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Studies on Crystal Forms of Gatifloxacin: Preparation, Characterization and Dissolution Profile

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Abstract

Different crystal forms of Gatifloxacin were prepared using solvents of varying polarity. X-ray diffractometry (XRD), differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermogravimetric analysis (TGA), infrared absorption spectroscopy (FT-IR), melting point, particle size, solubility, and *in vitro* dissolution rate studies were conducted to investigate various characteristics of different crystalline forms of the gatifloxacin. Three types of polymorphs were identified based on thermal analysis but fails to make any distinction among GATI-I and GATI-III. FT-IR spectral technique and X-ray diffractometry confirmed that existence of four different polymorphs. The polymorphs differed in their solubility and dissolution profile. Crystallization of gatifloxacin from ethanol (GATI-II) produced spongy opaque crystals that exhibited highest solubility and dissolution rate than other crystals due to its lowest melting point and smaller particle size. It is concluded finally that the study has indicated the existence of four polymorphic forms of Gatifloxacin (1).

Keywords: Crystal forms, gatifloxacin, characterization, thermal analysis, solubility, dissolution.

Introduction

Most pharmaceutical molecules are polymorphic. Increasing numbers of polymorphs have been recorded over the past decades proving the growing interest in polymorphism in science and industry (Denis et al. 2009). It is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements or conformations of the molecules in the crystal lattice. In the solid state, the atoms, molecules or ions may be arranged in one of the fundamental crystal systems: triclinic, monoclinic, orthorhombic, tetragonal, trigonal, hexagonal or cubic. Polymorphs show the same properties in the liquid or gaseous state but they behave differently in the solid state (John et al. 1975). Different polymorphs of an API have different density, habit, melting properties, vapor pressure, physical and chemical properties, leading to changes in its solubility, stability, dissolution and bioavailability and, finally, in changes in the efficacy of drugs (Young and Sang 2008).

The most stable polymorphs should be used in the marketed formulation to prevent the polymorphic transition during manufacturing, delivery or storage. The polymorphs selected during the drug development process should be thermodynamically stable and remain stable during the manufacturing process (Talluri et al. 2010).

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Fluoroquinolones are broad spectrum antimicrobials which are highly effective in the treatment of a wide variety of clinical infections. Gatifloxacin is a fourth-generation 8-methoxyfluoroquinolone derivative 1-Cyclopropyl-6-fluoro-8-methoxy-7-(3-methylpiperzine-1yl)-4-oxo-3-quinoline carboxylic acid (Figure1), improved activity against Gram positive as well as Gram negative micro-organisms (Ann and Christopher 2000). In contrast to the numerous articles on fluoroquinolones such as polymorphism of norfloxacin (Barbas et al. 2006) and thermal behavior of norfloxacin (Sadeek et al. 2006 and Prohens et al. 2007) crystal structure of ofloxacin (Petra et al. 2006), crystal forms of pefloxacin (Mange et al. 2008), literatures on polymorphism of gatifloxacin is not available to date.

In the present work, it was planned to prepare crystal forms of gatifloxacin and to characterize them using instrumental techniques. Since crystal forms may differ in their solubility and dissolution behavior, it was also planned to study the solubility and dissolution profile of the prepared crystal forms.

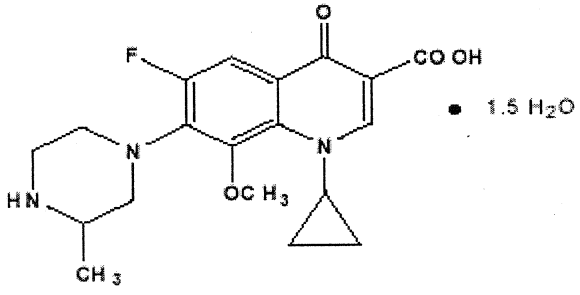

Figure 1. Structure of Gatifloxacin (1)

Materials and Methods

Materials

Gatifloxacin (1) was obtained from Alkem laboratories Ltd, Mumbai. India. The solvents used for crystallization were methanol, ethanol, isopropanol (70%) and ethanol: water (1:1). These solvents were obtained from S.D Fine Chemicals Ltd. Mumbai, India.

Preparation of polymorphs of Gatifloxacin

The raw material was subjected to crystallization process from solvents of different polarity. A range of solvents like benzene (nonpolar, aprotic), ethyl acetate, acetone, chloroform, dichloromethane (polar, aprotic), methanol, ethanol, isopropanol, distilled water (polar, protic), and dimethylformamide (polar, aprotic) were used for crystallization. The drug (1) (Figure 1) showed poor solubility in less polar solvents like benzene, ethyl acetate, chloroform and dichloromethane hence, these solvents could not be used for crystallization process. Four crystal forms were obtained from different solvents: GATI- I (methanol), GATI- II (ethanol), GATI- III (isopropanol (70%) and GATI - IV (ethanol and water (1:1)) (Table 1).

Table 1. Crystal shape, Mean Particle Size and Percent Crystal Yield of Crystal sforms of Gatifloxacin.

Solvent Used for Crystallization	Crystal shape	Mean particle size (µm)	Crystal yield (%)
Methanol	Prismatic	90	76
Ethanol	Spongy opaque	85	74
Isopropanol (70%)	Thin pole like	94	78
Ethanol: Water (1:1)	Rod shaped	101	85

Analytical techniques used for characterization of crystal forms

Microscopy

Photomicrographs of crystals were obtained under Olympus microscope (ModelBX40). All the crystals so prepared were viewed under optical microscope for their physical characterization. The samples were prepared by placing a small amount of respective crystal powder (previously passed through No.100 sieve) on the slide, dispersed in a drop of mineral oil (liquid paraffin) and covered with cover slip. The slides were visualized by means of binocular polarizing microscope under 10X/0.25 Ph1 and 40X/0.45 Ph 2. When polarized transmitted light was used to illuminate the sample, the background of the image appeared dark and the sample appeared bright. Samples were observed at a magnification of 100X also. Photomicrographs were taken by using Kodak film roll (Table 1 and Figure 2).

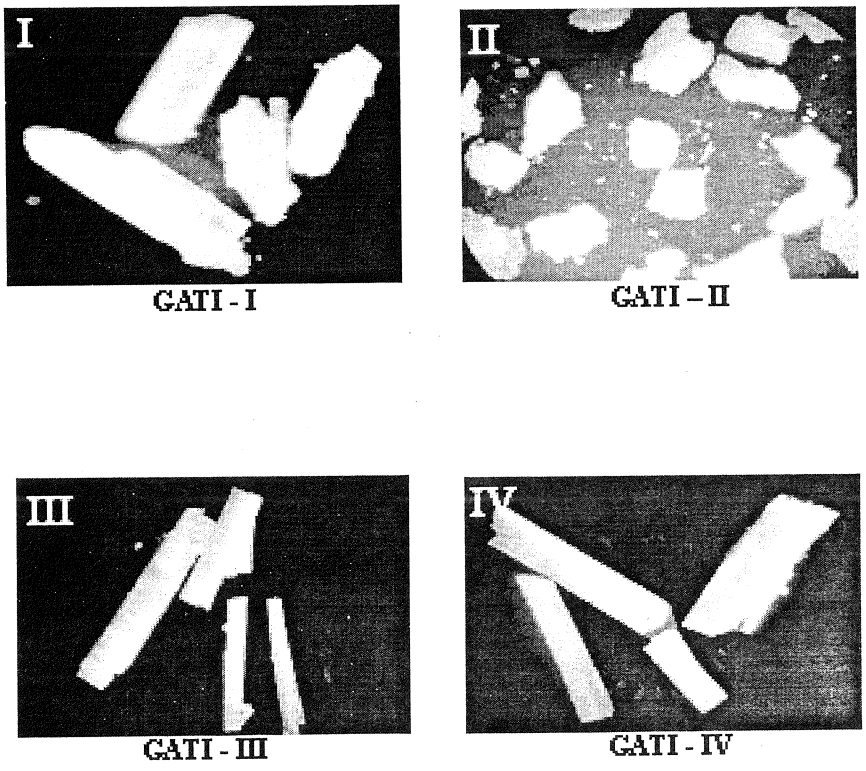

Figure 2. Photomicrographs of GATI-I, GATI-II, GATI-III and GATI-IV

Particle size determination

Particle size was determined by using optical microscope (Olympus-Model BX40). The eye-piece micrometer was calibrated using a standard stage micrometer. The powder sample previously passed through 100 mesh sieve was dispersed with paraffin oil and this sample was mounted on a slide and placed it on the mechanical stage and the size of the particle was (not less than 100) estimated with the help of eye piece micrometer and the average size of the particles were calculated by using standard procedure (Table 1) (Istvan et al. 2000).

Thermal analysis

Differential Scanning Calorimetry (DSC)

The thermographs of different crystalline forms were recorded on Universal V4.7A TA Instruments model DSC 2010 apparatus calibrated with 8 mg indium and zinc at a heating rate of 10°C/min. The thermal behavior was studied by heating 5 mg of the sample at a scan rate of 10°C/min in a covered sample pan under nitrogen gas flow and the investigations were carried out over the temperature range 30– 350°C. Measurements were in triplicate. Melting points were defined as being the point of intersection between the base line and the linear section of the ascending endothermic curve ("onset") (Figure 3). Melting points were taken by open capillary method using heating block type melting point apparatus.

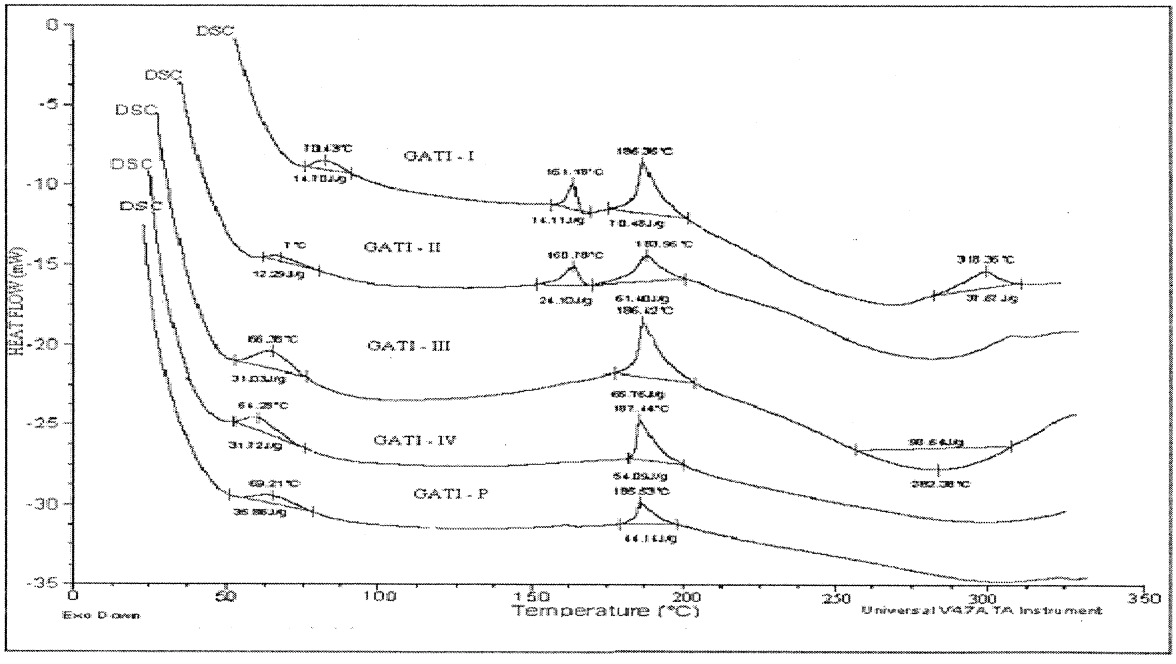

Figure 3. Overlaid DSC thermographs of GATI-I, GATI-II, Gati-III, GATI-IV and GATI-V

Differential Thermal Analysis (DTA)

The DTA curves were measured for each of the prepared samples. An accurately weighed sample (5 mg) was thermally treated using aluminum oxide as a reference material in the derivatograph. The sensitivity of the galvanometer was 1/10, the heating rate was 10°C per minute, and the time was 25 min. The temperature of the sample to be examined was raised starting from room temperature (Figure 4).

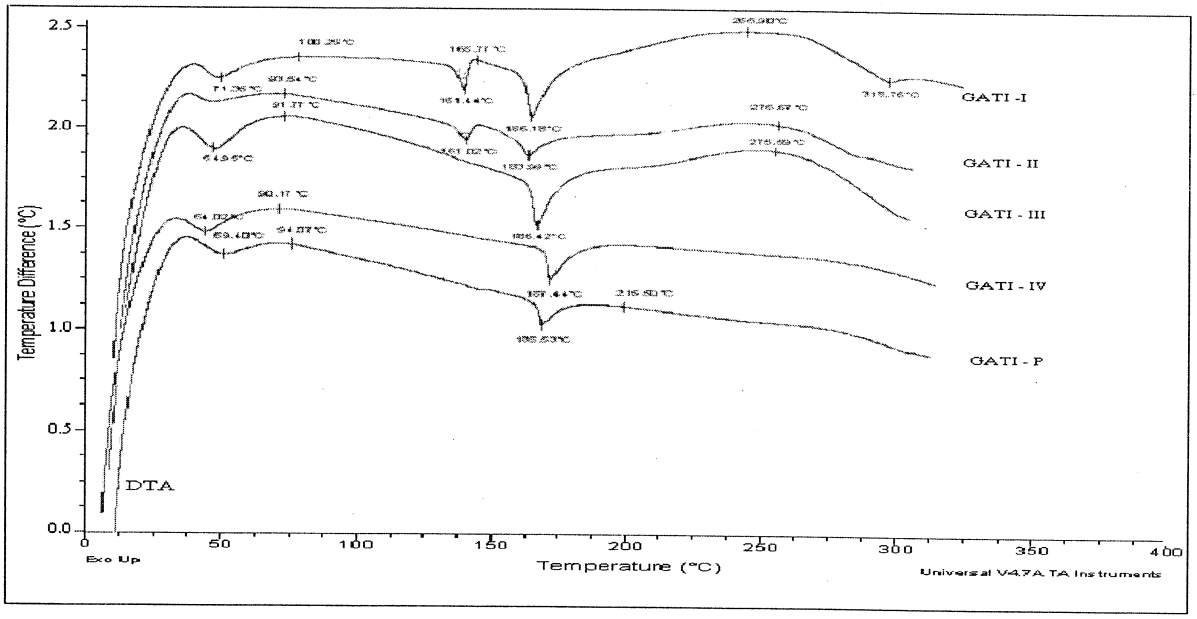

Figure 4. Overlaid DTA thermographs of GATI-I, GATI-II, Gati-III, GATI-IV and GATI-P

Thermo Gravimetric Analysis (TGA)

TG curve was obtained with a thermo gravimetric analyzer (Model Universal V4.7A TA). Thermogravimetry was performed under the following conditions: Sample weight about 8mg, sample cell, a platinum open cell, nitrogen flow rate; 70ml/min, heating rate, 10°C/min (Figure 5).

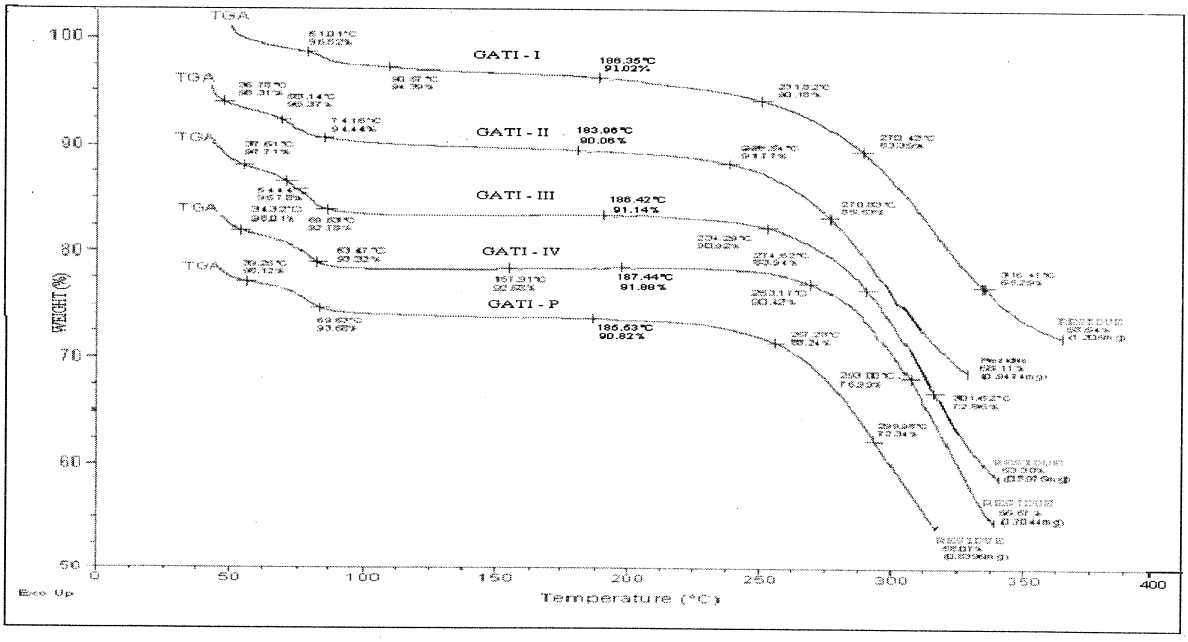

Figure 5. Overlaid TGA thermographs of GATI-I,GATI-II, Gati-III,GATI-IV and GATI-P

Powder X-Ray Diffractometry (PXRD)

A PXRD Diffractometer (Philips Analytical, MODEL - X' per PRO Model) was used to identify the polymorphs. The samples were exposed to Cu Kα radiation (40 kV and 30 mA) and were scanned from 2° to 50° 2theta at step size of 0.01° and 1s step. The divergent slit size was 0.9570°, the receiving slit 1 mm, and the detector slit 0.1 mm. Data were collected by a Kevex solid-state (SiLi) detector. Data was analyzed using DMax-3 software.

Crystals as powdered specimen were packed in a specimen holder made of aluminum. The powders were passed through a 100 mesh sieve and were placed into the sample holder by the side drift technique. The holder consisted of central cavity. In order to prepare a sample for analysis, a glass slide was clipped up to the top face of the sample holder so as to form a wall. Each powder was filled into the holder, gently and used for XRD analysis (Figure 6).

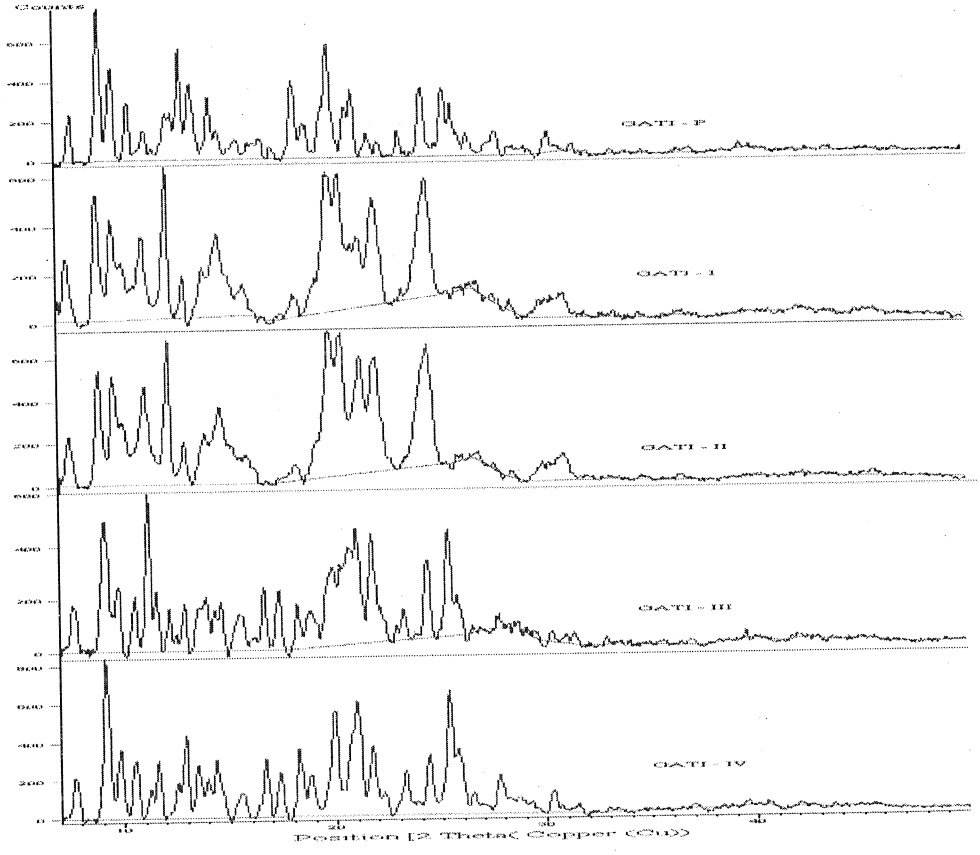

Figure 6. Overlaid PXRD spectra of GATI-P, GATI-I, GATI-II,Gati-III and GATI-IV

Infrared Spectroscopy (IR)

IR spectra of the crystal forms were obtained on Perkin Elmer Spectrum, using KBr pellets. Pellets were prepared by slowly grinding the crystals with KBr in a ratio of 2 mg of crystals with 100 mg of KBr and then applying a pressure of 500 psi in a die-punch (Figure 7).

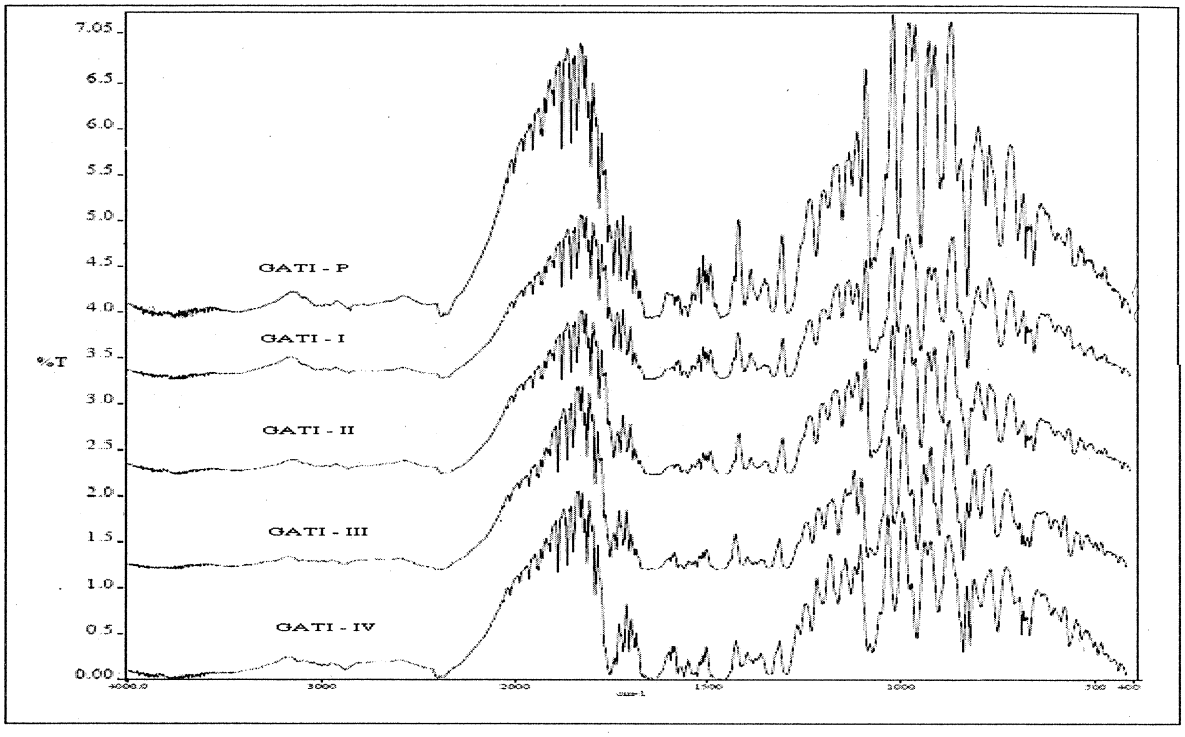

Figure 7. Overlaid IR spectra of GATI-P, GATI-I, GATI-II, Gati-III and GATI-IV

Solubility studies

Solubility studies of different crystal samples of Gatifloxacin were carried out at pH 1.2. Saturated solutions were prepared by adding excess drug to the medium and shaking on the shaker for 4 h at 25 ± 0.5°C under constant vibration. After that period the solution was filtered, diluted and analysed by Double beam UV/VIS-spectrophotometer at 292nm (Roya et al 2009). The experiment was conducted in triplicate for each sample (Table 5, Figure 8).

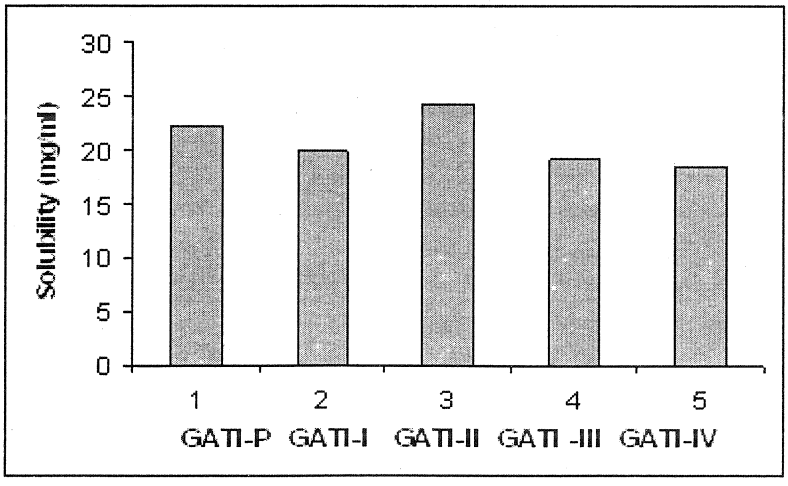

Figure 8. Comparative solubility study of prepared crystal forms of Gatifloxacin

Dissolution profile

Quantitative estimation of Gatifloxacin (1) was done by UV-spectrophotometer using the model Shimadzu 1650PC. A standard plot of the drug (1) was obtained by dissolving in acid buffer (pH 1.2) and made appropriate dilutions to obtain concentrations ranging from 1 to 10 µg/mL. Absorbance of the solution was determined at λ_{max}292 nm and (Lakshmi and Muthu 2006). The readings were obtained in triplicate ($r^2 = 0.9999$, S = 0.0914).

The powder dissolution study was carried out using USP Apparatus 2 in 900 ml of pH 1.2 acid buffer at 37±1°C and 75rpm. A powdered sample of crystal forms (100 mg) previously passed through sieve No.100 was introduced directly in to the dissolution medium. At regular time intervals, a suitable amount of sample was withdrawn, and the same volume was replaced by fresh medium in order to maintain sink condition. Samples were suitably diluted and filtered through syringe filters (Axiva SFCA25X, 0.45µm). The amount of drug released was analyzed spectrophotometrically (Shimadzu 1650PC) at a wavelength of 292 nm (Mange et al. 2008). All studies were carried out in triplicate (Table 6 and Figure 9).

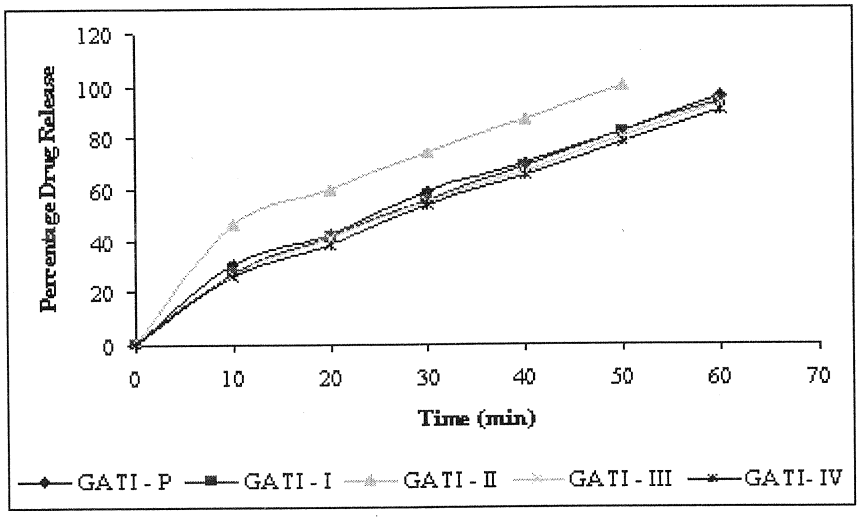

Figure 9. Comparative dissolution study of crystal forms of GATI-I, GATI-II, GATI-III, GATI-IV and Commercial Gatifloxacin (GATI-P)

Results and Discussion

Characterization of polymorphs

Photomicrographs of the crystals showed that the crystals obtained from different solvents existed in different shapes. But, shape alone cannot be a criterion for identifying polymorphs because a polymorph can exist in different crystal habits with varying shapes and sizes (Table 1 and Figure 2).

A DSC curve of commercial Gatifloxacin (GATI-P) shows that initial transition was observed at 69.21°C with heat of fusion 35.86 J/g followed by melting was found at 185.53°C with heat of fusion 44.14 J/g. Two transitions were observed in GATI-I at 70.43°C, 161.18°C and sharp endothermic peak was found at 186.35°C with heat of fusion 14.70 J/g, 14.11 J/g and 70.48 J/g respectively. In case of GATI-II transition was observed between 67.77°C to 160.78°C with heat of fusion 12.29 J/g and 24.10 J/g and melting was observed at 183.96°C with heat of

fusion 61.40 J/g. For GATI-III initial transition was observed at 66.38°C with heat of fusion 31.03 J/g followed by endotherm was observed at 186.42°C with heat of fusion 65.76 J/g. Whereas GATI-IV initial transition was observed at 64.28°C with heat of fusion 31.72 J/g followed by melting at 187.44°C with heat of fusion 54.09 J/g. The temperature of this transition observed in all crystal forms were highly dependent on crystal size and quality, with smaller crystals having more defects observed to transform before larger more perfect crystals. An exothermic peak (energy released from the bond breaking) was observed in GATI-III at 282.38°C might be due to oxidative decomposition which was absent in the form of GATI-II and GATI-IV (Table 4 and Figure 3).

Table 4. Crystal Forms, DSC Data, Peak fusion Point and Heat of Fusion of Crystal Forms of Gatifloxacin

Crystal Form	Solvent Used -	DSC Data	
		Peak fusion Point (°C)	Heat of fusion (J/g)
GATI-I	Methanol	186.35	70.48
GATI-II	Ethanol	183.96	61.4
GATI-III	Isopropanol(70%)	186.42	65.76
GATI-IV	Ethanol and water(1:1)	187.44	54.09
GATI-P	-	185.53	44.14

From the results in case of GATI-II it was having low melting point (183.96°C) when compare with commercial Gatifloxacin (GATI-P) as well as rest of the crystals and it could be identified as metastable. GATI-I, GATI-III and GATI-IV were having higher melting point when compare with GATI-P as well as GATI-II. But, GATI-IV was having highest melting point (87.44°C) when compare with rest of the crystals could be identified as stable polymorph. In case of GATI-I and GATI-III were having more or less similar melting points (186.35°C, 186.42°C) as well as heat of fusion (70.48 J/g, 65.76 J/g). Hence, three types of polymorphs were identified based on DSC but fails to make any distinction among GATI-I and GATI-III.

From DTA curves it was evident that same melting points were observed in all the crystal forms as well as commercial gatifloxacin as like that of DSC results (Figure 4). TGA was performed at the heating rate of 10°C per min to detect change in the weight of a substance is recorded as a function of temperature and time. From the results (Figure 5) it was found that 91.02 % weight remains at 186.35°C for GATI-I, 90.06 % weight remains at 183.96°C for GATI-II, 91.14 % weight remains at 186.42°C for GATI-III and 91.88 % weight remains at 187.44°C for GATI-IV. It was evident that, 90.82 % weight remains at 185.53°C for commercial gatifloxacin. According to the results, all forms of gatifloxacin (GATI-I, GATI-II, GATI-III and GATI-IV) were found to be not apparently solvates.

Considering powder X-ray diffractometry (PXRD) to be the ideal technique for characterizing polymorphs. Hence, all the crystal forms were submitted for PXRD studies. In PXRD (Figure 6), all crystal l forms (GATI-I, II, III and IV) gave different patterns. Spectra of these form neither matching with one another nor with commercial gatifloxacin. On this basis it was concluded that these crystals existed in four different polymorphic forms.

Table 2 gives the PXRD data obtained for the four crystal forms as well as commercial gatifloxacin in terms of lattice spacing and the relative intensities. GATI-I showed characteristic intense line at 21.98 °2 theta which was absent in rest of the crystal forms.

GATI-II showed intense lines at 21.28 and 21.98 °2 theta which were absent in rest of the crystal forms. GATI-III showed characteristics intense lines at 14.64, 16.70 and 17.40 °2 theta which was absent in rest of the forms. In case of GATI-I, II and III it was observed that similar intense line at 12.24, 12.29 and 11.23 °2 theta which was absent in GATI-IV and also the intense line at 12.91 °2 theta observed in GATI-IV was absent in rest of the crystal forms.

Table 2. X-ray Diffraction Data in Terms of °2 Theta and Intensity for Commercial Gatifloxacin, GATI – I, GATI – II, GATI – III and GATI – IV

Gatifloxacin	GATI – I	GATI – II	GATI – III	GATI – IV
°2Th.Intensity	°2Th.Intensity	°2Th. Intensity	°2Th. Intensity	°2Th.Intensity
7.83 31.55	7.40 34.17	7.62 33.81	7.73 29.84	7.71 26.13
9.20 100.00	**8.95 85.77**	**9.02 76.57**	**9.12 86.71**	**9.17 100.00**
9.75 63.84	**9.64 68.60**	9.62 75.78	9.84 37.85	**9.83 42.94**
10.43 34.82	11.08 56.11	**11.10 66.93**	10.55 36.57	10.55 35.78
12.95 75.91	**12.24 100.0**	**12.29 91.76**	**11.23 100.00**	11.66 31.80
13.49 52.22	13.03 27.13	12.99 29.29	11.63 37.85	**12.91 52.01**
14.34 42.92	**14.65 55.62**	13.91 32.97	12.16 28.48	13.41 31.93
17.28 6.68	**19.77 92.93**	18.24 11.29	13.44 21.06	15.58 14.16
18.29 52.96	**21.98 71.72**	**19.78 100.00**	14.07 23.19	16.68 35.88
21.06 45.90	28.54 5.19	**21.28 81.44**	15.58 22.77	**18.19 41.00**
21.76 16.10	31.00 15.18	**21.98 78.76**	**16.70 36.58**	18.79 25.58
23.21 17.80		24.50 80.93	**17.40 35.88**	**19.93 65.13**
24.32 46.77		29.71 7.66	18.19 29.56	**21.05 66.47**
27.94 15.75		34.76 2.10	19.61 44.21	23.26 28.26
30.30 13.49			**20.94 68.12**	24.36 38.38
36.83 2.88			**21.69 73.16**	**25.34 78.39**
			23.15 16.78	25.80 39.19
				30.14 10.11

Bold peaks indicates different intensities

Above PXRD data was compared with the PXRD data of commercial gatifloxacin. It was found that commercial gatifloxacin showed three intense lines at 12.95, 19.92 and 24.32 °2 theta which were absent in rest of the crystal forms indicating that to be different from commercial gatifloxacin.

Infrared (IR) spectroscopy, is another important technique for characterization of polymorphs. On comparing the IR spectra of the crystals, differences in the peak patterns were observed in all the crystal forms between the ranges of 1800-1100 cm^{-1} (Table 3 and Figure 7). GATI – II and GATI – III offered distinctly different spectra in the above given range from each other, and also from GATI-I and II. Peaks at 1719.81 cm^{-1}, 1557.60 cm^{-1} 1395.39 cm^{-1} are appeared in GATI – II whereas they shifted to 1716.12cm^{-1}, 1616.58 cm^{-1}, 1391.70 cm^{-1} respectively in GATI - III. Peak at 1321.65cm^{-1} appeared in GATI – II and GATI – III but disappeared in GATI – IV. Peaks at 1391.70 cm^{-1}, 1716.12 cm^{-1} and 1277.41 cm^{-1} appeared in GATI – III, where as shifted to 1395.39 cm^{-1} , 1719.81 cm^{-1} in Form-IV and peak at 1277.41 cm^{-1} disappeared in GATI – IV. Peak at 1616.58 cm^{-1} appeared in GATI – I, where as it is shifted to 1557.60 cm^{-1} in GATI – II. Peak at 1317.95 cm^{-1} appeared in GATI – I, where as it is shifted to 1278.60 cm^{-1} and 1277.60 cm^{-1} in GATI – III and GATI – IV respectively. Peak at 1240.65 cm^{-1} appeared in GATI – IV, where as it disappeared in all other crystal forms. Peaks

in commercial gatifloxacin (GATI – P) were different when compared with all other crystal forms. Based on IR spectroscopy it could be pointed out the existence of four crystal forms (crystal habit or polymorphs).

Table 3. Interpretation of FT-IR spectra of prepared crystals forms with pure Gatifloxacin

Groups	Characteristics peaks (cm^{-1})					
	Range of Groups (cm^{-1})	GATI – P	GATI – I	GATI – II	GATI – III	GATI – IV
COOH	3400-2800	3011.07	3011.07	3011.07	3011.07	3011.07
C-F	1400-1000	1321.65	1317.97	1321.65	1321.65	1240.65
Epoxy	1170-1050	1068.5	1067.28	1067.6	1067.06	1067.28
OCH3Stretch	1325-1250	1277.41	1277.41	1317.95	1277.41	1277.6
C=O	1700	1719.81	1716.12	1719.81	1716.12	1719.81
C-N Stretching	1073	1056.22	1056.22	1052.5	1052.6	1052.53
N-H bending	1617	1616.58	1616.58	1557.6	1616.58	1616.58
N-H Stretch	1400-1300	1395.39	1395.39	1395.39	1391.7	1395.39

The particle size, crystal yield, solubility and percentage drug release of gatifloxacin crystals are shown in Table 1, 5 and 6 and Figure 8 and 9. The mean particle size (101 μm) with the highest crystal yield (85%) was observed with GATI-IV prepared from the ratio of ethanol: water (1:1). The gatifloxacin crystals showed differences in solubility and dissolution profiles depending on the particle size and its nature of the crystal forms. Crystallization of gatifloxacin from ethanol (GATI-II) produced small, spongy opaque crystals that exhibited highest solubility and dissolution rate than other crystals due to its smaller particle size (85μm) having maximum surface area. Prismatic crystals (GATI-I) from methanol , Thin pole like crystals (GATI-III) from isopropanol (70%) and rod shape crystals (GATI-IV) from ethanol and water(1:1) were having particle size 90μm, 94μm and 101μm respectively and exhibited drug release 93.73 %, 92.70 % and 90.22 % at the end of 60min.

Table 5. Solubility of Crystal forms of Gatifloxacin in Various Solvents

Crystal code	Solubility (mg/mL ± SD)
GATI - I	20.00 ± 0.05
GATI - II	24.29 ± 0.03
GATI - III	19.23 ± 0.04
GATI - IV	18.51 ± 0.05
GATI - P	22.15 ± 0.07

Table 6. Dissolution Rate Profiles of Crystal Forms and Gatifloxacin (1)

Time	Cumulative Percentage Drug Release				
	GATI - P	GATI - I	GATI - II	GATI - III	GATI - IV
10min	25.85 ± 0.05	25.57 ± 0.07	46.28 ± 0.06	27.02 ± 0.06	26.58 ± 0.05
20min	42.62 ± 0.07	41.52 ± 0.05	60.30 ± 0.04	40.86 ± 0.04	38.66 ± 0.08
30min	59.57 ± 0.04	56.15 ± 0.04	74.25 ± 0.07	55.49 ± 0.07	53.71 ± 0.06
40min	70.33 ± 0.07	68.74 ± 0.08	87.24 ± 0.05	66.76 ± 0.05	65.71 ± 0.04
50min	82.05 ± 0.05	82.05 ± 0.04	99.47 ± 0.08	80.21 ± 0.06	78.08 ± 0.07
60min	95.67 ± 0.06	93.73 ± 0.06		92.70 ± 0.04	90.22 ± 0.05

Conclusion

Crystallization of Gatifloxacin in different polar protic solvents offered crystals with different shapes as revealed by photomicrography. Characterization of the crystal forms were done on the basis of their melting points, DSC, TGA, DTA thermographs, IR and XRD Spectra. All the crystals gave different melting points and DSC, DTA and TGA thermographs thereby giving much information about the existence of polymorphism in Gatifloxacin. An exothermic peak was observed in GATI-III might be due to oxidative decomposition which was absent in rest of the crystal forms. Three types of polymorphs were identified based on thermal analysis but fails to make any distinction among GATI-I and GATI-III. IR spectral technique indicated the existence of four polymorphic forms of the drug in the current study. XRD data confirmed the above observations in the form of existence of four polymorphic forms for the drug Gatifloxacin (1).

The mean particle size (101 μm) with the highest crystal yield (85%) was observed with GATI-IV prepared from the ratio of ethanol: water (1:1). Crystallization of gatifloxacin from ethanol (GATI-II) produced spongy opaque crystals that exhibited highest solubility and dissolution rate than other crystals due to its lowest melting point and smaller particle size (85μm) having maximum surface area. It is concluded finally that the study has indicated the existence of four polymorphic forms of Gatifloxacin (1).

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