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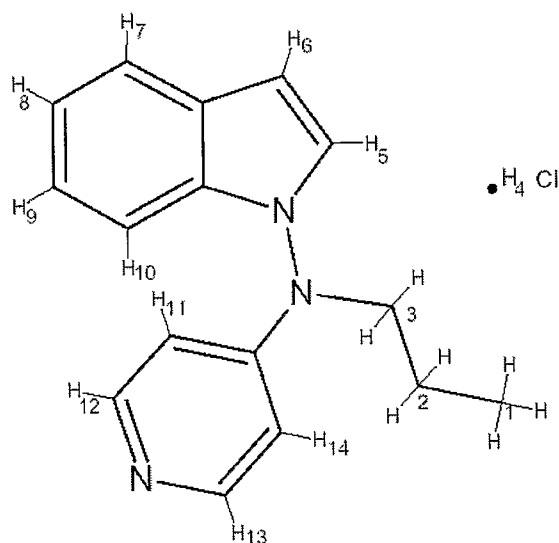
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(54) Title: CRYSTAL FORM OF BESIPIRDINE CHLORHYDRATE, PROCESS PREPARATION AND USE THEREOF



(I)

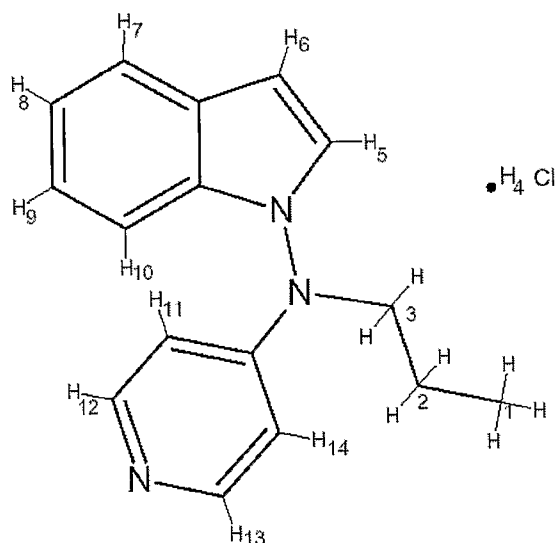
(57) Abstract: Crystal form of besipirdine
chlorhydrate (Form I) corresponding to the
Formula (A) below: the aforementioned
form being characterized at least by one of
the following physico-chemical properties:
a) In FTIR, it displays at least the following
absorption bands of the infrared spectrum:
778, 1198, 1121, but not the following
absorption bands of the infrared spectrum:
3395, 1583, 732, the aforementioned bands
being expressed in cm^{-1} at $\pm 5 \text{ cm}^{-1}$; b)
In PXRD, it shows at least the following
reflections, which are the most intense ones
but whose intensity hereafter is given for
information only: Formula (II) c) In DSC,
it displays at least an endothermic peak at
 $187,3 \pm 2,0 \text{ }^\circ\text{C}$ using $5 \text{ }^\circ\text{C/min}$ scanning
conditions, and a fusion enthalpy ΔH of
 $130,4 \pm 2,0 \text{ J/g}$. The invention also relates
to the processes used for the preparation of
form I as well as its applications in urology.

CRYSTAL FORM OF BESIPIRDINE CHLORHYDRATE, PROCESS PREPARATION AND USE THEREOF

The present invention relates to a stable crystal form, called form I,
5 of N-propyl-N-(4-pyridinyl)-1H-indol-1-amine chlorhydrate (or besipirdine HCl),
to its characterisation, to the processes used for obtaining it and to its
applications, more particularly in the pharmaceutical field.

N-propyl-N-(4-pyridinyl)-1H-indol-1-amine or besipirdine, repre-
sented in its chlorhydrate form by the formula A below, belongs to the N-(4-
10 pyridinyl)-1H-indol-1-amine family.

Formula A



15

In the description hereafter, the term "besipirdine" is equally used to
refer to besipirdine and its salts; the expression "besipirdine.HCl" strictly refers
to besipirdine chlorhydrate.

US4970218, WO02/064126 and WO2005/035496 documents
20 describe the obtention of N-(4-pyridinyl)-1H-indol-1-amines, these processes
make it possible to prepare besipirdine and its salts. According to
WO02/064126 document, it is known that some N-(4-pyridinyl)-1H-indol-1-
amines can have pharmaceutical applications; for example, N-(3-fluoro-4-
pyridinyl)-N-propyl-3-methyl-1H-indol-1-amine (or HP184) was shown to slightly

decrease the frequency of bladder contractions induced by bladder irritation *in vivo*, in rats.

The applicant recently found that besipirdine can be used in the treatment of symptoms associated with bladder irritation or related to effort
5 incontinence and mixed incontinence.

In view of the prevalence of these disorders, besipirdine appears of great interest in pharmacy.

The present invention is based on the discovery that besipirdine.HCl exists as several different crystal forms differing from each
10 other in stability, in particular. The besipirdine synthesis processes described at present lead to a compound whose polymorphic profile is not reproducible from one batch to another. Hence different batches can contain different polymorphs in variable proportions. Moreover, the polymorphic profile of certain batches synthesised using these methods has been shown to change with time, over a
15 several months period.

This lack of reproducibility and stability of the polymorphic profile over time makes it impossible to precisely control the pharmaceutical quality of the active compound. It can also influence the properties of final products containing this compound. Therefore identifying the stable form of
20 besipirdine.HCl and determining the process(es) allowing its reproducible obtention appears highly desirable.

Three polymorphic forms, called I, II, III, and two solvates called IV (methanol solvate) and V (ethanol solvate) of besipirdine.HCl were identified that are obtained as a mixture after the synthesis processes described above.
25 Form II is the most predominant form obtained following on from the process described in WO2005/035496, in which it is isolated from conventional techniques ; more precisely, according to the exemplified method of synthesis, the product is obtained by precipitation of besipirdine solution in its base form using methanolic chlorhydric acid in n-butyl acetate solution.

30 These five forms were characterized and the form I, *i.e.* the stable form of besipirdine.HCl which, once obtained, does not evolve with time in storage conditions at room temperature, was characterized and compared with the other crystal and solvate forms II, III, IV and V.

Hence the present invention relates to a crystal form of
35 besipirdine.HCl, called form I, corresponding to the formula A above and characterized by at least one of the following physico-chemical properties:

a) In FTIR, form I displays at least the following absorption bands of the infrared spectrum: 778, 1198, 1121, but not the following absorption bands of the infrared spectrum: 3395, 1583, 732, the aforementioned bands being expressed in cm^{-1} at $\pm 5 \text{ cm}^{-1}$;

5 b) In PXRD, diffractogram of form I shows at least the following reflections, which are the most intense ones but whose intensity hereafter is given for information only:

Angle (2θ)	12.61	14.11	18.98	19.93	21.03	25.13	25.91
Intensity* (%)	77.13	71.82	73.00	67.21	61.08	60.44	100.00

** for information only*

10

c) In DSC, form I displays at least an endothermic peak at $187.3 \pm 2.0 \text{ }^\circ\text{C}$ using $5 \text{ }^\circ\text{C/min}$ scanning conditions, and a fusion enthalpy ΔH of $130.4 \pm 2.0 \text{ J/g}$.

Thanks to at least one of the characteristics mentioned above,
15 form I can be distinguished from each one of the other forms II, III, IV and V. It is preferentially characterized by at least two of the characteristics a), b) and c) above, if not all of them.

The experimental conditions in which these physicochemical characteristics were measured are precisely described hereafter in dedicated
20 subsections.

By RMN ^1H , besipirdine.HCl is characterized by a spectrum recorded in deuterated chloroform (CDCl_3) using a Bruker 200 MHz instrument and presents the peaks reported in table 1 below, the proton numbering being the one used in formula A herebefore.

25

Table 1

Protons	Chemical displacement δH (ppm)
H4	16.32 (br.s)
H12, H13	8.22 (d)
H7	7.62 (d)
H8, H9	7.17 (d)
H5	7.06 (d)
H10	7.02 (d)
H6	6.62 (d)
H11, H14	6.59 (br.s)
H3	4.00 (m)
H2	1.76 (m)
H1	0.99 (t)

5 The characterisation of crystal form I of interest according to the invention is explained hereafter. To this aim, each of the other forms II, III, IV and V was also identified and this characterisation is also part of the present invention.

1) Infra-Red Spectroscopy

10 IR spectroscopy was performed using a FTIR (Fourier Transform Infrared Spectroscopy) spectrometer Bruker IFS 113V, between 4000 and 600 cm^{-1} , using diamond Attenuated Total Reflectance (ATR).

Sample of each one of besipirdine.HCl crystal forms I, II, III, IV and V was prepared without compression.

15 Spectra obtained are shown in figures 1 to 5 and are characterized by the absorption bands reported in table 2.

Table 2

λ (cm ⁻¹)				
Form I (Figure 1)	Form II (Figure 2)	Form III (Figure 3)	Form IV (Figure 4)	Form V (Figure 5)
3188	3191	3195	3395	3395
3080	3158	3163	3191	3196
3062	3117	3084	3155	3168
2999	3075	3061	3086	3084
2967	3051	3001	3059	3065
2917	3001	2973	2996	3005
2868	2963	2931	2968	2968
2814	2940	2870	2926	2936
2684	2880	2815	2870	2870
2611	2805	2689	2815	2824
2048	2675	2601	2685	2708
1945	2546	2244	2610	2615
1859	2517	2039	2048	2244
1631	2494	1942	1951	2044
1593	2048	1858	1853	1951
1510	1951	1770	1631	1923
1471	1923	1634	1595	1892
1454	1863	1598	1509	1858
1416	1756	1583	1472	1774
1406	1636	1517	1453	1737
1380	1610	1470	1417	1634
1364	1595	1453	1405	1595
1350	1519	1415	1382	1518
1327	1474	1405	1364	1472
1321	1453	1398	1352	1451
1301	1420	1347	1325	1417
1293	1402	1318	1320	1383
1243	1390	1298	1300	1368
1230	1362	1291	1294	1354
1198	1345	1246	1244	1316

1160	1335	1222	1229	1296
1146	1313	1203	1197	1250
1121	1301	1159	1161	1220
1111	1265	1148	1146	1207
1095	1252	1122	1122	1161
1078	1227	1113	1113	1148
1036	1209	1095	1095	1122
1011	1163	1063	1078	1068
998	1148	1036	1038	1036
990	1131	1012	1011	1012
930	1112	987	997	993
904	1100	930	988	927
892	1072	902	930	902
879	1055	889	902	892
848	1033	875	890	879
820	1014	849	879	851
778	919	819	847	817
745	898	779	819	809
720	879	769	777	775
697	860	743	744	766
	838	720	720	741
	824	707	697	720
	760	697		699
	749			
	732			
	699			
	671			

FITR analysis shows that forms I, II, III, IV and V have different absorption frequencies, indicating that these forms have different crystal structures. In particular, a large band at 3395 cm^{-1} can be attributed to a hydroxyle group and allows for the characterisation of solvates IV et V. The displacement of these bands from their position in ethanol or methanol spectra indicates the presence of hydrogen bonds.

Therefore, in order to define form I, the following profile was used that combines the presence and the absence of absorption bands of the infrared spectrum: presence of bands 778, 1198, 1121 and absence of bands 3395, 1583, 732, the aforementioned bands being expressed in cm^{-1} at $\pm 5 \text{ cm}^{-1}$.

Generally speaking, the FITR spectrum of form I looks similar to that of figure 1, obtained in aforementioned conditions.

Figures 6, 7 and 8 show stacking of forms I to V spectra at determined wavelength intervals: figure 6 for 900-650 cm^{-1} range, figure 7 for 250-900 cm^{-1} range, and figure 8 for 1700-1250 cm^{-1} range.

2) X-ray diffraction

X-ray crystallography was performed on each of the forms I to V as a powder (Powder XRD). This technique allows the identification of crystal forms and solvates. Diffractograms were recorded using a Philips X'pert Pro diffractometer equipped with a copper anticathode (wavelength $\lambda=1,54051 \text{ \AA}$) et d'un générateur ($I=20 \text{ mA}$; $U=40 \text{ kV}$).

Measures were performed on a diffraction scale angles ranging from 2 to $60^\circ 2\theta$ with a $0.03^\circ 2\theta$ pitch.

Each sample was put on a glass slide without any prior grinding.

The diffractograms obtained are shown in figures 9, 10, 11, 12 and 13 for forms I, II, III, IV and V, respectively, and the most intense diffraction peaks, characteristic of each form, are reported in table 3, together with the aspect and the chemical purity of each of forms I to V.

Table 3

Forms	Aspect	Chemical purity**(%)	PXRD* Characteristic peaks (2 θ)	Intensity (%)
I	White powder	99.13	12.61-14.11-18.98-19.93- 21.03-25.13- <u>25.91</u>	77.13-71.82- 73.00-67.21- 61.08-60.44- 100.00
II	Brown powder	100	10.54- <u>16.54</u> -21.18-22.71- 24.25	49.71-100.00- 86.30-53.57- 55.16
III	Beige powder	100	7.25-10.84- <u>11.68</u> -13.66- 24.71-26.34	59.55-58.65- 100.00-45.14- 68.00-61.23
IV	Translucent crystal	100	10.51- <u>10.70</u> -19.05-24.88- 25.92	83.95-100.00- 70.44-95.65- 54.46
V	Translucent crystal	95.45	10.05-10.42- <u>12.54</u> -19.89- 20.93	10.28-11.90- 100.00-15.18- 13.61

*Peaks correspondig to 100% are underlined.

**Determined by HPLC

5 For each form, the most intense peak, normalised to 100%, is characteristic and allows to distinguish the different forms from each other. Hence the most intense relections (indicated in table 3 above) were selected for defining form I according to the invention.

10 Generally speaking, powder diffractogram of form I looks similar to that of figure 6, obtained in aforementioned conditions.

3) Structure determination from powder diagram

Crystal structure of form I was determined from its powder diffractogram using a range of software:

- 15 - indexation software, Dicvol91 : Boultif, A. et Louër, D., « Indexing of powder diffraction patterns for low-symmetry lattices by the successive dichotomy method », J. Appl. Cryst., 24, 987-993, 1991,

- Rietveld refining software: Petricek, V., Dusek, M. & Palatinus, L., 2000, Jana2000. The crystallographic computing system. Institute of Physics, Praha, Czech Republic,
- and simulation software, ENDEAVOUR : H. Putz, J.C. Schön, M. Jansen, Combined Method for 'Ab Initio' Structure Solution from PowderDiffraction Data, J. Appl. Cryst. 32, 864-870, 1999.

The crystal parameters obtained using this methods are the following:

Monoclinical lattice

Space group P21/c

$a = 12.1698(7)\text{\AA}$, $b = 7.3815(4)\text{\AA}$, $c = 16.777(1)\text{\AA}$

$\alpha = 90^\circ$, $\beta = 92.825(4)^\circ$, $\gamma = 90^\circ$

$Z = 2$

Table 4 indicates the coordinates of carbon and nitrogen atoms in the crystal structure.

Table 4

Atom	x	y	z	Uiso
Cl1	0.4520(10)	-0.5748(14)	0.1141(7)	0.069(6)
N1 (amine)	0.765(3)	0.233(4)	0.141(2)	0.032(13)
N2 (pyridine)	0.567(2)	-0.211(4)	0.105(2)	0.060(16)
N3 (indole)	0.769(4)	0.316(5)	0.225(2)	0.047(14)
C1 (pyridine)	0.577(3)	-0.145(6)	0.173(2)	0.07(2)
C2 (indole)	0.724(3)	0.497(4)	0.310(2)	0.028(15)
C3 (indole)	0.829(4)	0.435(6)	0.333(3)	0.039(17)
C4 (indole)	0.873(5)	0.326(6)	0.268(3)	0.05(2)
C5 (pyridine)	0.610(3)	-0.127(5)	0.043(2)	0.06(2)
C6 (pyridine)	0.681(3)	0.026(6)	0.052(3)	0.051(17)
C7 (propyl)	0.828(3)	0.329(6)	0.079(2)	0.09(2)
C8 (propyl)	0.773(3)	0.465(5)	0.036(2)	0.10(2)
C9 (propyl)	0.839(2)	0.525(5)	-0.0397(18)	0.098(18)
C10 (indole)	0.699(3)	0.445(5)	0.240(2)	0.07(2)
C11 (indole)	0.964(4)	0.228(5)	0.269(2)	0.05(2)
C12 (indole)	0.915(4)	0.454(4)	0.390(2)	0.029(16)
C13 (pyridine)	0.688(4)	0.085(6)	0.130(3)	0.027(15)
C14 (pyridine)	0.642(3)	0.004(5)	0.196(2)	0.042(18)
C15 (indole)	1.045(3)	0.271(5)	0.329(3)	0.07(2)
C16 (indole)	1.013(4)	0.380(5)	0.384(2)	0.029(16)

Figure 24 shows the diffractogram of form I powder that was used for the determination as well as the difference between the observed and the calculated diffractograms, the latter being represented by the lowest "trace".

5 4) Thermogravimetry (TG)

Thermogravimetry involves monitoring the weight loss of a sample thermically induced, as a function of the applied temperature.

Thermogravimetric analyses were performed on a TA Instruments TGA 2950 instrument, with a 0.1 µg resolution over a scale ranging from 0 to 100 mg. Samples were placed under a nitrogen stream (60 mL/min) and heated at a 5°C/min speed over a temperature interval between 20 and 400°C. TG diagrams are represented in figures 14, 15, 16, 17 et 18 corresponding to forms I, II, III, IV, and V, respectively.

Form II TG indicates a sublimation (and/or vaporisation) process from 145.3°C.

Form IV TG shows a weight loss between 53.7 and 125.4°C, attributed to a desolvation process corresponding to 0.49 mols of solvent.

Form V TG shows a weight loss in two steps between 43.6 and 148.2°C, attributed to a desolvation process corresponding to 0.55 mols of solvent.

5) Differential Scanning Calorimetry (DSC)

This technique measures the thermic flux (absorption/emission) response of a sample as a function of temperature and time.

Differential calorimetric analysis of crystal forms I to V was performed on a DSC Q100 (TA Instruments) differential calorimetric analysis instrument. Sensitivity is 0.2 µW in power, 1% in enthalpy and 0.1 % in temperature. Samples are placed in capsules crimped and heated under a nitrogen stream (50 mL/min) at a 5°C/min speed within a temperature interval ranging from 10 to 240°C. Calorimetric events are characterized by the temperature at onset of the event (T_{onset}) and temperature at its peak (T_{max}). For each form, the peak corresponding to fusion is measured. Thermic profiles of forms I, II, III, IV and V are represented by figures 19, 20, 21, 22 and 23, respectively.

Results are summarised in table 5.

Table 5

Forms	DSC T _{onset} / T _{max} (°C)
I	183.0 / 187.3
	189.8 / 191.6 (exothermic)
	211.2 / 214.4
II	210.1 / 213.8
III	169.4 / 183.4
	212.9 / 215.2
IV	89.0 / 108.7
	213.6 / 215.9
V	68.3 / 71.8
	nd* / 96.5
	190.2 / 193.6
	195.1 / 196.0 (exothermic)
	213.1 / 215.3

* nd = non determined

Form I shows two endothermic and one exothermic peak. The first peak corresponds to the fusion of form I (T_{onset} = 183.0 °C). The exothermic peak corresponds to the cristallisation of form II (T_{onset} = 189.8 °C). The third peak corresponds to the fusion of form II (T_{onset} = 211.2 °C).

Analysis of form I at a 40°C/min speed allowed the determination of an enthalphy ΔH of 130.4 J/g.

Form II shows a fusion peak at 210.1°C.

DSC analysis of form III indicates that this form is converted into form II during the heating process.

Form IV presents an endotherm at 108.7°C that corresponds to the desolvation of the crystal. The second peak corresponds to fusion of form II (215.9°C).

DSC analysis of form V indicates a desolvation in two steps then shows the peaks characterising form I.

6) Stability studies

Stability of crystal form I compared to that of forms II and III was determined by maturation studies. 100 mg suspensions of the different polymorphic forms, separated or in mixtures, in 2 ml of n-butyl-acetate, were

left for maturation during 8 or 72 hours at different temperatures. The result of these experiments is shown in table 6 below.

Table 6

5

Form	Maturation time	Form(s) identified after maturation		
		Temperature (°C)		
		25	50	80
I	8 hours	I	I	I
	3 days	I	I	I
II	8 hours	II	II	II
	3 days	II	II	II
III	8 hours	I	I	I
	3 days	I	I	I
I+II	8 hours	I + II	I + II	I + II
	3 days	I	I	I

Form I is stable under the tested conditions. Form II also appears to be a stable form. However, a mixture of forms I and II changes towards form I in all tested conditions. Form III quickly turns into form I.

10 These different experiments showed that form I is thermodynamically the most stable of the three crystal forms.

The present invention also relates to the processes used for the preparation of crystal form I of besipirdine.HCl.

15 According to the invention, such a process used to obtain the crystal form I of besipirdine.HCl involves the following steps:

- preparation of besipirdine.HCl; as an open-ended example, besipirdine.HCl can be prepared following any known process, including in particular the processes described in US4970218 and WO2005/035496,
- besipirdine.HCl is solubilised into a solvent, a mixture of solvents, or a mixture solvent(s)/water, the aforementioned solvents being chosen among the ones in which besipirdine.HCl is soluble,
- solvent or mixture is at least partially evaporated,
- crystals obtained in that way are collected and dried.

25 The solvent in which besipirdine.HCl is dissolved is advantageously chosen among polar solvents, alcohols, cetons and esters. Thus, it can be

chosen among acetonitrile, acetone, ethanol, ethanol, butanol. As previously mentioned, it can be dissolved in a mixture of these solvents, but also in a mixture of solvent(s), particularly the aforementioned ones, with water; for example, acetonitrile/water and acetone/water mixtures. Proportion of water
5 within these mixtures can vary from 0.01 to 50% in weight of mixture. Thus, acetonitrile/water, 90/10 (v/v) and acetone/water, 90/10 (v/v) mixtures are the preferential mixtures.

According to the invention process, the solvent or the mixture is evaporated at a temperature between 0°C and the boiling point of the solvent
10 or the mixture. Temperature preferentially lies between 0°C and room temperature, even between 0°C and 10°C. At 4°C, evaporation occurs in advantageous conditions.

The aforementioned invention process can be completed with additional steps.

15 In this way, before or during evaporation, the suspension can be seeded with a low amount of besipirdine.HCl crystal form I in order to favour cristallisation of form I.

The solubilisation step of besipirdine.HCl can be complemented by a solubilisation in the aforementioned solvent or mixture until saturation and,
20 during solvent or mixture evaporation, diffusion of a non-solvent more volatile than the aforementioned solvent or mixture and in which besipirdine.HCl is less soluble than in the aforementioned solvent or mixture.

The non solvent is preferentially diffused at room temperature.

In order to achieve this step, the solvent or mixture and the non
25 solvent are advantageously chosen among the following couples, respectively: acetonitrile and acetone, acetonitrile and hexane, acetonitrile/water (for example in a 90/10 proportion) and cyclohexene, acetonitrile/water (for example in a 90/10 proportion) and acetone, acetone/water (for example in a 90/10 proportion) and cyclohexene, butanol and cyclohexene.

30 The crystals obtained using this method can be retrieved by filtration after washing.

Another process of the invention for obtaining crystal form I of besipirdine.HCl includes the following steps:

- preparation of besipirdine.HCl ; as an open-ended example,
35 besipirdine.HCl can be prepared following any known process, including in particular the processes described in US4970218 and WO2005/035496,

- obtained besipirdine.HCl is placed and maintained, possibly under agitation, in a humid environment, in which relative humidity is at least 75%, preferentially at least 85%,

- crystals obtained in that way are collected and dried.

5 A humid environment may, for example, be generated by an aqueous solution saturated in potassium nitrate or by a gas flux laden with steam.

The invention also relates to one another process for obtaining crystal form I of besipirdine.HCl; this process includes the following steps:

10 - preparation of besipirdine.HCl; as an open-ended example, besipirdine.HCl can be prepared following any known process, including in particular the processes described in US4970218 and WO2005/035496,

- a suspension of besipirdine.HCl is prepared in a solvent in which it is not completely soluble, and this suspension is agitated,

15 - crystals obtained in that way are washed, collected and dried.

Advantageously, before or during evaporation, the suspension is seeded with a low amount of besipirdine.HCl crystal form I.

20 The retrieved solvent can contain at least water traces. It can be chosen among esters, cetons, ethers and alcohols with at least two carbon atoms. Advantageously, It is chosen among n-butyle acetate, methyl-ethyl-ceton and methyl-isobutyl-ceton.

The maturation step has a variable length, from 5 minutes to one week but is preferentially less than or equal to 24 hours.

25 The invention also relates to crystal form I of besipirdine.HCl obtained by any of the aforescribed processes.

Polymorphic form I of besipirdine.HCl is thermodynamically the most stable of all characterized forms under use and storing conditions of the powder. Maturation studies and follow-up of clinical batches of besipirdine.HCl show that a mixture of polymorphic forms changes towards turning into form I.
30 Moreover, polymorphic form I of besipirdine.HCl can be obtained specifically using the process of the invention. This constitutes an advantage for the production of besipirdine.HCl as a form of reasonable pharmaceutical quality.

Thus, polymorphic form I of besipirdine.HCl is particularly suitable for the fabrication of pharmaceutical compositions useful for applications in the
35 treatment of all disorders for which besipirdine is indicated.

In particular, in the case of a prolonged-release formulation, the use of a well characterized and stable polymorphic form will avoid the risk of variation in the dissolution and liberation characteristics of the compound.

From another of its aspects, the present invention relates to
5 pharmaceutical compositions in which besipirdine.HCl as polymorphic form I is the active compound.

Thus, the invention relates to the following purposes:

The use of a crystal form of besipirdine.HCl according to the invention for obtaining a stable form of a pharmaceutical composition. This
10 composition can be a therapeutic composition, which can have an immediate or delayed liberation form.

Since crystal form I of besipirdine.HCl has at least all the therapeutic properties of besipirdine as obtained according to processes of the anterior art, the indications of this specific crystal form are all applications for
15 which besipirdine is indicated. In particular, this form is intended to be used for the treatment of symptoms of bladder irritation associated with indications such as overactive bladder (OAB) or interstitial cystitis, effort incontinence or mixed incontinence.

An advantageous therapeutic composition of the invention contains
20 as the active compound, at least 90% of crystal form I of besipirdine.HCl as previously defined.

Within pharmaceutical compositions of the present invention for oral, sublingual, sub-cutaneous, intramuscular, intravenous, transdermic or local administration, the active compound, alone or in association with another
25 active compound, can be administered as a single entity of administration form, as part of a mixture with classical pharmaceutical media, to animals and humans. The suitable entities of administration forms include the forms to be given *per os* such as tablets, gelules, pills, granules and solutions or oral suspensions, forms for sublingual and buccal administration, aerosols, implants,
30 forms for local, transdermic, subcutaneous, intramuscular, intraveinuous, intranasal or intraocular administration.

Within pharmaceutic compositions of the present invention, the active compound or the active compounds are generally formulated in dosage units. One dosage unit contains 0.5 to 300 mg, advantageously 5 to 60 mg and
35 preferentially 5 to 40 mg per dosage unit for daily administrations, one or several times a day.

Although these dosages are examples of intermediate situations, particular cases in which higher or lower dosages are suitable, such dosages are also included in the invention. In usual practice, the dosage appropriate for each patient is determined by the doctor as a function of the mode of administration and the age, weight and response of the aforementioned patient.

When preparing a solid composition as the form of tablets or gelules, a mixture of pharmaceutical excipients made up of diluents such as, for example, lactose, mannitol, microcrystallin cellulose, amidon, dicalcic phosphate, binding agents such as polyvinylpyrrolidone or hydroxypropylmethylcellulose for example, bursting agents such as, for example, crosslinked polyvinylpyrrolidone, crosslinked carboxymethylcellulose, sodium croscarmellose, flowing agents such as silice, talc, lubricants such as magnesium stearate, stearic acid, glycerol tribehenate, sodium stearyl fumarate, is added to the active compounds, micronised or not.

Wetting or tensioactive agents such as sodium laurylsulfate, polysorbate 80, poloxamer 188 can be added to the formulation.

Tablets can be produced using different techniques, direct compression, dry granulation, humid granulation, hot-melt.

Tablets can be nude, sugar-coated (using saccharose for example) or coated with different polymers or other suitable materials.

Tablets can have an immediate, delayed or extended liberation by using polymeric matrices or specific polymers during the coating process.

Gelules can be hard or soft, coated or not, in order to have an immediate, extended or delayed (for example a form for parenteral administration) activity. They can contain not only a solid formulation formulated as previously described for tablets, but also liquids or semi-solids.

A preparation as a syrup or elixir form can contain the active compound or the active compounds together with a sweetener, preferentially acaloric, methylparaben and propylparaben as antiseptic agents as well as a flavouring agent and an appropriate colouring agent.

Water-dispersible powders or granules in water can contain the active compound or the active compounds as a mixture with dispersing or wetting agents, or suspending agents such as polyvinylpyrrolidone or polyvidone, as well as sweeteners or flavouring agents.

For rectal administration, suppositories are used that are prepared with linking agents melting at rectal temperature, for example cocoa butter or polyethyleneglycols.

For parental, intranasal or intraocular administration, aqueous
5 suspensions, isotonic saline solutions or sterile injectable solutions containing dispersing agents and/or pharmaceutically compatible solubilising agents such as propyleneglycol or butyleneglycol, are used.

Hence, in order to prepare an aqueous solution injectable intraveinously, a cosolvent, for example an alcohol such as ethanol or a glycol
10 such as polyethyleneglycol or propyleneglycol, and a hydrophilic tensioactive such as polysorbate 80 or poloxamer 188 can be used. In order to prepare an oleous solution injectable intramuscularly, the active compound can be solubilised using a triglyceride or a glycerol ester.

For local administration, creams, ointments, gels, eye lotions and
15 sprays can be used.

For transdermic administration, patches can be used which can be in multilaminar form or with a reservoir in which the active compound is in alcoholic solution.

For an administration by inhalation, an aerosol containing, for
20 example, sorbitane trioleate or oleic acid as well as trichlorofluoromethan, dichlorofluoromethan, dichlorotetra-fluoroethan, freon substitutes or any other biologically compatible propulsing gas is used; a system containing the active compound, alone or associated with an excipient, all as powders, can be used.

The active compound or the active compounds can also be
25 presented as a complex with a cyclodextrin, for example α -, β - ou γ -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin or methyl- β -cyclodextrin.

The active compound or the active compounds can also be formulated as microcapsules or microspheres, possibly with one or several
30 carriers or additives.

Among the extended liberation forms useful for chronic treatments, implants can be used. These implants can be prepared as an oleous suspension or a suspension of microspheres in an isotonic environment.

Preferentially, besipirdine.HCl as crystal form I is administered per os,
35 once daily.

From another angle, the invention also relates to a method involving the administration of a therapeutically effective amount of besipirdine.HCl as polymorph I.

5 The following examples show several methods of obtention of form I, except example 1, which indicates the method of obtention of other forms of besipirdine.HCl.

 Examples 3 to 11 illustrate methods of cristallisation allowing the obtention of monocrystals. In examples 6 to 11, the vapour diffusion technique
10 is used: a solution saturated in compound in a relatively non-volatile solvent, is placed in a small container. This container is placed into a dessicator containing a solvent more volatile than the one in which besipirdine.HCl is not soluble. The vapour of this solvent diffuses slowly into the container, favouring the precipitation of the compound as unique crystals (*X-ray Structure*
15 *Determination A Practical Guide*, 2nd edition, George H. Stout and Lyle H. Jensen, John Wiley & Sons, New York, 1989). Characterisation of the crystals is preformed by optical microscopy and DSC.

 Example 12 shows a method of obtention of form I by maturation in a humid environment, without any recrystallisation step.

20 Examples 13 to 18 present methods of production in which transformation is achieved by maturation in suspension (slurry transformation).

 EXAMPLE 1 : obtention of crystal forms II, II, IV and V from besipirinde.HCl synthesised according to the process described in patent
25 application WO 2005/035496

 Characterisation of the samples is performed by DSC, TG and PXRD.

 In order to obtain the polymorphic form II of besipirdine.HCl, 200 mg of powder are heated at 200°C until complete melt, then it is
30 recrystallised at 25°C for 10 days. No solvent restraint is observed.

 Polymorphic form III is obtained by solubilising 200 mg of powder in a 6 ml volume of acetonitrile at 70°C under agitation, followed by the evaporation of the solvent at 25°C in a dessicator for 8 days. No solvent restraint is observed.

Sovate form IV is obtained by solubilising 200 mg of powder in a 4 ml volume of methanol at room temperature, followed by the evaporation of the solvent at 4°C in a dessicator for 7 days.

5 Solvate form V is obtained by solubilising 200 mg of powder in a 4 ml volume of ethanol at room temperature, followed by the evaporation of the solvent at 4°C in a dessicator for 7 days.

EXAMPLE 2 : obtention of crystal form I in a mixture of 90% acetonitrile and 10% water mixture

10 200 mg of besipirdine.HCl in 1 ml acetonitrile/water (90/10 : v/v) mixture are solubilised at room temperature under agitation. Solvent is evaporated at 4°C in a dessicator for 8 days.

EXAMPLE 3 : obtention of crystal form I in acetonitrile

15 A solution saturated in besipirdine.HCl in acetonitrile is prepared at room temperature and under agitation. Solvent is evaporated at 4°C. Crystals are dried in a dessicator then characterized by DSC and optical microscopy. The crystals that are formed look like white needles.

20 EXAMPLE 4 : obtention of crystal form I in ethanol

A solution saturated in besipirdine.HCl in ethanol is prepared at room temperature and under agitation. Solvent is evaporated at 4°C. Crystals are dried in a dessicator then characterized by DSC and optical microscopy. The crystals that are formed look like a mixture of white prisms and beige blocks.

EXAMPLE 5 : otention of crystal form I in a mixture of 90% acetone and 10% water mixture

30 200 mg of besipirdine.HCl in 1 ml acetone/water (90/10 : v/v) mixture are solubilised at room temperature under agitation. Solvent is evaporated at 4°C in a dessicator for 8 days. Crystals are dried in a dessicator then characterized by DSC and optical microscopy. The crystals that are formed look like beige sheets.

EXAMPLE 6 : obtention of crystal form I in acetonitrile using the vapour diffusion method

A solution saturated in besipirdine.HCl in acetonitrile is prepared at room temperature and under agitation. Sample is placed in a dessicator at room temperature in an environment rich in acetone to favour precipitation. Crystals are dried in a dessicator then characterized by DSC and optical microscopy. The crystals that are formed look like beige sheets and microcrystals.

EXAMPLE 7 : obtention of crystal form I in acetonitrile using the vapour diffusion method

A solution saturated in besipirdine.HCl in acetonitrile is prepared at room temperature and under agitation. Sample is placed in a dessicator at room temperature in an environment rich in hexan to favour precipitation. Crystals are dried in a dessicator then characterized by DSC and optical microscopy. The crystals that are formed look like beige sheets.

EXAMPLE 8 : obtention of crystal form I in a mixture of 90% acetonitrile and 10% water mixture using the vapour diffusion method

A solution saturated in besipirdine.HCl in an acetonitrile/water (90/10: v/v) mixture is prepared at room temperature and under agitation. Sample is placed in a dessicator at 4°C whose air is rich in cyclohexen to favour precipitation. Crystals are dried in a dessicator then characterized by DSC and optical microscopy. The crystals that are formed look like beige sheets.

EXAMPLE 9 : obtention of crystal form I in a mixture of 90% acetonitrile and 10% water using the vapour diffusion method

A solution saturated in besipirdine.HCl in an acetonitrile/water (90/10: v/v) mixture is prepared at room temperature and under agitation. Sample is placed in a dessicator at room temperature whose air is rich in acetone to favour precipitation. Crystals are dried in a dessicator then characterized by DSC and optical microscopy. The crystals that are formed look like white stars.

EXAMPLE 10 : obtention of crystal form I in a mixture of 90% acetone and 10% water using the vapour diffusion method

A solution saturated in besipirdine.HCl in an acetone/water (90/10: v/v) mixture is prepared at room temperature and under agitation. Sample is placed in a dessicator at 4°C whose air is rich in cyclohexen to favour precipitation. Crystals are dried in a dessicator then characterized by DSC and optical microscopy. The crystals that are formed look like beige sheets.

EXAMPLE 11 : obtention of crystal form I in butanol using the vapour diffusion method

A solution saturated in besipirdine.HCl in butanol is prepared at room temperature and under agitation. Sample is placed in a dessicator at 4°C whose air is rich in cyclohexen to favour precipitation. Crystals are dried in a dessicator then characterized by DSC and optical microscopy. The crystals that are formed look like beige sheets.

EXAMPLE 12 : obtention of crystal form I by transformation in solid phase (maturation in a humid atmosphere)

100 mg of besipirdine.HCl as crystal form III or as a mixture of forms II and III are placed overnight in a closed dessicator whose lowest part is filled with a solution saturated in potassium nitrate. Such conditions induce an atmosphere with about 85% relative humidity. Samples are then placed in a standard dessicator Drierite to provide form I.

EXAMPLE 13 : obtention of crystal form I by transformation in solid phase (maturation in a humid atmosphere)

20 g of besipirdine.HCl as a mixture of forms II and III are placed in a 200 ml evaporation balloon flask. This balloon flask is placed on a rotative evaporator whose lowest part is charged with an aqueous saturated solution of potassium nitrate. The whole thing is closed so that the relative humidity reaches an equilibrium at about 85%, with a rotation speed of about 30 turns/min. The balloon flask is regularly weighted and samples are taken up for differential calorimetry analysis. After 4 days, the DSC analysis, confirmed by the X-ray powder diagram, indicates that transformation into form I is total. HPLC analysis indicates a purity of 99.95 %, identical to that of the original material.

EXAMPLE 14 : obtention of crystal form I by transformation in methyl-isobutyl-cetone (slurry transformation)

100 mg of besipirdine.HCl as a mixture of forms II and III is mixed with methyl-isobutyl-cetone containing water traces for about 24 hours. Crystals
5 are then isolated, dried under nitrogen and characterized by DSC and optical microscopy. DSC analysis indicates the transitions associated with form I.

EXAMPLE 15 : obtention of crystal form I by transformation in ethylmethylcetone (slurry transformation)

10 1 g of besipirdine.HCl as a mixture of forms II and III is mixed overnight, at room temperature, with 3 ml of ethylmethylcetone containing 2 µl of water. The mixture is then filtered, washed with methyl-ethyl-cetone and vacuum-dried for 3 hours. About 0.9 g of besipirdine.HCl as form I are obtained.

15 The compound is characterized by DSC and optical microscopy. DSC analysis indicates the transitions associated with form I.

EXAMPLE 16 : obtention of crystal form I by transformation in n-butyle acetate (slurry transformation)

20 1 g of besipirdine.HCl as a mixture of forms II and III is mixed overnight, at room temperature, with 3 ml of n-butyle acetate saturated in water (about 1%). The mixture is then filtered, washed with n-butyle acetate and vacuum-dried for 3 hours. About 0.9 g of besipirdine.HCl as form I are obtained.

25 The compound is characterized by DSC and optical microscopy. DSC analysis indicates the transitions associated with form I.

EXAMPLE 17 : obtention of crystal form I by transformation in water-saturated n-butyle acetate (slurry transformation)

30 20 g of besipirdine.HCl as a mixture of forms II and III are suspended in 100 ml water-saturated n-butyle acetate. The obtained suspension is mixed under a nitrogen atmosphere for 24 hours at room temperature. The solution is then filtered then washed 3 times with 20 ml of pure undiluted n-butyle acetate. After 30 min air-drying, the white solids are
35 vacuum-dried overnight at 25°C to eliminate residual solvent. The efficiency of the operation is 97%. HPLC analysis indicates a purity > 99.97 %. Transformation into form I is confirmed by DSC and PXRD analyses.

EXAMPLE 18: preparation of an immediate release form from polymorphic form I of besipirdine.HCl

From polymorphic form I of besipirdine.HCl, immediate release
5 gelules are prepared by granulation in humid phase using the composition indicated in the table below:

Ingredient	Amount (mg)
Besipirdine HCl, form I	20.00
Amidon (corn)	95.75
Pregelatinised amidon (starch 1500)	35.00
Sodic croscarmellose	12.00
Microcristallin cellulose	80.00
Magnesium stearate	1.50
Colloidal silicon dioxide	0.75
Purified water qsf	
Total	245.00

Corn amidon and besipirdine.HCl are introduced in the granulator
10 and mixed for about 5 minutes.

Microcristallin cellulose, pregelatinised amidon and a proportion
(50%) of sodic croscarmellose are added. The whole ingredients are mixed for
about 5 minutes. Granulation of the powder is performed by adding
demineralised water (39% w/w) with a 15 ml/min flow, until obtention of a
15 density of between 0.45 and 0.5 g/cm³. Granules are dried on a fluidised bed at
60°C for 30 minutes until obtention of a residual humidity ratio below 5%.

Dried granules are calibrated on a 630 µm sieve, introduced in a
container with the remainder of sodium croscarmellose and mixed for
5 minutes. Magnesium stearate and colloidal silicon dioxide are then added
20 and mixed for 15 minutes.

Size 1 gelatin gelules are manually filled with the final mixture.

EXAMPLE 19: preparation of an immediate release form from polymorphic form I of besipirdine.HCl

From polymorphic form I of besipirdine.HCl, immediate release
25 tablets are prepared that have the composition indicated in the table below:

Ingredient	Amount (mg)
Besipirdine HCl, form I	20.00
Microcrystalline cellulose	174.00
Aerosil	1.00
Sodic croscarmellose	4.00
Magnesium stearate	1.00
Total	200.00

All ingredients, except magnesium stearate, are mixed in a Turbula mixer for 10 minutes. Magnesium stearate is then added and mixed for 5 minutes. Tablets are obtained by direct compression using a rotative press.

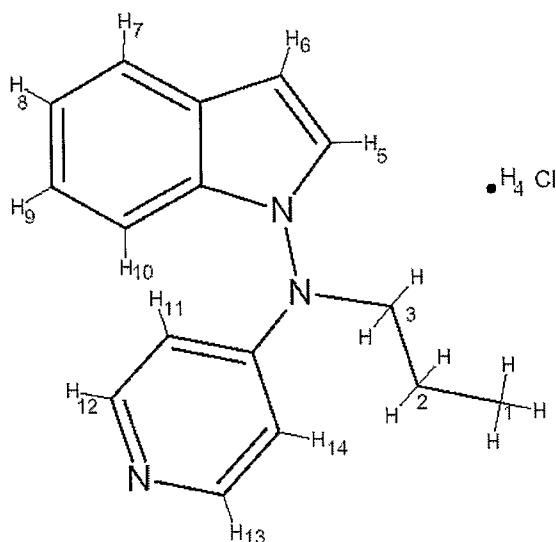
25

CLAIMS

1. Crystal form of besipirdine.HCl (Form I) corresponding to the formula A below:

Formula A

5



The aforementioned form being characterized by at least one of the following physico-chemical properties:

10 a) In FTIR, it displays at least the following absorption bands of the infrared spectrum: 778, 1198, 1121, but not the following absorption bands of the infrared spectrum: 3395, 1583, 732, the aforementioned bands being expressed in cm^{-1} at $\pm 5 \text{ cm}^{-1}$;

15 b) In PXRD, it shows at least the following reflections, which are the most intense ones but whose intensity hereafter is given for information only:

Angle (2θ)	12.61	14.11	18.98	19.93	21.03	25.13	25.91
Intensity (%)	77.13	71.82	73.00	67.21	61.08	60.44	100.00

20 c) In DSC, it displays at least an endothermic peak at $187.3 \pm 2.0 \text{ }^\circ\text{C}$ using $5 \text{ }^\circ\text{C/min}$ scanning conditions, and a fusion enthalpy ΔH of $130.4 \pm 2.0 \text{ J/g}$.

2) Crystal form according to claim 1, characterized by at least two of the characteristics a), b) and c).

3) Crystal form according to claim 1 or 2, characterized by the three of the characteristics a), b) and c).

5 4) Process for obtaining crystal form I of besipirdine.HCl, as defined in any one of claims 1 to 3, characterized in that it includes the following steps:

Preparation of besipirdine.HCl, for example according to a known process such as the ones described in US4970218 and WO2005/035496,

10 Solubilisation of besipirdine.HCl in a solvent, a mixture of solvents or a mixture solvent(s)/water, the aforementioned solvent(s) being chosen among those in which besipirdine.HCl is soluble,

Evaporation, at least partial, of solvent or mixture,

Retrieval and drying of obtained crystals.

15 5) Process according to claim 4, characterized in that besipirdine.HCl is solubilised in a solvent chosen among polar solvents, alcohols, cetones and esters.

6) Process according to claim 5, characterized in that the solvent is chosen among acetonitrile, acetone, ethanol, butanol.

20 7) Process according to claim 4, characterized in that the mixture of solvent(s) with water is chosen among acetonitrile/water and acetone/water mixtures.

8) Process according to claim 7, characterized in that the mixture of solvent(s) with water is chosen among acetonitrile/water, 90/10 (v/v) and acetone/water, 90/10 (v/v) mixtures.

25 9) Process according any of claims 4 to 6, characterized in that the solvent or the mixture is evaporated at a temperature between 0°C and room temperature.

10) Process according to claim 9, characterized in that evaporation is performed between 0°C and 10°C.

30 11) Process according to claim 10, characterized in that evaporation is performed at a temperature of about 4°C.

12) Process according to any of claims 4 to 11, characterized in that, before or during evaporation, suspension is seeded with a low amount of crystal form I of besipirdine.HCl.

35 13) Process according to any of claims 4 to 12, characterized in that besipirdine.HCl is solubilised in the said solvent or mixture until saturation,

and, during evaporation of the solvent or mixture, a non solvent more volatile than the said solvent or mixture and in which besipirdine.HCl is less soluble than in the said solvent or mixture, is diffused during evaporation of the solvent or mixture.

5 14) Process according to claim 13, characterized in that the non-solvent is diffused at room temperature.

 15) Process according to claim 13 or 14, characterized in that the solvent or mixture and the non-solvent are chosen among one of the following couples: acetonitrile and acetone, acetonitrile and hexane, acetonitrile/water
10 and cyclohexene, acetonitrile/water and acetone, acetone/water and cyclohexene, butanol and cyclohexene.

 16) Process according to any of claims 4 to 15, characterized in that crystals are retrieved by filtration.

 17) Process for obtaining crystal form I of besipirdine.HCl,
15 characterized in that it includes the following steps:

 Preparation of besipirdine.HCl, for example according to a known process such as the ones described in US4970218 and WO2005/035496,

 Besipirdine.HCl obtained in that way is maintained, possibly under agitation, in a humid environment in which relative humidity is at least 75%,
20

 Retrieval and drying of obtained crystals.

 18) Process according to claim 17, characterized in that relative humidity is at least 85%.

 19) Process according to claim 17 or 18, characterized in that the humid atmosphere is generated by an aqueous solution saturated in potassium
25 nitrate.

 20) Process for obtaining crystal form I of besipirdine.HCl, characterized in that it includes the following steps:

 Preparation of besipirdine.HCl, for example according to a known process such as the ones described in US4970218 and WO2005/035496,
30

 Preparation of a suspension of besipirdine.HCl in a solvent in which it is not completely soluble, and agitation of this suspension,

 Washing, retrieval and drying of obtained crystals.

 21) Process according to claim 20, characterized in that, before or during evaporation, the suspension is seeded with a low amount of crystal
35 form I of besipirdine.HCl.

28

22) Process according to claim 21, characterized in that the solvent contains water traces, at least.

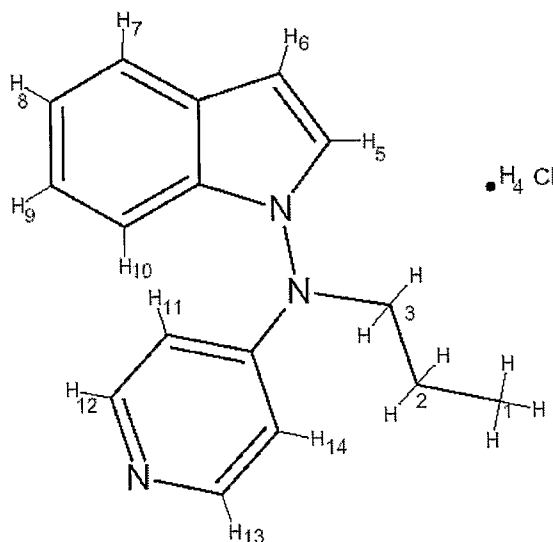
23) Process according to any of claims 20 to 23, characterized in that the said solvent is chosen among esters, cetones, ethers and alcohols including at least two carbon atoms.

24) Process according to claim 20, characterized in that the said solvent is chosen among n-butyle acetate, methyl-ethyl-cetone and methyl-isobutyl-cetone.

25) Process according to claim 17 or 20, characterized in that the suspension is agitated for at least one day.

26) Crystal form of besipirdine.HCl corresponding to formula A below:

Formula A



Which is likely to be obtained by a process according to any of claims 4 to 25.

27) Use of crystal form I of besipirdine.HCl according to any of claims 1, 2, 3 or 26, for obtaining a stable form of a pharmaceutical composition.

28) Use according to claim 27, characterized in that the pharmaceutical composition is a therapeutic composition.

29) Use according to claim 28, characterized in that the pharmaceutical composition is under a form with immediate or delayed liberation.

30) Use according to claim 28 or 29, characterized in that the therapeutic composition is intended to the treatment of symptoms of bladder irritation associated with indications such as overactive bladder (OAB) or interstitial cystitis, or to the treatment of stress urinary incontinence or mixed
5 incontinence.

31) Therapeutic composition containing as the active compound, at least 90% of crystal form I of besipirdine.HCl as defined in any of claims 1,2, 3 or 26.

FIGURE 1

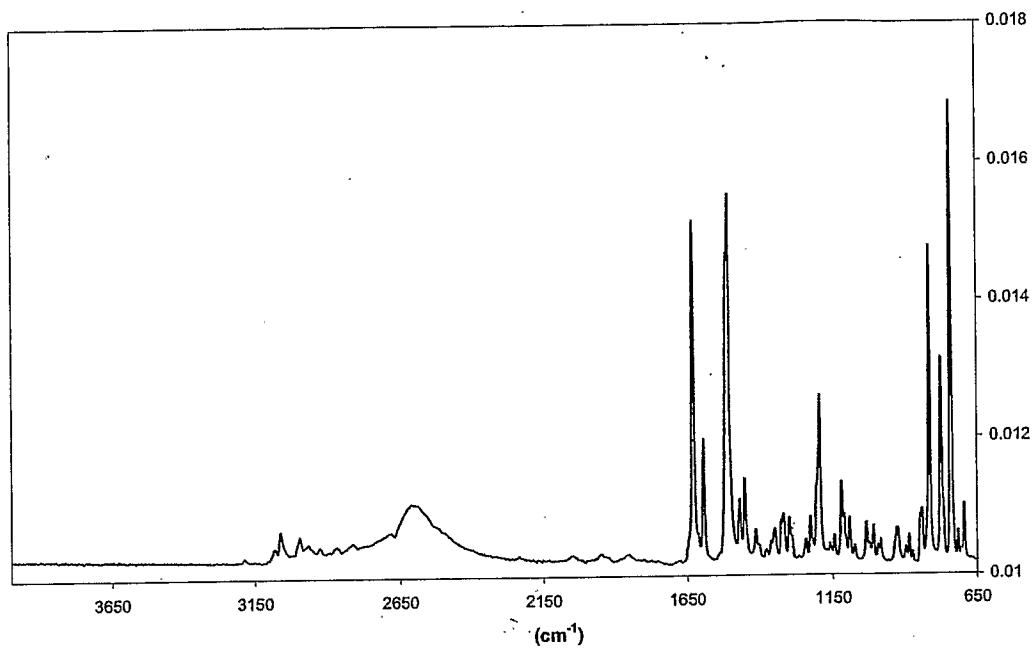


FIGURE 2

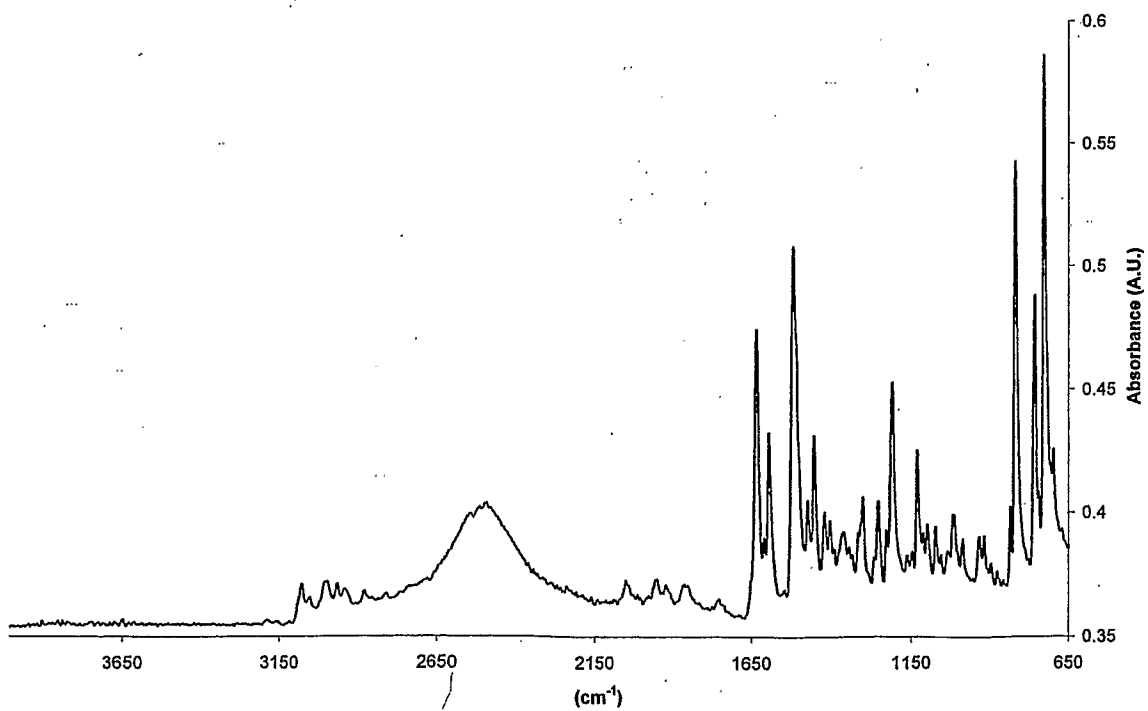


FIGURE 3

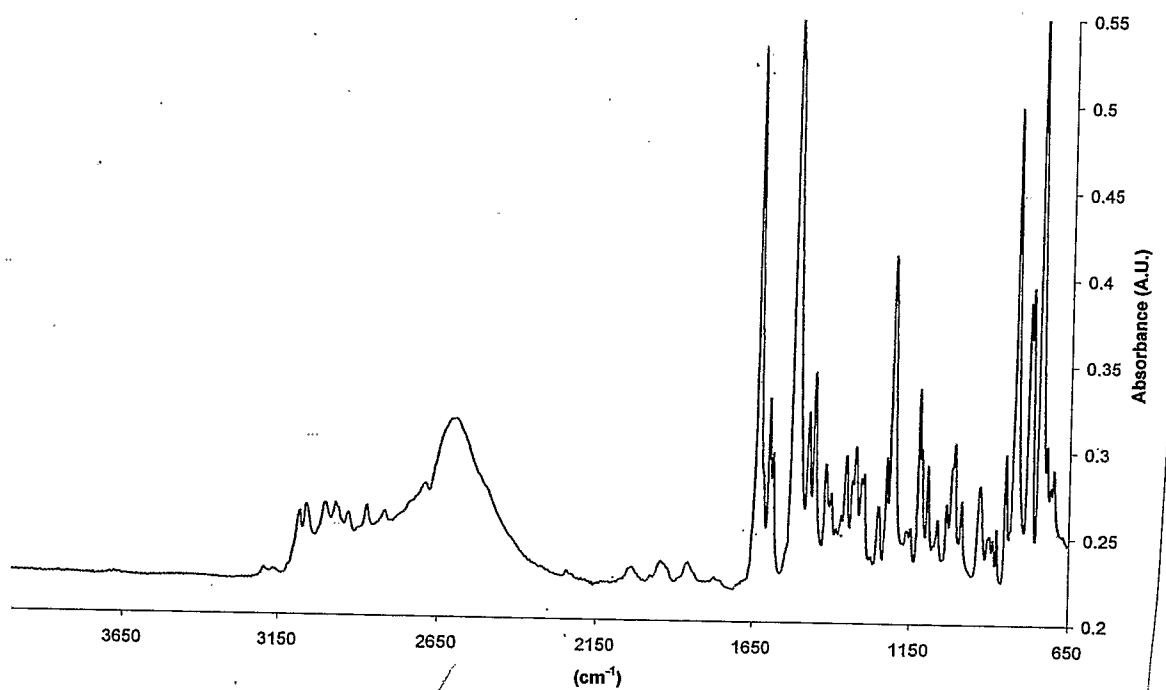


FIGURE 4

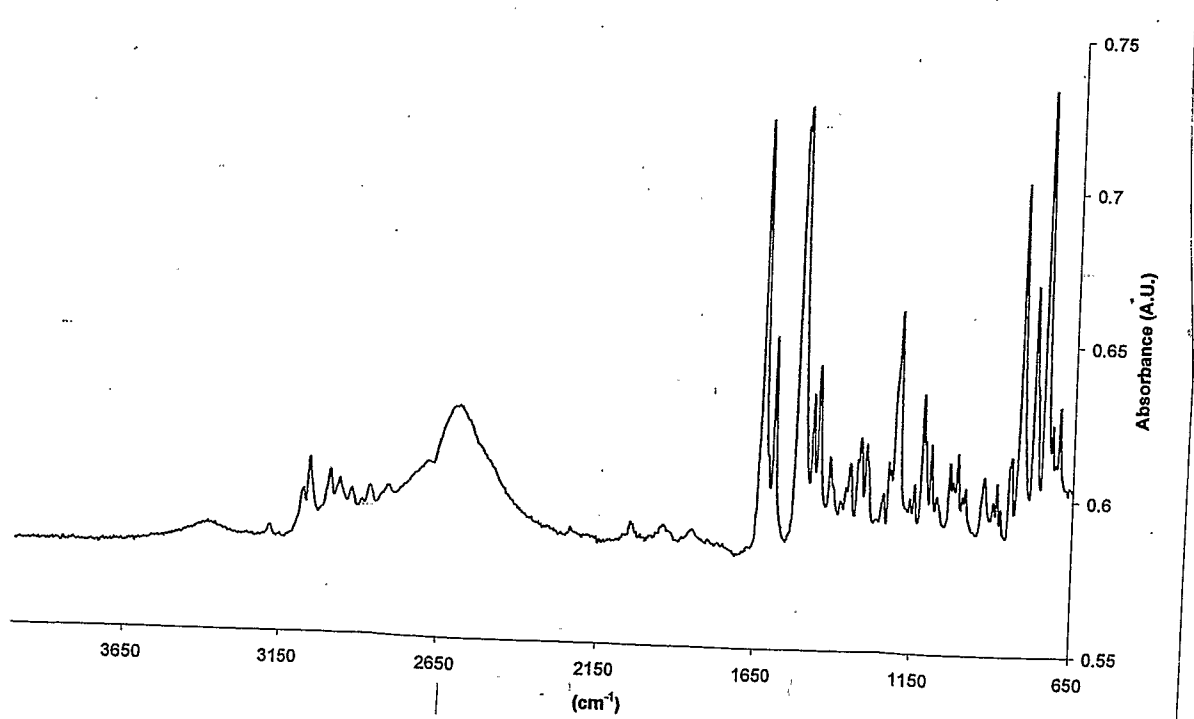


FIGURE 5

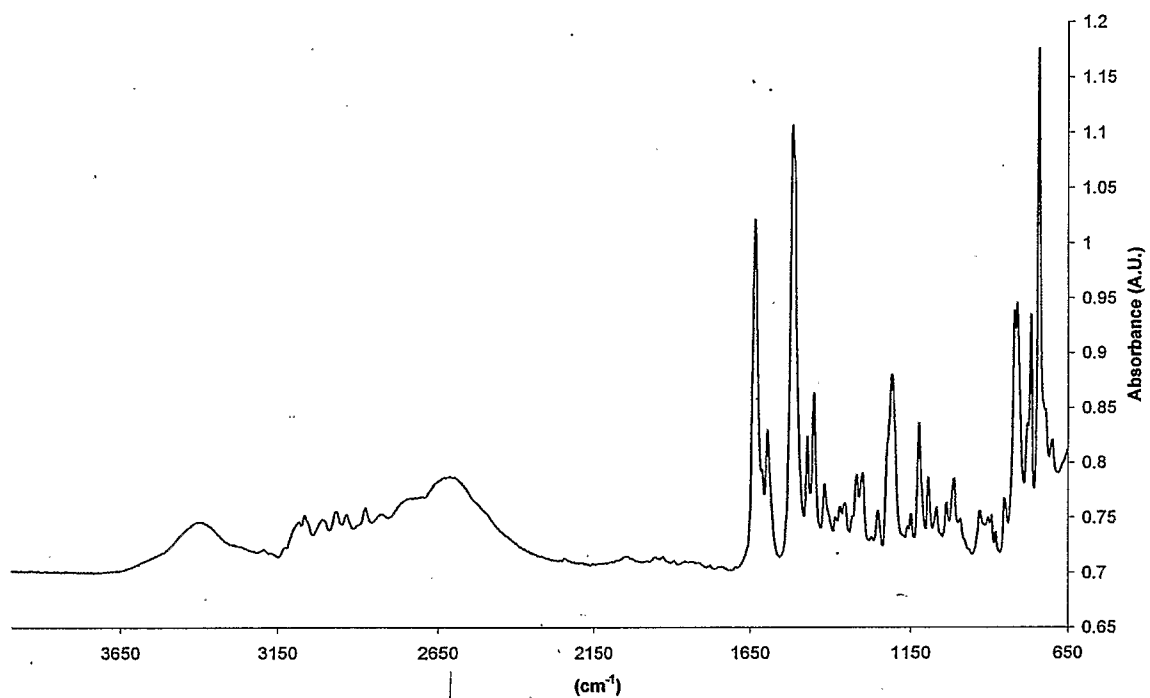


FIGURE 6

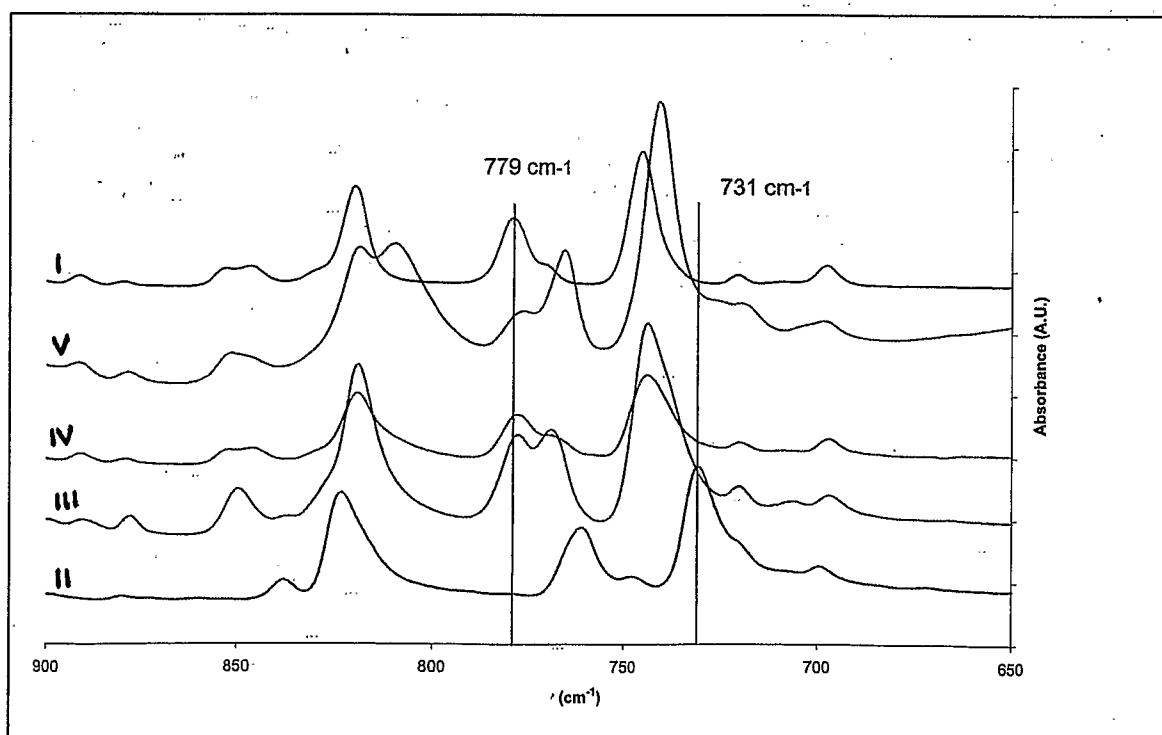


FIGURE 7

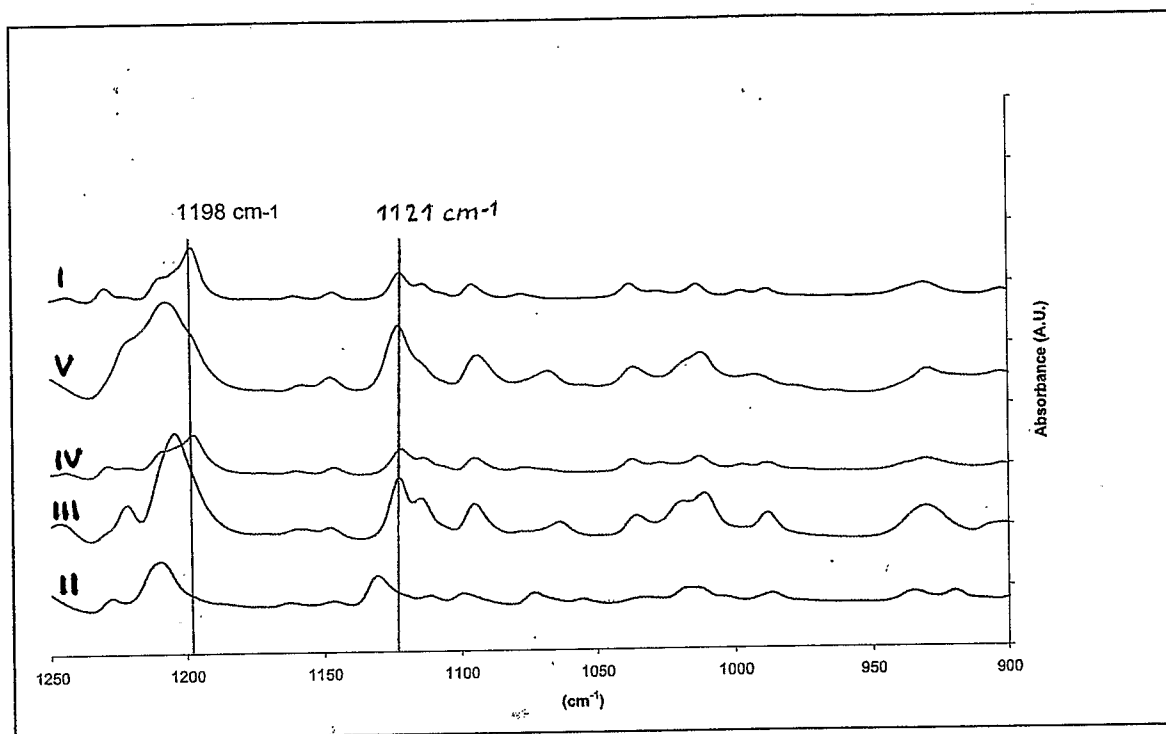


FIGURE 8

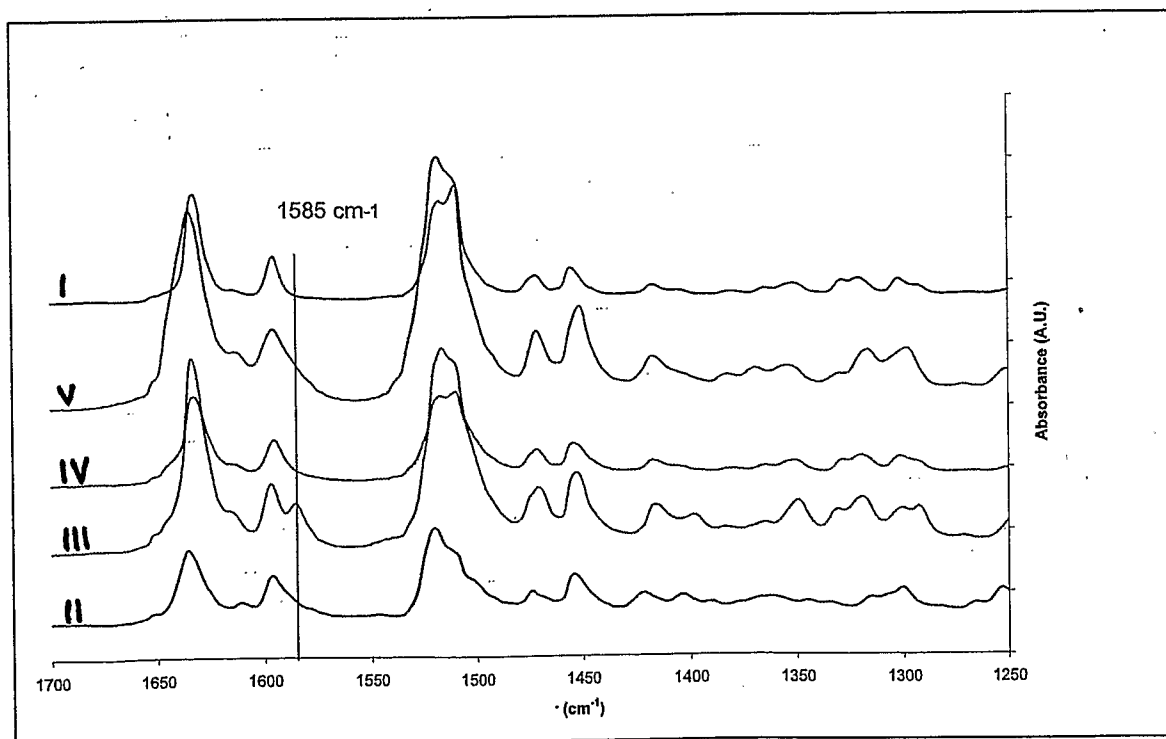


FIGURE 9

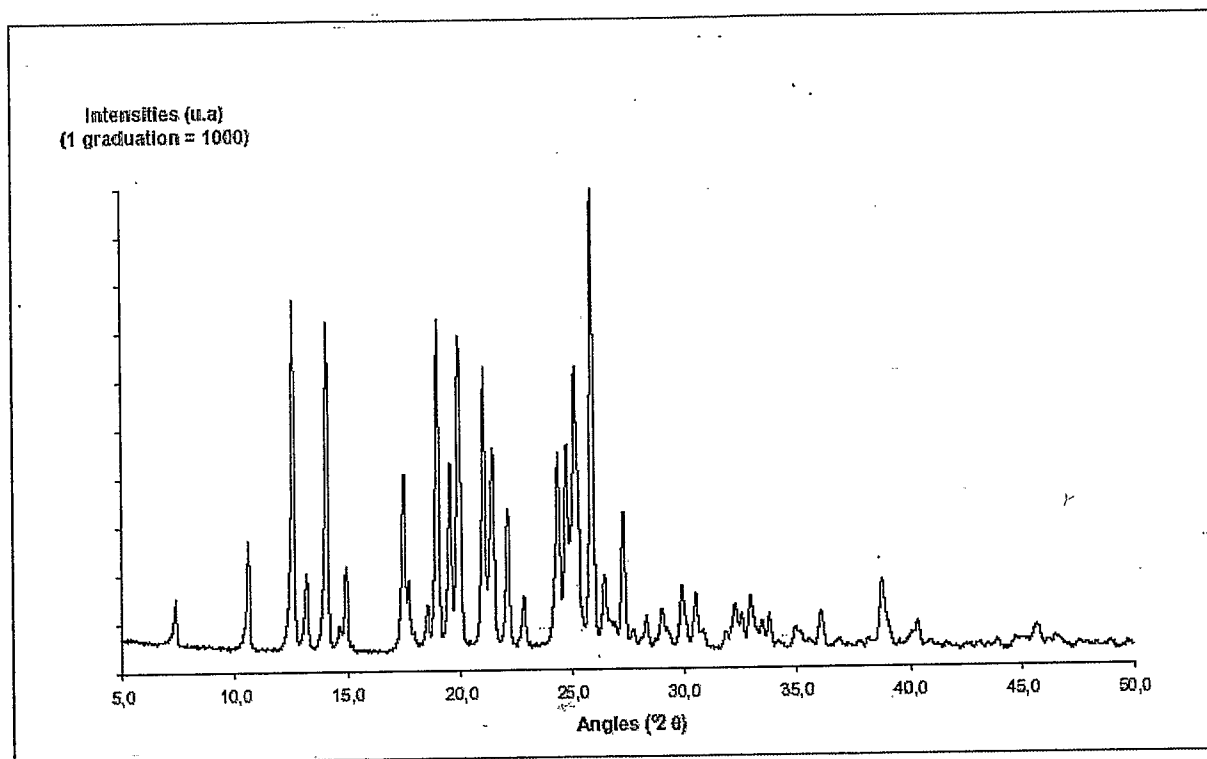


FIGURE 10

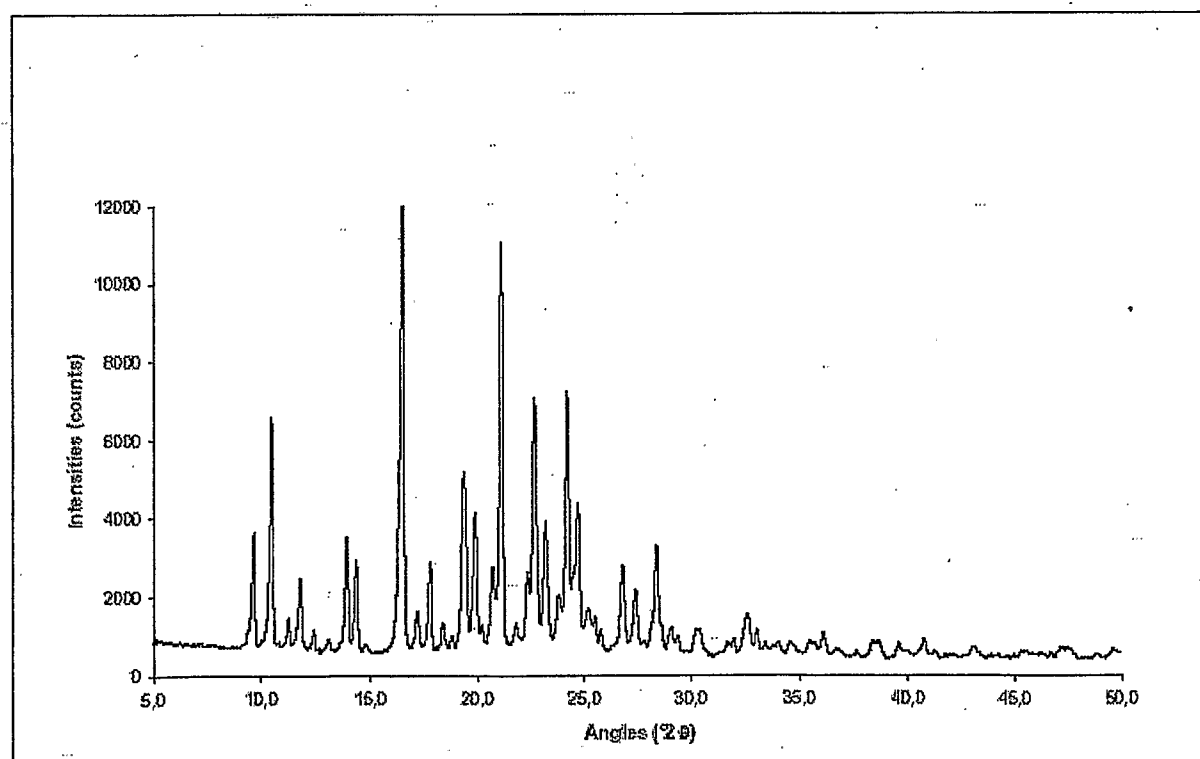


FIGURE 11

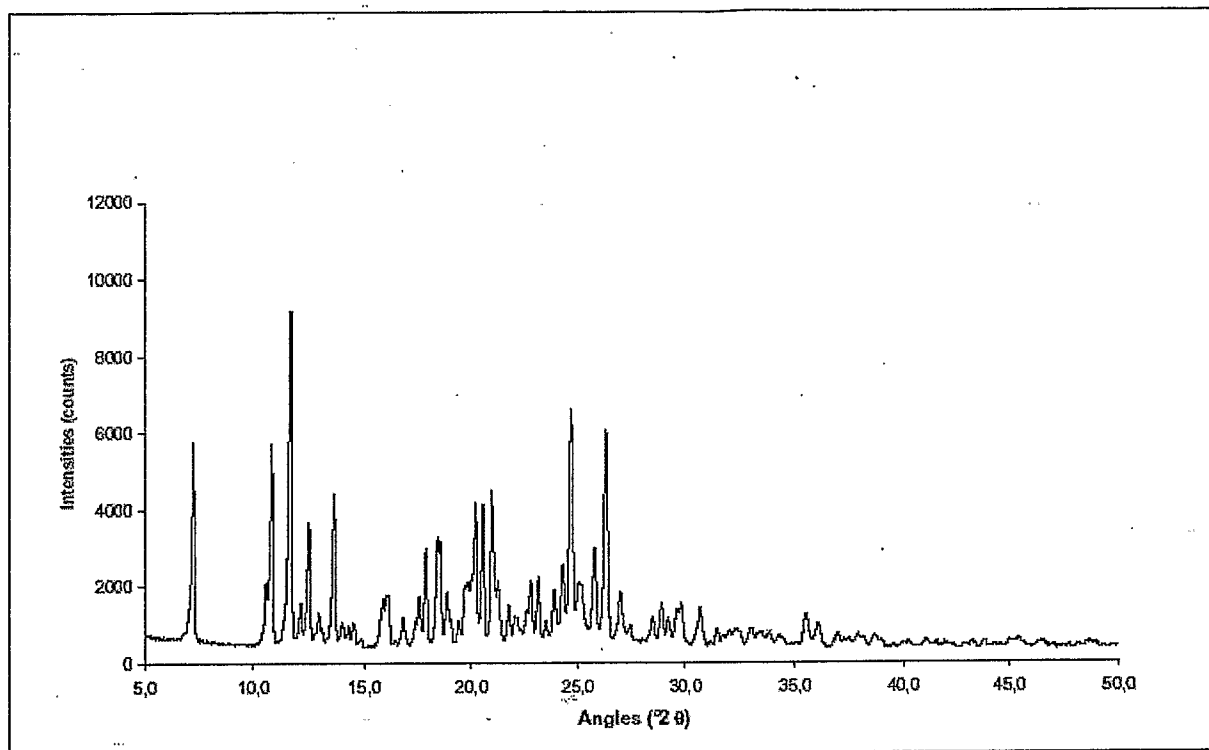


FIGURE 12

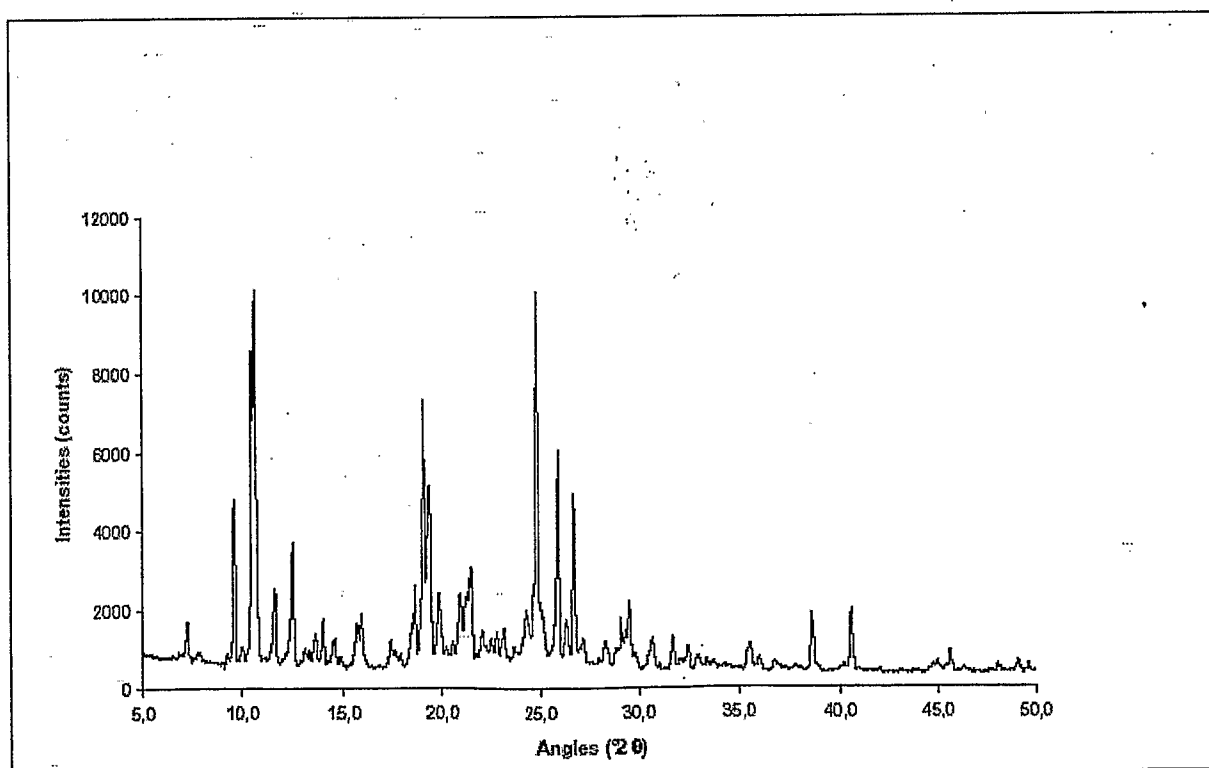


FIGURE 13

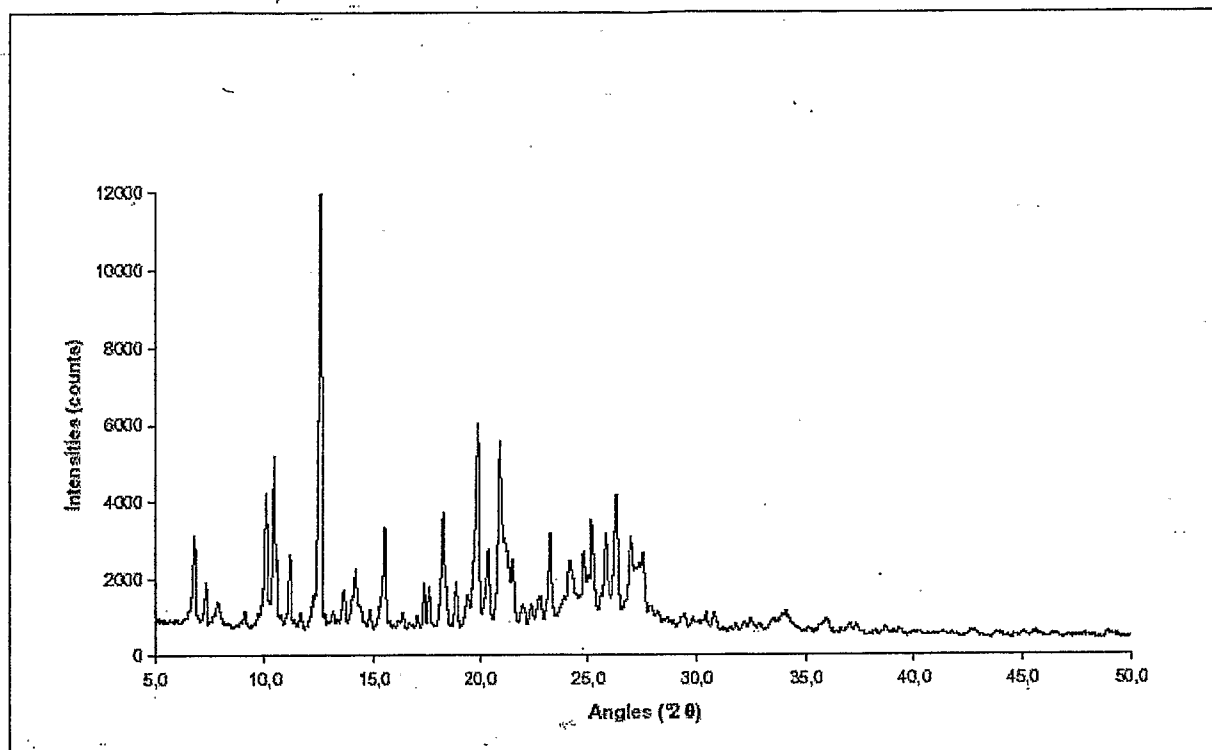


FIGURE 14

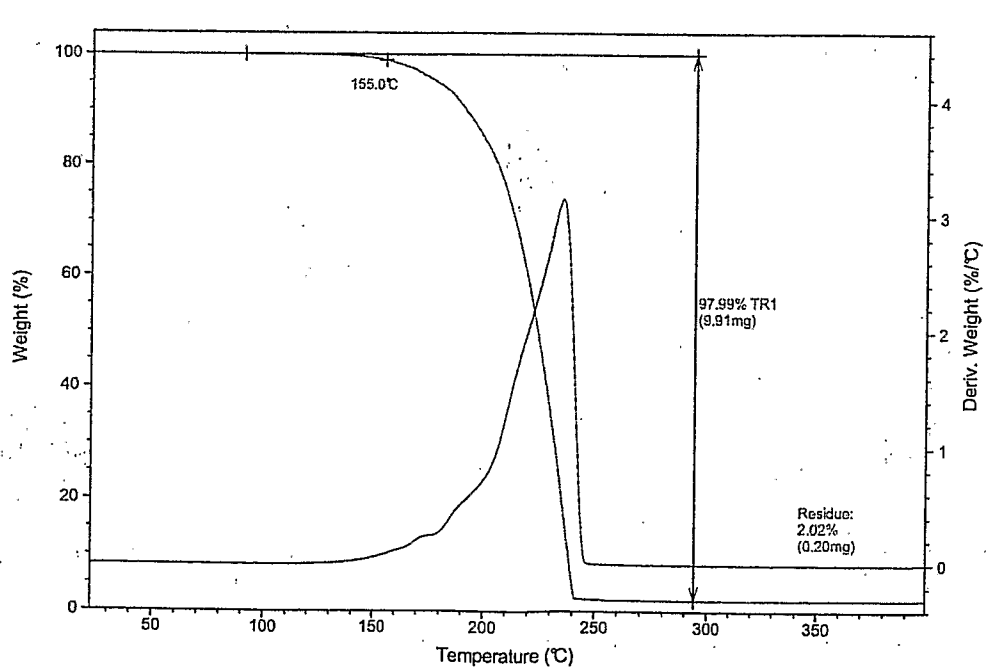


FIGURE 15

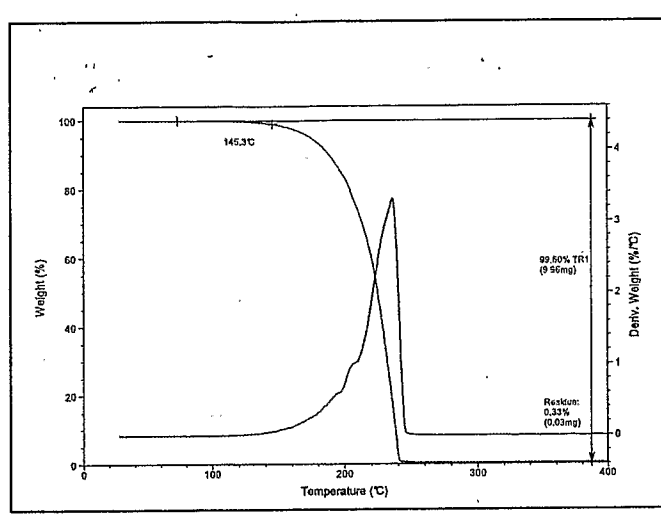


FIGURE 16

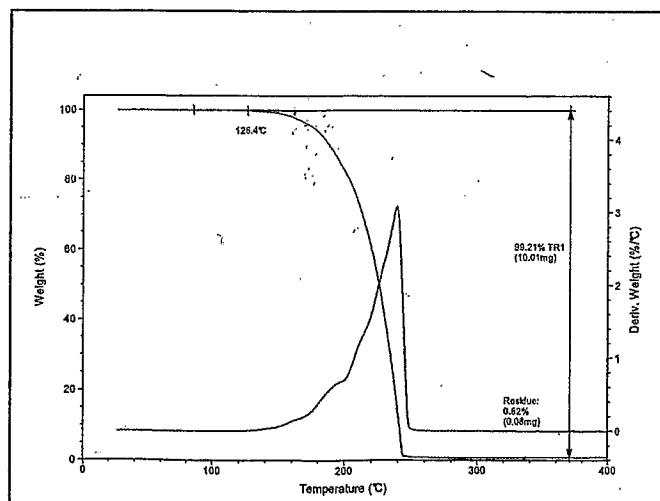


FIGURE 17

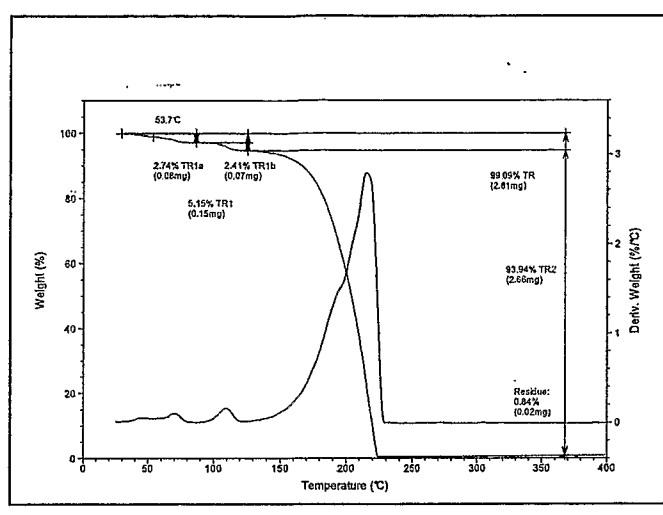


FIGURE 18

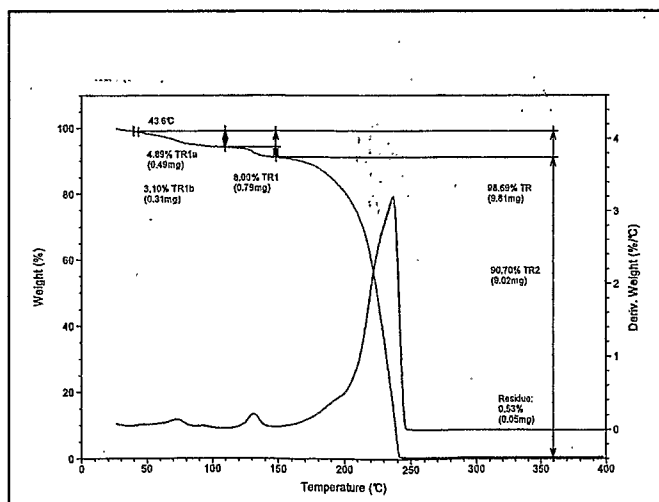


FIGURE 19

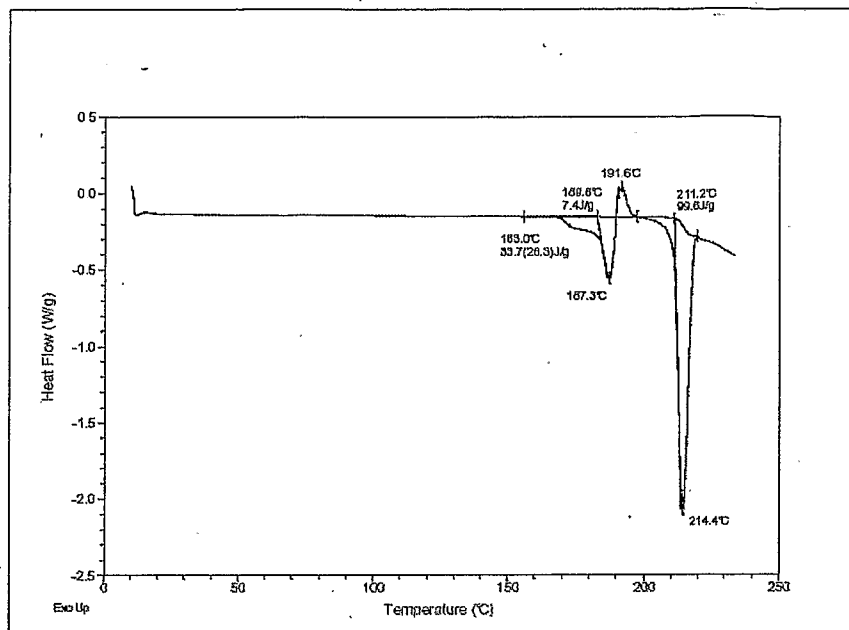


FIGURE 20

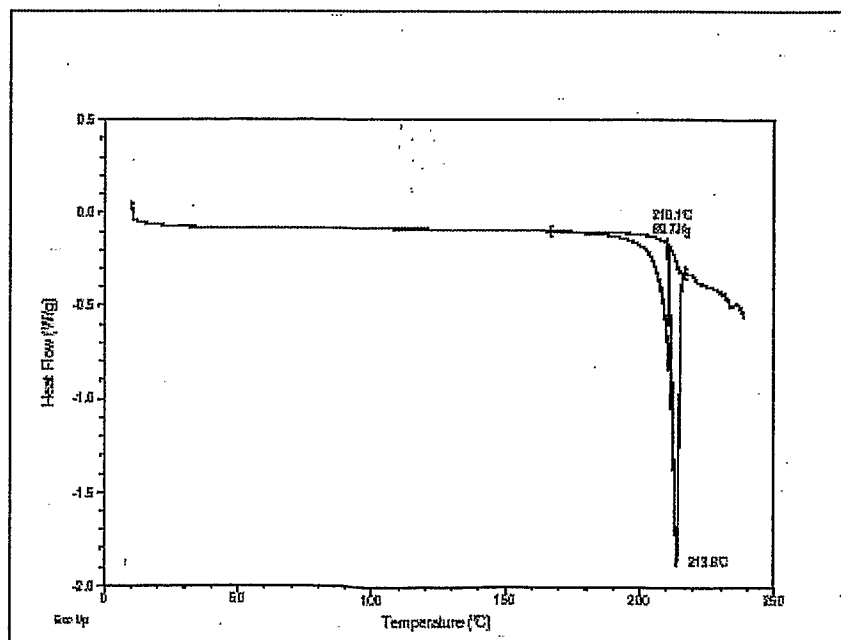


FIGURE 21

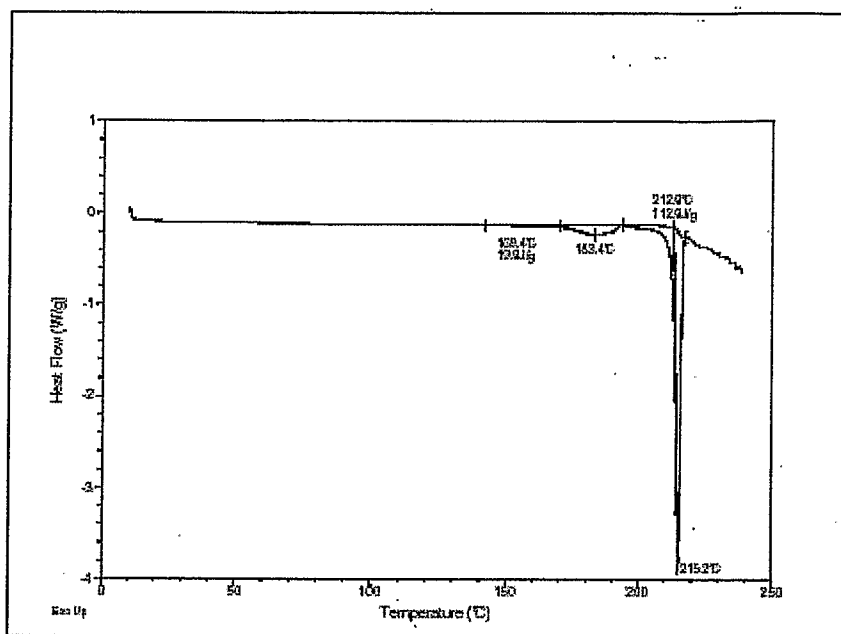


FIGURE 22

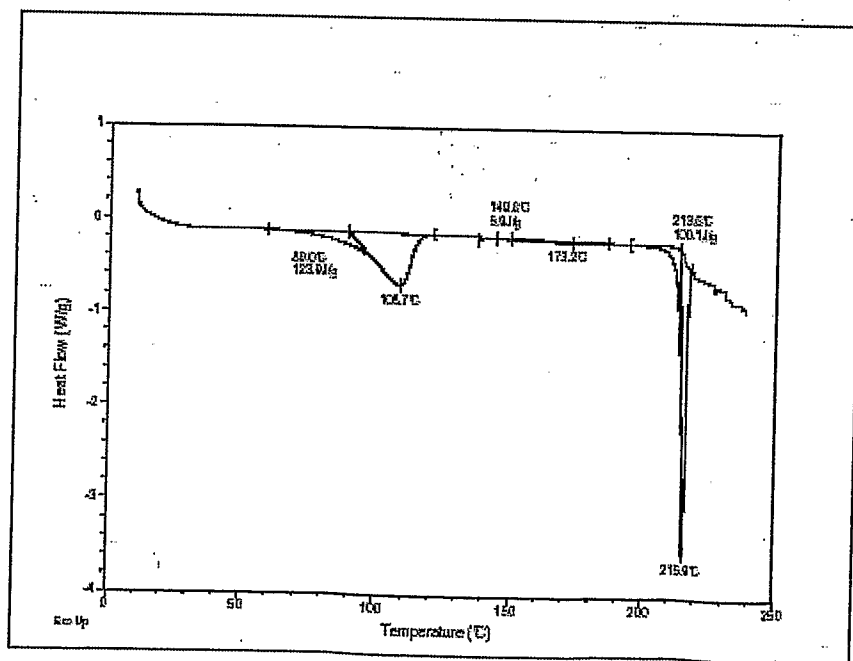


FIGURE 23

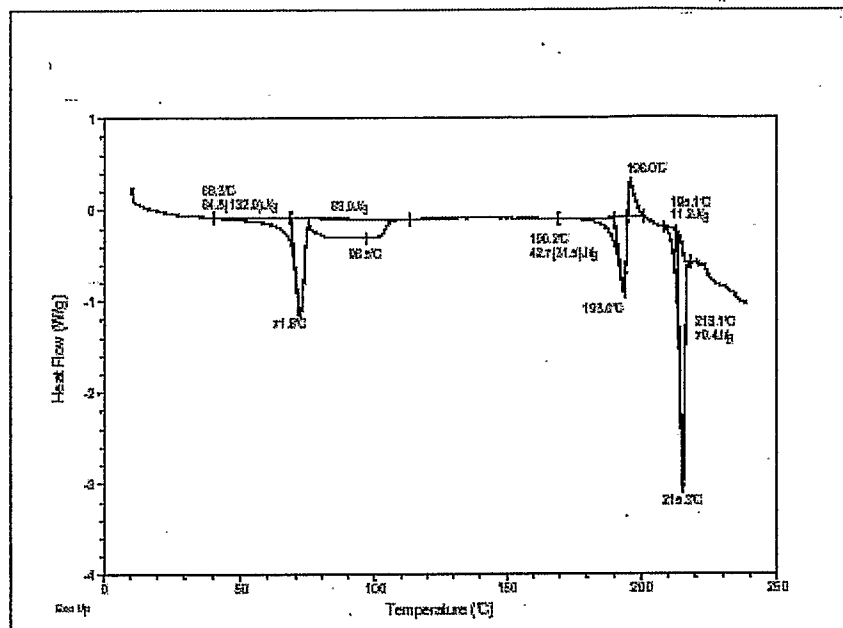


FIGURE 24

