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(54) Title: NOVEL FORM OF ANHYDROUS PAROXETINE HYDROCHLORIDE AND METHOD FOR PREPARATION THEREOF

(57) Abstract: A novel form of anhydrous Paroxetine hydrochloride is prepared by dissolving Paroxetine base in isopropanol, which is treated with a solution of hydrogen chloride in isopropanol. 50 to 60% of isopropanol used in the reaction is then distilled at atmospheric pressure. The product thus obtained after drying contains isopropanol not more than 3% and water content which is less than 2.0%. The product is found to be stable even after 3 days upon direct exposure to 75% RH at 40°C and the crystallinity of product is unchanged as confirmed by X-ray powder diffractogram. The product is also found to be stable for three months as per ICH stability conditions.



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Novel form of anhydrous Paroxetine hydrochloride and method for preparation thereof**Field of Invention**

Paroxetine is a potent and selective inhibitor of 5-hydroxy tryptamine (serotonin) uptake, with a reduced propensity to cause the side effects usually associated with a tricyclic anti-depressant. The present invention relates to a novel method for preparing a novel form of high purity anhydrous paroxetine hydrochloride.

Background:

US Patent 4721723 disclose the preparation of hemihydrate form of Paroxetine hydrochloride and unstable anhydrous form of Paroxetine hydrochloride. This fact is again conformed by the innovator through the Publication, *Int. J. Pharmaceutics* **42** 135 (1988), which describes that the anhydrous form of the Paroxetine hydrochloride that is denoted as form-II is a pseudomorph that converts to paroxetine hydrochloride hemihydrate form-I when it is exposed to moisture.

In US Patents 6080759 and 5900423 the innovator states that subsequent preparation of anhydrous paroxetine hydrochloride as disclosed in US 4721723 failed to yield any type of anhydrous Paroxetine hydrochloride.

WO 96/24595 discloses four forms of anhydrous Paroxetine hydrochloride i.e. Form-A, Form-B, Form-C and Form-D. WO 96/24595 describes the preparation of Paroxetine hydrochloride Form-A from Paroxetine hydrochloride hemihydrate by azeotropic removal of water from isopropanol and toluene mixture to afford Paroxetine hydrochloride isopropanol solvate, which is containing 13% isopropanol. Isopropanol is displaced from the solvate by stirring with water and amount of isopropanol content in the crystal is reduced to 0.05 %, which is filtered and dried under high vacuum over P_2O_5 . Repetition of this process fails to yield any Paroxetine hydrochloride anhydrate.

The drawback of the above process is that large quantity of isopropanol is required to remove toluene and efficient fractionating column needs to be provided. Also, the step of drying over P_2O_5 under high vacuum limits the process to laboratory scale preparation only.

Yuji Ohashi, et al, (Bull. Chem. Soc. Jpn.1999, 72., 1731-1736) have analyzed form-I and form-II by X-ray and reported that the form-II crystal contain isopropanol molecules in channels formed by Paroxetine molecules and chloride ions and is easily decomposed in open air at room temperature because the isopropanol molecules are easily released through the channels.

Biers James A. (*Acta Crystallogr.* Sect. C: cryst. Struc. Commun. 55(3), , 432-434(1999) supports this by giving crystallographic data. Drying properties of Form I and

Form II have been published in *Chem. Pharm. Bull.*, **48(4)** 529-536(2000). It states that dry form II crystals absorb water slowly, which is not present as bound water but is present as absorbed water, and it is released easily in dry atmosphere.

US Patent 6541637 describes reacting Paroxetine N-BOC compound with hydrogen chloride in the presence of isopropyl alcohol and crystallising the resulting product to obtain Paroxetine hydrochloride anhydrate having 30 to 70% by weight of isopropanol. The resulting product dried < 60°C temperature under atmospheric or lower pressure until the content of isopropanol is less than 15% by weight. Further drying of Paroxetine hydrochloride anhydrate at temperature range 80 to 110°C under reduced pressure until the content of isopropanol is not more than 5% by weight. It also states that during the first drying step if temperature exceeds 60°C, a portion of the crystal of Paroxetine hydrochloride anhydrate is dissolved in the isopropanol contained, deforming the crystals, so that desired crystal form cannot be obtained.

Our experiments have shown that anhydrous Paroxetine hydrochloride prepared by using methods disclosed in prior art, destabilizes soon by leaving isopropanol and absorbing water to transform into hemihydrate form. We have confirmed this fact of hemihydrate formation by infrared spectroscopy wherein characteristics peaks published in *Int. J. Pharmaceutics* **42** 137 (1988) disappears and product finally exhibits hemihydrate characteristics. Moreover filtration under stream of nitrogen which requires special equipment and also there is always a chance to absorb moisture.

Furthermore in the drying step of the process, drying is done at 80 - 110°C at below 20 mm of vacuum, there is a possibility that at such a higher temperature the product may also degrade and the resulting material may contain these degraded products.

The stage wise drying operation as discussed in US 6541637 is not necessary and conditions mentioned in this patent to reduce isopropanol content from 53.5% to 15% by drying at room temperature (20°C) under vacuum is not necessary. We have dried the material by keeping in a preheated dryer at 75°C and dried at 70-75°C under vacuum. Paroxetine hydrochloride anhydrate, free of any contamination of Paroxetine hydrochloride hemihydrate is achieved. Moreover, the methodology of preparing anhydrous Paroxetine hydrochloride adopted by us gives 25 to 30% isopropanol contents in wet cake.

JP-20011395572 describes the preparation of anhydrous Paroxetine hydrochloride isopropanol solvate by dissolving Paroxetine hydrochloride hemihydrate in isopropanol and crystallizing from the solution or by mixing Paroxetine base or N-ter. BOC Paroxetine with isopropanol solution of hydrogen chloride crystallizing from the mixture. However the above

patent does not teach the content of water in isopropanol and also when water is present in isopropanol there is a possibility of causing crystal conversion to Paroxetine hydrochloride hemihydrate and this water of crystallization is difficult to remove by conventional drying system.

5 CA 2187128 patent discloses preparation of three forms of anhydrous Paroxetine hydrochloride that is denoted as form-I, form-II and form-III, however form-I and form-II is not claimed in the patent. Form-III is reported to prepared by treating form-I and form-II with MIBK under inert atmosphere followed by heating up to 90-95°C than cooled to obtain precipitates of Paroxetine hydrochloride that was recovered by filtration and finally dried.

10 The patent also describes that form-III can also be obtained by dissolving Paroxetine free base in MIBK and treated with conc. HCl followed by removal of MIBK under reduced pressure to afford crystals that was filtered and dried to produce form-III. IR, X-ray powder diffractogram and DSC have also characterized the form-III.

The present invention discloses a new process for the preparation of anhydrous Paroxetine hydrochloride consistently, which eliminates the drawback of the previous arts. In 15 another aspect, the present invention relates to a new crystalline form of anhydrous Paroxetine hydrochloride, which is characterized by a powder X-ray diffraction pattern as well as infrared spectrograph.

Summary of the Invention:

20 Accordingly, the present invention provides a novel form of anhydrous Paroxetine having characteristic peaks on Infrared spectroscopic studies at 3411, 1630, 1450, 1425, 1286, 1193, 1170, 886, 816 cm^{-1} and characteristic peaks on X-ray powder diffractogram at 2θ $6.0 \pm 0.1^\circ$, $7.7 \pm 0.1^\circ$, $16.8 \pm 0.1^\circ$, $23.7 \pm 0.1^\circ$, $30.7 \pm 0.1^\circ$, $31.7 \pm 0.1^\circ$, $35.5 \pm 0.1^\circ$.

The present invention also provides a process for the preparation of anhydrous 25 paroxetine hydrochloride comprising:

- (a) dissolving paroxetine base in Isopropyl alcohol to obtain a solution;
- (b) adding isopropanolic hydrogen chloride to the solution obtained in step (a) above to obtain Paroxetine hydrochloride salt;
- (c) removing traces of water azeotropically from the solution obtained in step (b) by 30 distilling isopropyl alcohol prior to crystallization of product;
- (d) cooling the solution obtained in step (c) and filtering paroxetine hydrochloride crystals obtained thereby, followed by drying under reduced pressure to provide pure anhydrous Paroxetine hydrochloride.

In one embodiment of the invention, the dissolution temperature of Paroxetine base in isopropyl alcohol is in the range of 20°-50°C, preferably 30 - 35°C, more preferably at room temperature.

5 In yet another embodiment of the invention, the Paroxetine base is dissolved in 10 - 30 volumes of isopropyl alcohol, preferably 15-25 volumes and more preferably 17-20 volumes.

In another embodiment of the invention, the concentration of hydrogen chloride in isopropyl alcohol is 18-22% w/v, preferably 20% w/v.

10 In yet another embodiment of the invention, water is removed azeotropically by distilling-off isopropyl alcohol at 80°-82°C, using a fractionating column under atmospheric pressure of up to 45-60%, preferably 50-60% of volume of isopropyl alcohol used in the preparation.

In another embodiment of the invention, wherein in step (b) and/or step (c) the solution is cooled to a temperature in the range of 25°-40°C, preferably 30°-35°C to obtain 15 crystals of Paroxetine hydrochloride that is filtered or centrifuged.

In another embodiment of the invention, the solution obtained in step (b) is in the form of a wet-cake of Paroxetine hydrochloride which is then dried at a temperature in the range of 30°-35°C for 2 hrs, then at 50°-55°C for 6 hrs and finally at 70°-75°C for 12 hrs under reduced pressure less than 50 mm, preferably less than 30 mm till isopropyl alcohol content is 20 between 2-3% w/w.

In another embodiment of the invention, the anhydrous Paroxetine hydrochloride obtained has purity of 99.7-99.9% & percentage of isopropyl alcohol is between 2-3% w/w and percentage of water is less than 2% w/w.

25 In another embodiment of the invention, the Paroxetine base is preferably treated with a solution of isopropanol containing hydrogen chloride at 30-35°C to distil out approximately 50% of the isopropanol from the reaction mass at atmospheric pressure and then cooled to 30° - 35°C.

30 In another embodiment of the invention, the drying after filtration in step (c) is carried out at first 30°-35°C for 2 hrs, 50°- 55°C for 6 hrs and at 70° - 75°C for 9 to 12 hrs at reduced pressure of 30-50 mm till isopropanol content is less than 3% and water content is less than 2.0%.

In another embodiment of the invention, the water content in the isopropanol used is less than 0.1% was used.

In another embodiment of the invention, the drying is carried out in a single step comprising keeping the product in a preheated dryer at 75°C and drying for 16 hrs at 30-50°C mm of vacuum.

Brief description of the accompanying drawings

Figures 1 to 4 are X-ray powder diffractogram of the novel form of anhydrous Paroxetine hydrochloride according to the process of the invention.

Figures 5 to 7 are infrared spectrographs of the novel form of anhydrous Paroxetine hydrochloride according to the process of the invention.

Detailed Description:

The present invention provides a novel form of anhydrous Paroxetine having characteristic peaks on Infrared spectroscopic studies at 3411, 1630, 1450, 1425, 1286, 1193, 1170, 886, 816 cm^{-1} and characteristic peaks on X-ray powder diffractogram at 2θ $6.0 \pm 0.1^\circ$, $7.7 \pm 0.1^\circ$, $16.8 \pm 0.1^\circ$, $23.7 \pm 0.1^\circ$, $30.7 \pm 0.1^\circ$, $31.7 \pm 0.1^\circ$, $35.5 \pm 0.1^\circ$.

The novel form of anhydrous paroxetine hydrochloride is prepared by a process comprising:

- (a) dissolving paroxetine base in Isopropyl alcohol to obtain a solution;
- (b) adding isopropanolic hydrogen chloride to the solution obtained in step (a) above to obtain Paroxetine hydrochloride salt;
- (c) removing traces of water azeotropically from the solution obtained in step (b) by distilling isopropyl alcohol prior to crystallization of product;
- (d) cooling the solution obtained in step (c) and filtering paroxetine hydrochloride crystals obtained thereby, followed by drying under reduced pressure to provide pure anhydrous Paroxetine hydrochloride.

In step b) above addition of IPA.HCl converts Paroxetine Base into its HCl salt, which precipitates out. But, this solid gets redissolves upon heating during azeotropic distillation, for removal of moisture, in step (c) and the desired product finally crystallizes from almost anhydrous condition on cooling.

The dissolution temperature of Paroxetine base in isopropyl alcohol is in the range of 20°-50°C, preferably 30 - 35°C, more preferably at room temperature. The Paroxetine base is dissolved in 10 - 30 volumes of isopropyl alcohol, preferably 15-25 volumes and more preferably 17-20 volumes. The concentration of hydrogen chloride in isopropyl alcohol is 18-22% w/v, preferably 20% w/v.

In step (b) and/or step (c) the solution is cooled to a temperature in the range of 25°-40°C, preferably 30°-35°C to obtain crystals of Paroxetine hydrochloride that is filtered or

centrifuged. Water is removed azeotropically by distilling-off isopropyl alcohol at 80°-82°C, using a fractionating column under atmospheric pressure of up to 45-60%, preferably 50-60% of volume of isopropyl alcohol used in the preparation.

The solution obtained in step (b) can be in the form of a wet-cake of Paroxetine hydrochloride which is then dried at a temperature in the range of 30°-35°C for 2 hrs, then at 50°-55°C for 6 hrs and finally at 70°-75°C for 12 hrs under reduced pressure less than 50 mm, preferably less than 30 mm till isopropyl alcohol content is between 2-3% w/w.

The anhydrous Paroxetine hydrochloride obtained has purity of 99.7-99.9% & percentage of isopropyl alcohol is between 2-3% w/w and percentage of water is less than 2% w/w.

As explained above, Paroxetine base is preferably treated with a solution of isopropanol containing hydrogen chloride at 30-35°C. Approximately 50% of the isopropanol is distilled out from the reaction mass at atmospheric pressure and then cooled to 30° - 35°C. Crystalline mass is filtered and dried at first 30°-35°C for 2 hrs, 50°- 55°C for 6 hrs and at 70° - 75°C for 9 to 12 hrs at reduced pressure of 30-50 mm till isopropanol content is less than 3% and water content is less than 2.0%.

In the present invention isopropanol with water content less than 0.1% was used. The removal of 50-60% isopropyl alcohol by azeotropic distillation further lowers water content in the reaction mixture before crystallization sets in, as demonstrated by the water content of the distillate, which is 0.5 to 0.6%.

The above procedure consistently gives Paroxetine hydrochloride anhydrate suggesting that azeotropic removal of water from the reaction mixture before the crystallization is necessary to get anhydrous condition before crystallization. However on repeated experiments employing isopropanol with water content less than 0.1%, without removing water content from reaction mixture before crystallization always gives Paroxetine hydrochloride hemihydrate form - I. Alternatively under similar conditions of operations, n-propanol gives similar results producing Paroxetine hydrochloride anhydrate consistently. The drying operation is carried out for 4 hours at 65°C and then 16 hours at 70-75°C at reduced pressure of 30-50 mm.

Optionally drying is done at 70-75°C for 16 hours at reduced pressure of 30-50 mm.

Thus obtained anhydrous form of Paroxetine hydrochloride may be distinguished from other forms by X-ray powder diffractograms (Figure-2 to Figure-4) as well as Infrared spectrographs (Figure-5 to Figure-7).

The invention will be described in greater detail below:

Paroxetine base (prepared by known art) is dissolved in 10 to 30 times preferably 15-20 times by volume of isopropanol having water content less than 0.1% preferably less than 0.05%. The solution thus obtained is filtered through filter pad to remove suspended particles, if any. To this, a solution of hydrogen chloride in isopropanol (20% w/v hydrogen chloride content) is slowly added at 20°-40°C preferably at 30° -35°C under stirring till the pH of the solution is adjusted to 3 to 4 [checked on pH paper].

The reaction mass after stirring for 15-20 minutes converts to thick slurry due to precipitation of the hydrochloride salt. Approximately 30 to 60% preferably 50-55% of isopropanol is then distilled at atmospheric pressure at 80-82°C.

This operation removes the water content if any from the reaction mass. If this is avoided or the distillation is carried out at low temperature 50-60°C under reduced pressure, the product obtained is hemihydrate. Hence this operation is necessary to obtain the anhydrous product.

The solution is cooled to 30-35°C. The product is filtered, giving wash of isopropanol.

The product is then dried for 2 hrs at 30-35°C, at 50-55°C for 6 hrs and finally at 70-75°C for 9-12 hrs at a reduced pressure of 30-50 mm till isopropanol content is less than 3% and water content is less than 2.0 %. Alternatively, instead of the above step wise drying, single stage drying is carried by keeping the product in a preheated dryer at 75°C and drying for 16 hrs at 30-50°C mm of vacuum.

HPLC analysis shows the purity of the product to be 99.7% and total impurities are less than 0.3% and also individual impurities are less than 0.1%. This shows that the product obtained is of high purity. The product obtained is stable to moisture and does not convert to hemihydrate even in traces. To verify this the product obtained above was placed in to a petri dish and exposed directly to varied humid conditions for 3 days at 25°C and 40°C as below.

1) 25°C and 60% RH

2) 40°C and 75% RH

The results are summarized as below.

	25°C, 60% RH		40°C, 75% RH	
	% water	IR correlation	% water	IR correlation
Initial	1.48%	--	1.48%	--
After 24 hours	3.80%	98%	3.99%	99%
After 48 hours	3.78%	99%	3.99%	99%
After 72 hours	3.85%	99%	3.95%	99%

Infrared spectrum and X-ray powder diffractogram do not show any changes when compared to the sample of anhydrous Paroxetine hydrochloride before exposing to above conditions (control sample).

The above results also reveal that the product absorbs water nearly up to 4%, which is a maximum limit for anhydrous Paroxetine hydrochloride prepared by us. Above studies also demonstrate that anhydrous Paroxetine hydrochloride anhydrate prepared by us does not convert into hemihydrate form as confirmed by Infrared spectrum and X-ray powder diffractogram of samples at each and every station. Thus, a novel process to manufacture a novel form of anhydrous Paroxetine hydrochloride having stability of approximately three months of three validation batches (batch size 20-22 Kg) is disclosed.

Further more the X-ray powder diffractogram as well as IR spectrograph of anhydrous paroxetine hydrochloride by the process as described herein above as well as in the illustrated examples do not correlate with the other known/ patented form as disclosed in prior arts.

X-ray powder diffractogram [Fig. 2, 3 & 4] shows very new pattern of peaks at 2θ $6.0 \pm 0.1^\circ$, $7.7 \pm 0.1^\circ$, $16.8 \pm 0.1^\circ$, $23.7 \pm 0.1^\circ$, $30.7 \pm 0.1^\circ$, $31.7 \pm 0.1^\circ$, $35.5 \pm 0.1^\circ$ and peaks disclosed in US 4721723 at 2θ 7.4° , 14.3° , 17.3° , 23.2° , 23.5° , 23.5° , 24.1° , 30.0° , 39.8° , 44.2° , 47.1° , in US 6080759 Form A is having characteristic peaks 6.6° , 8.0° , 11.2° , 13.1° as well as CA 2187128 at 2θ 12.0° , 17.3° , 17.6° , 19.2° , 20.7° , 20.9° , 26.1° , 29.2° are all absent.

Furthermore, Infrared spectrograph [Fig.-5, 6 & 7] of anhydrous Paroxetine hydrochloride prepared by us shows new characteristic peaks at 3411, 1630, 1450, 1425, 1286, 1193, 1170, 886, 816 cm^{-1} where as IR characteristic peaks in Paroxetine hemihydrate at 3403, 1560, 1380, 1278, 1185, 1160, 1112, 1042, 1004, 944, 930, 914, 846 cm^{-1} and IR frequency characterized in anhydrous Form-A disclosed in US 6080759 3402, 1562, 1006, 982, 966, 947, 906, 722, 665, 613, 513 cm^{-1} are not present in our novel form of anhydrous Paroxetine hydrochloride.

The product obtained by present embodiment is highly pure in polymorphic purity and is stable to highly humid conditions even at 40°C .

Advantages of the present embodiment over prior arts

The product obtained by the present invention is of the high purity as discussed above and also the process described herein consistently produce anhydrous Paroxetine hydrochloride on laboratory as well as on commercial scale.

The present invention does not need drying at high vacuum (2 to 20mm) and higher temperature (80°C to 110°C) and use of desiccants like P_2O_5 which itself is highly

hygroscopic making its use difficult on large-scale preparation. In another aspect, the present invention is also advantageous to afford novel stable anhydrous Paroxetine hydrochloride.

The present invention describes a simple and convenient method to maintain almost anhydrous conditions of reaction mixture before crystallization of Paroxetine hydrochloride by removing water during distillation of isopropanol. One batch of 13.5-Kg and three validation batches of 20-22 kg were successfully performed producing the desired quality of the product.

The present embodiment is now described in details by the following examples, without intending to limit the present invention to these examples.

Example 1

203-L isopropanol (water 0.05% w/v) and 13.5 Kg Paroxetine base are charged simultaneously in a reactor and stirred for 15 min to get clear solution. The solution is filtered through sparkler filter to remove suspended particles. The reactor and sparkler filters are washed with 2 x 13.5-L isopropanol.

The filtrate and washing solutions are collected into a glass-lined reactor. To this solution of Paroxetine base a solution of 20% w/v hydrogen chloride in isopropanol is added from addition funnel during 120 minutes at 30-35°C to bring the pH of the reaction mass between 3-4 (checked on pH paper), at this pH Paroxetine hydrochloride crystallizes. The slurry is stirred for 15 minutes and then slowly heated to 80-82°C, 135 L isopropanol is distilled off at atmospheric pressure and then cooled. The product crystallized out at 45°C, which is then further cooled to 30-35°C and stirred for 1 hr at this temperature. The product is centrifuged and washed with 2 x 13.5-L isopropanol. The wet cake is then transferred to a vacuum tray dryer. The product is dried at 30-35°C for 2 hrs, at 50-55°C for 6 hrs and finally at 70-75°C for 12 hrs under reduced pressure of 30 mm, reducing isopropanol content to less than 3%. The yield of anhydrous Paroxetine hydrochloride is 13.5 Kg

Water content of distillate 0.6%

Melting point 116-117°C

Purity (by HPLC) 99.72%

Water (by KFR) 1.48%

isopropanol (by GC) 2.4%

Example 2

20 g of Paroxetine base is dissolved in 360-ml isopropanol (water <0.05%). The solution is filtered through filter pad in Buchner funnel. The pad is washed twice with 20-ml isopropanol. To the clear filtrate is added 20% w/v hydrogen chloride solution in isopropanol

at 30-35°C to bring the pH of the reaction mass between 3-4 (checked on pH paper). Paroxetine hydrochloride is crystallised out. The slurry is stirred for 15 minutes and then slowly heated to 80-82°C to obtain a clear solution, which is then subjected to distillation for the removal of 200 ml isopropanol at atmospheric pressure. The solution is then cooled and the product crystallised out at 30-35°C. Slurry thus obtained is stirred for 1 hr at the same temperature. The product is filtered and washed with 4 x 20-ml isopropanol. The wet cake is dried in vacuum oven at 65°C for 4 hrs and between the range 70-75°C for 16 hrs under reduced pressure of 30 mm to afford 19.9 g Paroxetine hydrochloride.

Melting point 116-117°C

Water content of distillate 0.55%

Purity by HPLC 99.96%,

Isopropanol (by GC) 2.96%

Water (by KFR) 1.5%

Example 3

20 g of Paroxetine base is dissolved in 360-ml isopropanol (water <0.05%). The solution is filtered through filter pad in Buchner funnel. The pad is washed twice with 20 ml isopropanol. To the clear filtrate is added 20% hydrogen chloride solution in isopropanol at 30-35°C to bring the pH of the reaction mass between 3-4 (checked on pH paper). Paroxetine hydrochloride is crystallized out at this pH. The slurry is stirred for 15 min. and then slowly heated to 80-82°C to obtain a clear solution, which is then subjected to distillation for removal of 200 ml isopropanol at atmospheric pressure. The solution is then cooled to 30 to 35 C and the product crystallized out. The slurry thus obtained is stirred for 1 hour. The product is filtered and washed with 4 x 20-ml isopropanol. The wet cake is dried in vacuum oven between the range 70-75°C for 16 hrs under reduced pressure of 30 mm to afford 19.5 g of Paroxetine hydrochloride.

Melting point 116-117°C

Water content of distillate 0.6%

Purity by HPLC 99.96%,

Isopropanol (by GC) 2.18%

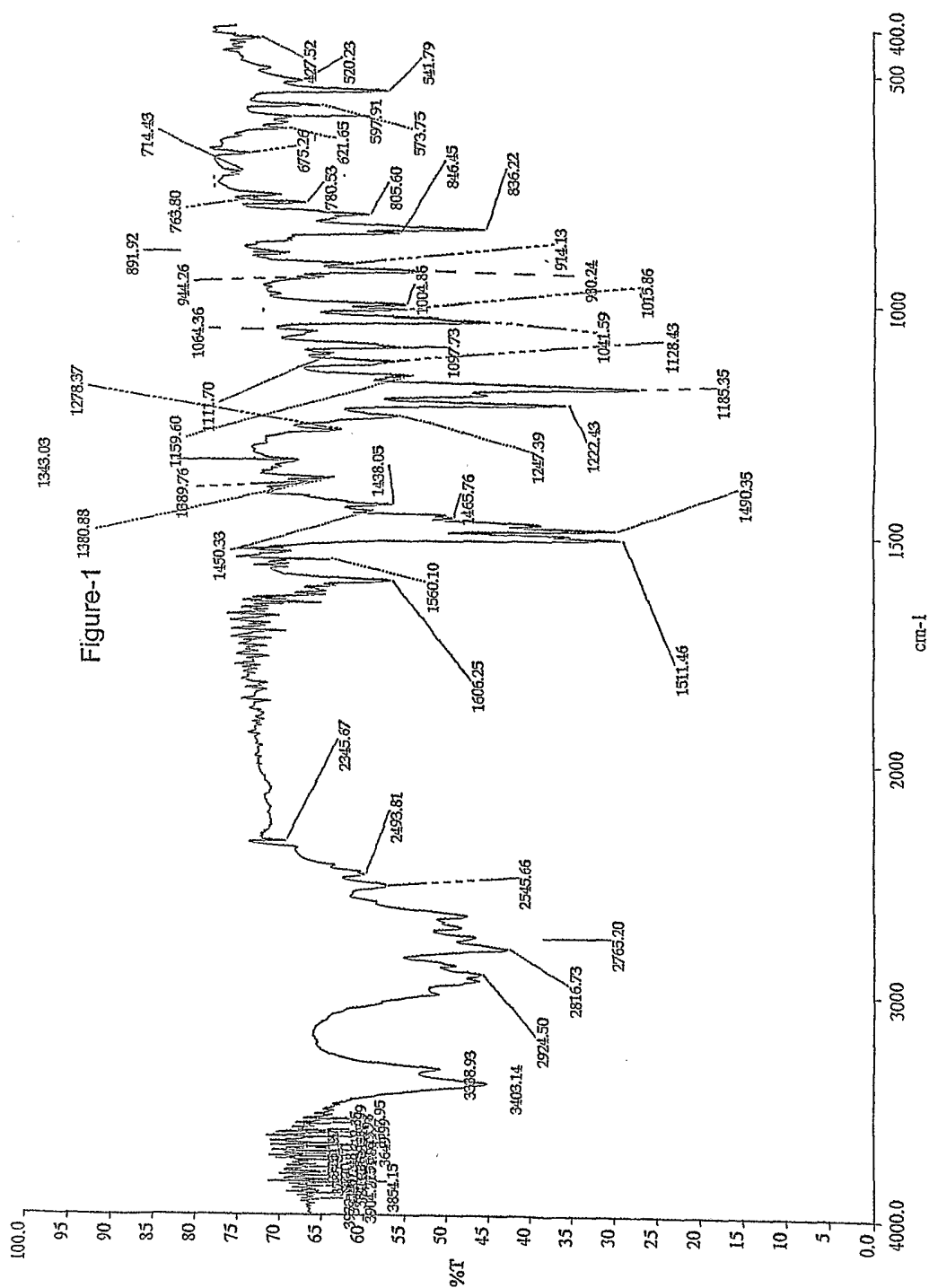
Water (by KFR) 1.46%

It must be understood that the present invention is not limited by the above description and variations and modifications are possible without departing from the spirit thereof.

We claim:

1. A novel form of anhydrous Paroxetine having characteristic peaks on Infrared spectroscopic studies at 3411, 1630, 1450, 1425, 1286, 1193, 1170, 886, 816 cm^{-1} and characteristic peaks on X-ray powder diffractogram at 2θ $6.0 \pm 0.1^\circ$, $7.7 \pm 0.1^\circ$, $16.8 \pm 0.1^\circ$, $23.7 \pm 0.1^\circ$, $30.7 \pm 0.1^\circ$, $31.7 \pm 0.1^\circ$, $35.5 \pm 0.1^\circ$.
2. A process for the preparation of anhydrous paroxetine hydrochloride comprising:
 - (a) dissolving paroxetine base in Isopropyl alcohol to obtain a solution;
 - (b) adding isopropanolic hydrogen chloride to the solution obtained in step (a) above to obtain Paroxetine hydrochloride salt;
 - (c) removing traces of water azeotropically from the solution obtained in step (b) by distilling isopropyl alcohol prior to crystallization of product;
 - (d) cooling the solution obtained in step (c) and filtering paroxetine hydrochloride crystals obtained thereby, followed by drying under reduced pressure to provide pure anhydrous Paroxetine hydrochloride.
3. A process as claimed in claim 2 wherein the dissolution temperature of Paroxetine base in isopropyl alcohol is in the range of 20° - 50°C , preferably $30 - 35^\circ\text{C}$, more preferably at room temperature.
4. A process as claimed in claim 2 wherein the Paroxetine base is dissolved in 10 - 30 volumes of isopropyl alcohol, preferably 15-25 volumes and more preferably 17-20 volumes.
5. A process as claimed in claim 2 wherein the concentration of hydrogen chloride in isopropyl alcohol is 18-22% w/v, preferably 20% w/v.
6. A process as claimed in claim 2 wherein in step (c) water is removed azeotropically by distilling-off isopropyl alcohol at 80° - 82°C , using a fractionating column under atmospheric pressure of up to 45-60%, preferably 50-60% of volume of isopropyl alcohol used in the preparation.
7. A process as claimed in claim 2 wherein in step (b) and/or step (c) the solution is cooled to a temperature in the range of 25° - 40°C , preferably 30° - 35°C to obtain crystals of Paroxetine hydrochloride that is filtered or centrifuged.
8. A process as claimed in claim 2 wherein the solution obtained in step (b) is in the form of a wet-cake of Paroxetine hydrochloride which is then dried at a temperature in the range of 30° - 35°C for 2 hrs, then at 50° - 55°C for 6 hrs and finally at 70° - 75°C for 12 hrs under reduced pressure less than 50 mm, preferably less than 30 mm till isopropyl alcohol content is between 2-3% w/w.

9. A process as claimed in claim 2 wherein the anhydrous Paroxetine hydrochloride obtained has purity of 99.7-99.9% & percentage of isopropyl alcohol is between 2-3% w/w and percentage of water is less than 2% w/w.
10. A process as claimed in claim 2 wherein the Paroxetine base is preferably treated with a solution of isopropanol containing hydrogen chloride at 30-35°C to distil out approximately 50% of the isopropanol from the reaction mass at atmospheric pressure and then cooled to 30° - 35°C.
11. A process as claimed in claim 2 wherein the drying after filtration in step (c) is carried out at first 30°-35°C for 2 hrs, 50°- 55°C for 6 hrs and at 70° - 75°C for 9 to 12 hrs at reduced pressure of 30-50 mm till isopropanol content is less than 3% and water content is less than 2.0%.
12. A process as claimed in claim 2 wherein the water content in the isopropanol used is less than 0.1% was used.
13. A process as claimed in claim 2 wherein the drying is carried out in a single step comprising keeping the product in a preheated dryer at 75°C and drying for 16 hrs at 30-50°C mm of vacuum.

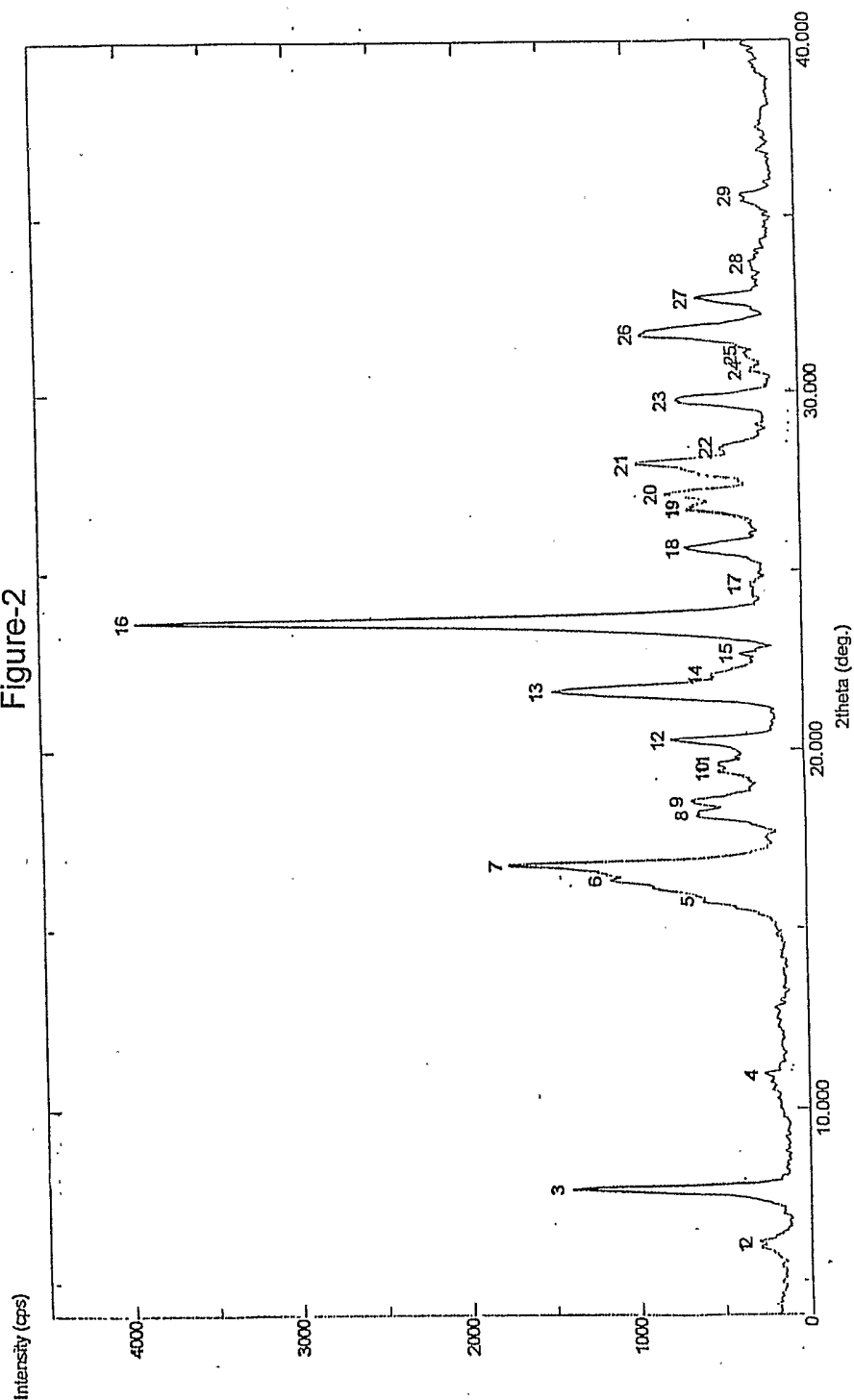


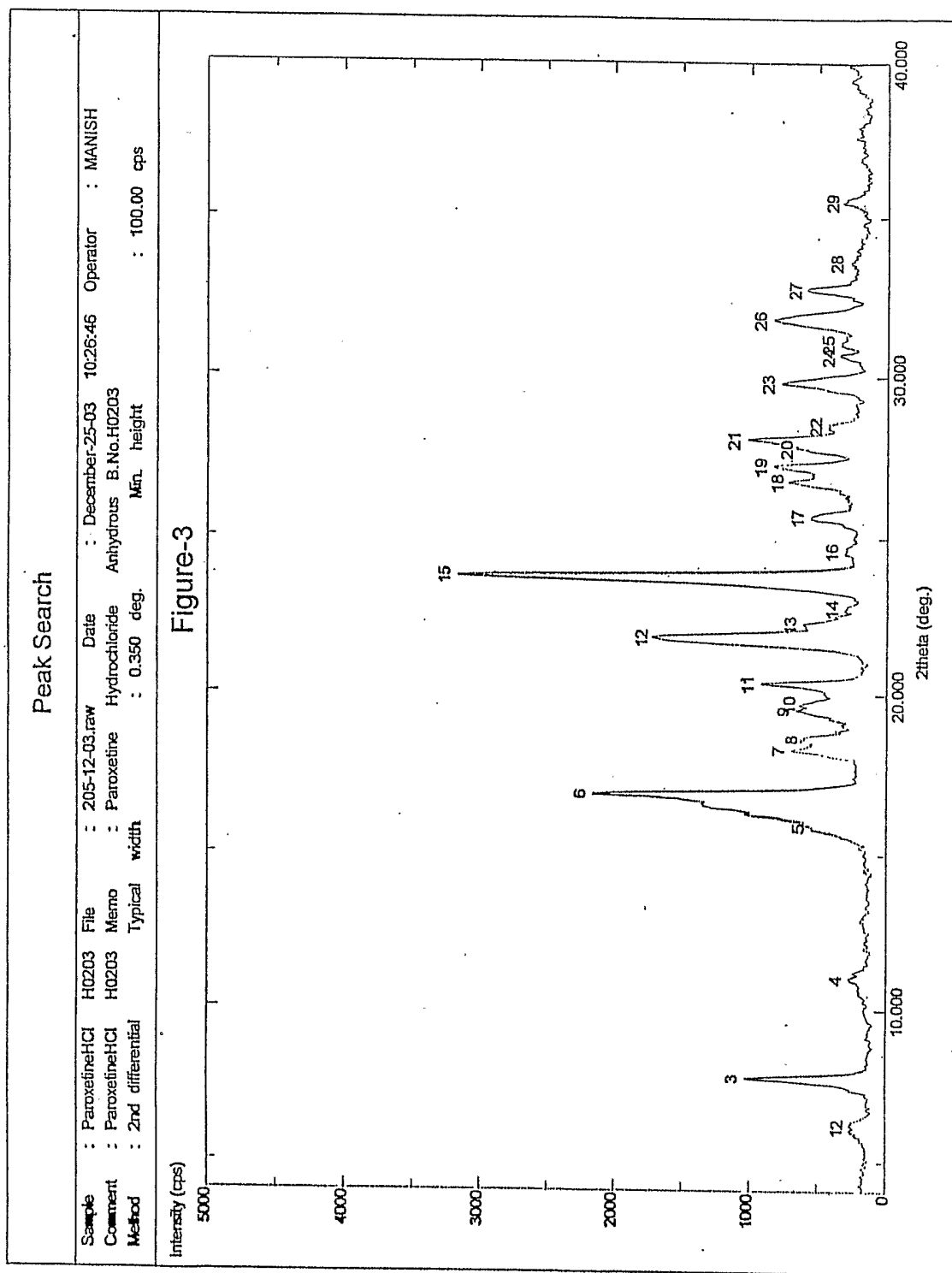
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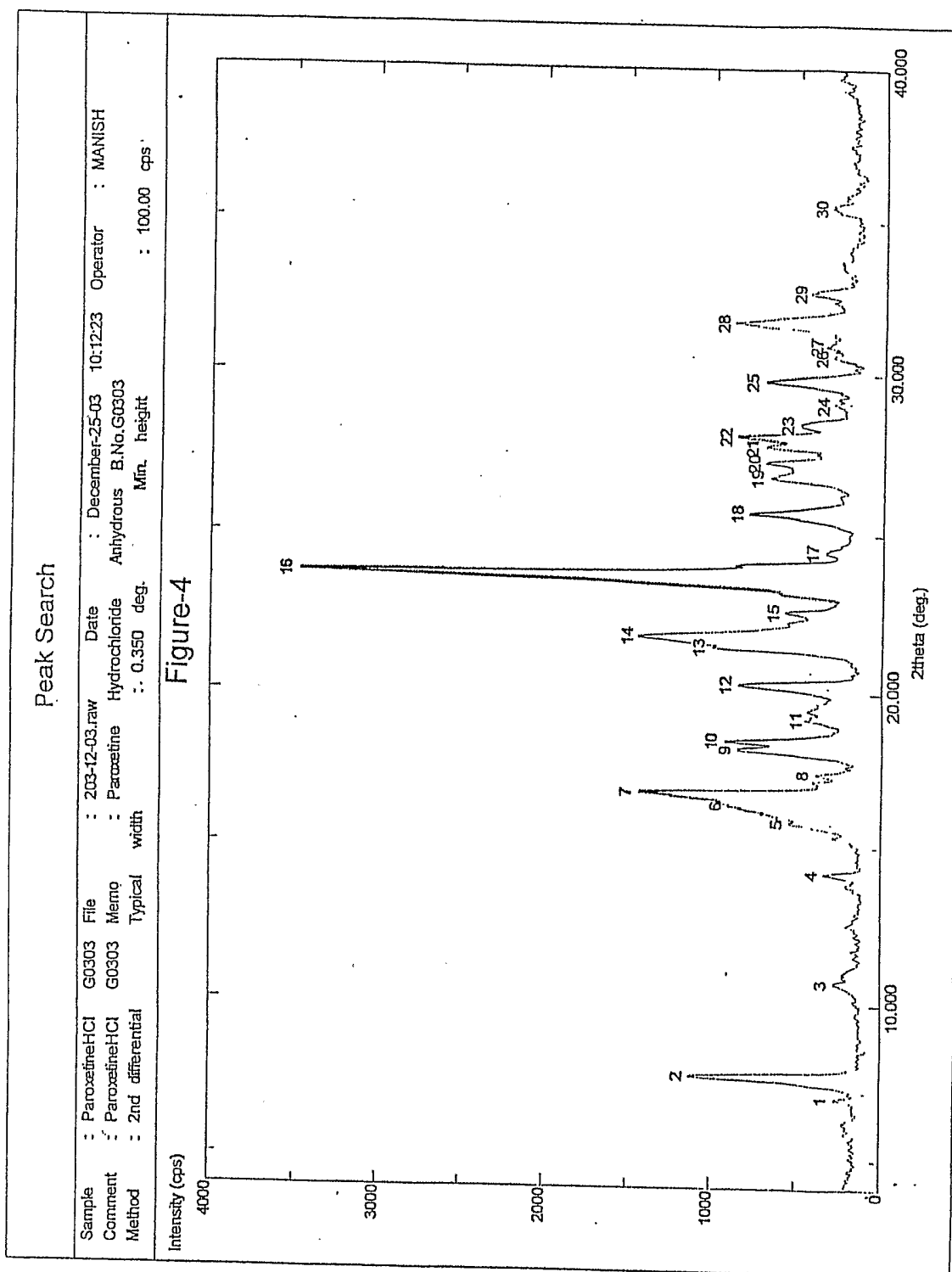
Peak Search

Sample	: ParoxetineHCl	H0103	File	: 204-12-03.raw	Date	: December-25-03	09:32:20	Operator	: MANISH
Comment	: ParoxetineHCl	H0103	Memo	: Paroxetine	Hydrochloride	Anhydrous	B.No.H0103		
Method	: 2nd differential		Typical	width		Min.	height		
					: 0.350	deg.		: 100.00	cps

Figure-2

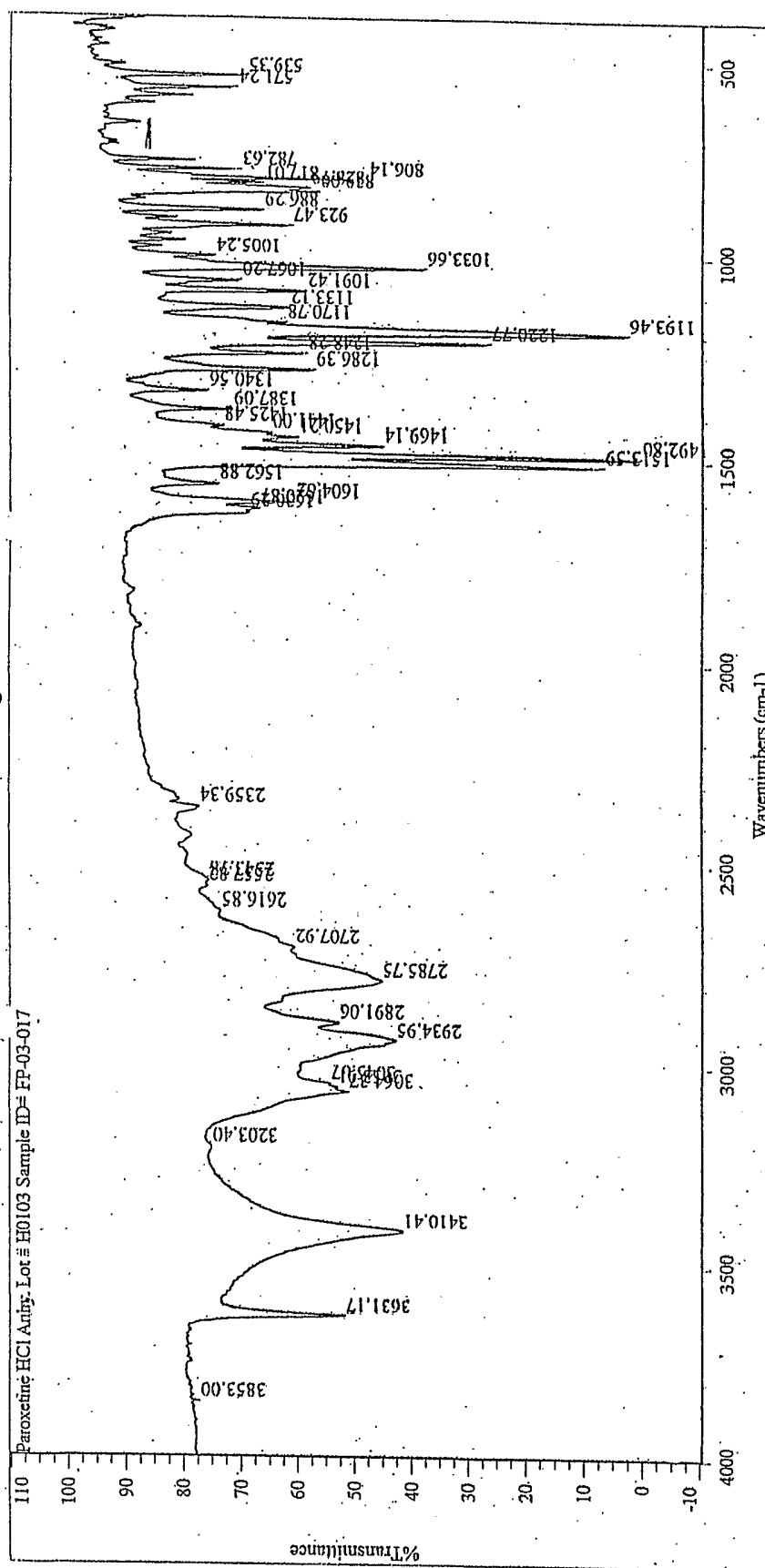






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Figure-5



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Figure-6

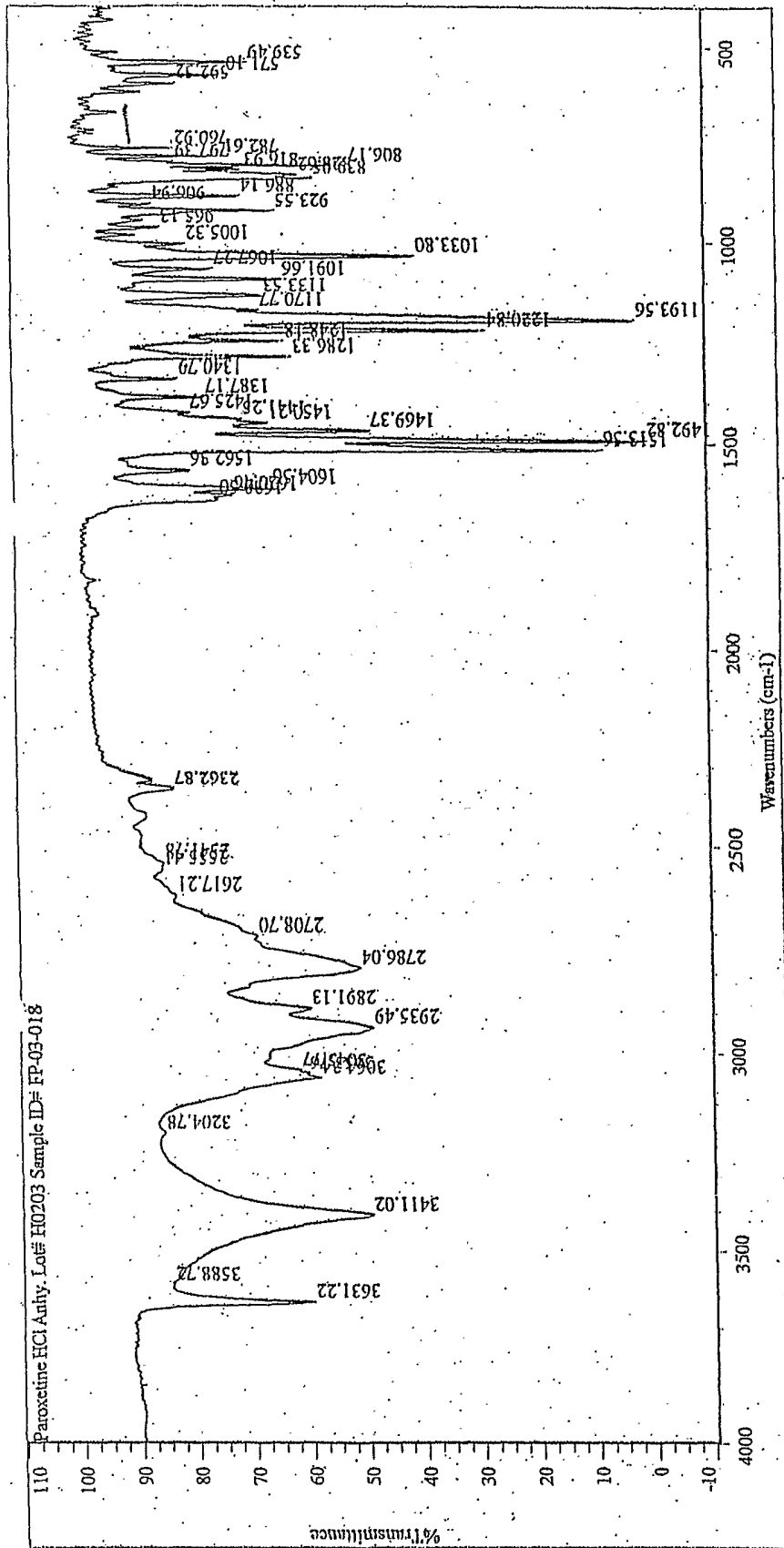


Figure-7

