2 ml of cedarwood oil & make a smooth

5 suspension. A thin uniform smear of the sample suspension is prepared on a clean dry

glass slide and covered with a cover slip. The prepared slide is taken on to the stage of

microscope. Focus a field with 400X oil immersion lens, freeze the frame having

discrete particles. Calibrate the system for 400X. Measure the length and breadth of

each particle in the field using "Measure Menu" Length being defined as longest

10 distance on one axis and Breadth being shortest distance on other axis

The aspect ratio of each particle is calculated using the following formula

$$\text{Aspect Ratio} = \frac{\text{Length}}{\text{Breadth}}$$

15

Calculate average Aspect ratio for atleast 50 particles

(c) The Particle size of the samples is determined by dry powder analysis method using

20 Sympatec Particle size analyser with RODOS Dry powder analysis assembly.

Trigger condition:

Time base: 100.00 ms

Start: c.opt >=3.0%

Valid: always

25 Stop: 5.0 sec. c.opt <=1.0 or 99.00 sec. real time

Dispersing Method

Set the assembly for dry powder method. Set the feed rate at 50% and maintain the air

pressure at 2 bar. Switch on the vacuum air. Take reference measurement with air.

After reference measurement is over sprinkle about 100mg sample on VIBRI feeder and start normal measurement and record the results

TABLE I : COMPARISION OF PHYSICAL PROPERTIES OF FORM I & FORM II.

S.NO	PHYSICAL PROPERTIES	FORM	RESULT	
1	Bulk density (g/ml)		Untapped	Tapped
		Form I	0.15-0.25	0.25-0.35
		Form II	0.25-0.40	0.45-0.60
2	Average Aspect ratio	Form I	7.25	
		Form II	1.59	
3	Particle size	Form I	25% of particles are less than 2.15 μm 50% of particles are less than 6.25 μm 75% of particles are less than 15.00 μm	
		Form II	25% of particles are less than 4.5 μm 50% of particles are less than 12.5 μm 75% of particles are less than 25.5 μm	

5

TABLE II: STABILITY STUDY DATA FOR FORM II

S.NO	PHYSICAL PROPERTIES	0 day	330 days
1	Bulk density (g/ml)	0.45-0.60	0.47-0.53
2	Average Aspect ratio	1.59	1.56

We Claim

- 5 1. Crystalline form II of memantine hydrochloride that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2 theta of about 12.50, 14.1, 16.5, 18.8.
2. Crystalline form II of memantine hydrochloride with average crystal aspect ratio less
10 than 6.
3. Crystalline form II of memantine hydrochloride with bulk density greater than 0.4 g/ml.
- 15 4. Crystalline form II of memantine hydrochloride with particle size distribution such that 75% of particles are less than 25 μ ..
5. A process for the preparation of crystalline memantine hydrochloride of claim 1 comprising dissolving memantine hydrochloride in solvent(s) at ambient or higher
20 temperature followed by crystallizing from the abovementioned solvent(s) at lower or ambient temperature.
6. A process as claimed in claim 6 wherein solvent (s) is selected from alcohols, ketones, esters, nitriles, sulfoxides, amides and water.
- 25 7. A pharmaceutical composition comprising crystalline memantine hydrochloride as claimed in claim 1 and pharmaceutically acceptable carrier.

8. Crystalline memantine hydrochloride as claimed in claims 1 to 7 substantially as herein described and illustrated by examples 1 to 3.

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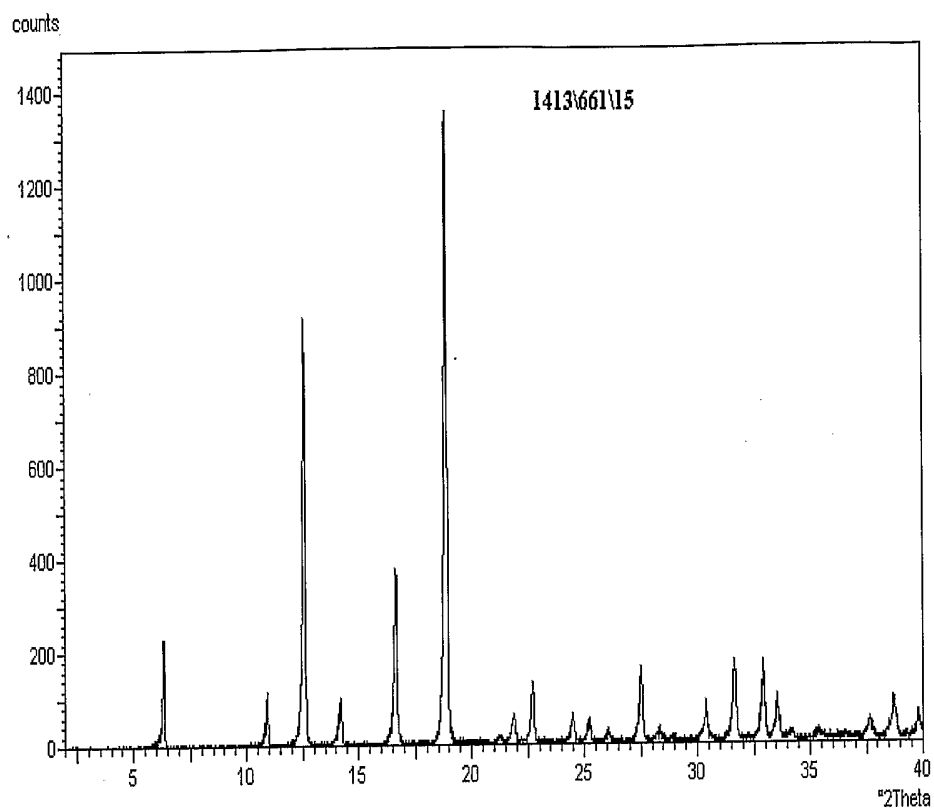


Fig. 1 : XRD PATTERN OF FORM I

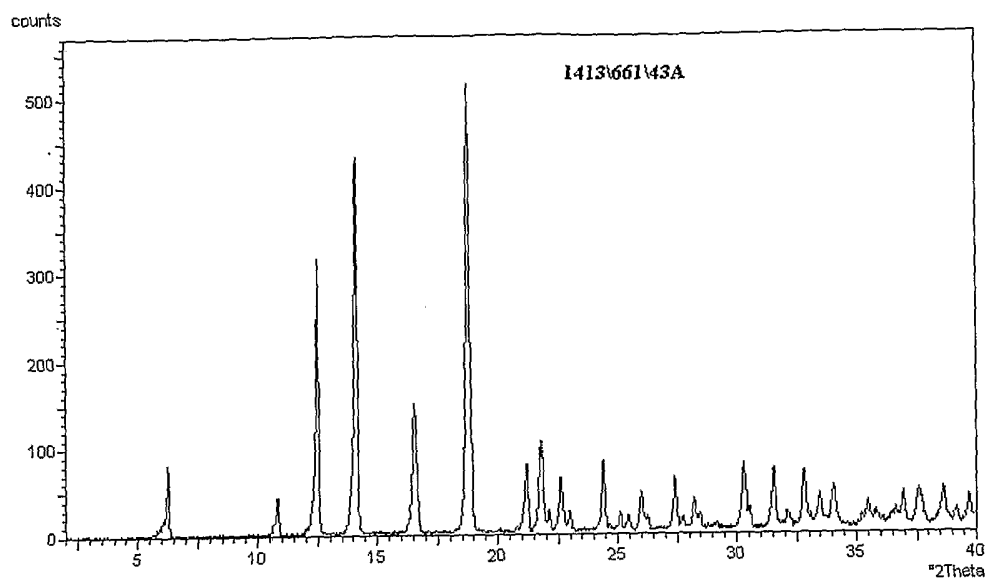


Fig. 2 : XRD PATTERN OF FORM II

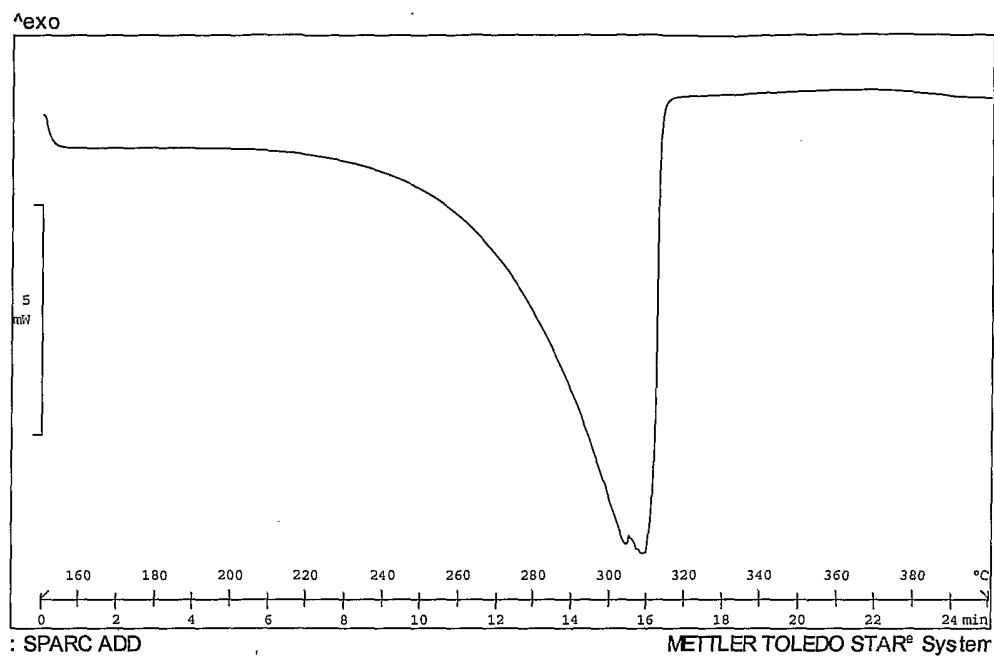


Fig.3: DSC THERMOGRAM OF FORM II

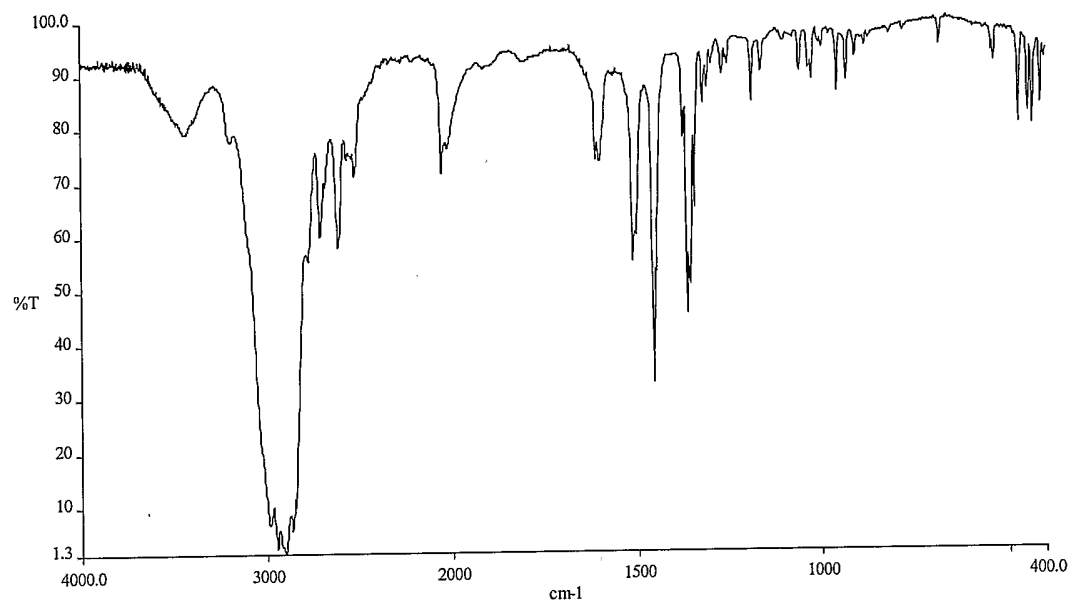


Fig. 4 : IR SPECTRA OF FORM II