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Thermoanalytical study of polymorphic transformation in Fluconazole drug

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Abstract

Polymorphic transformation in Fluconazole (I) drug has been studied employing differential scanning calorimetry (DSC), X-ray diffraction and FT-IR techniques. Fluconazole (I) exhibited the sharp melting point at 138.4 °C. Considerable under cooling was, however, observed for the drug during cooling. No indication of freezing of molten Fluconazole (I) was evident in the DSC curve recorded up to a temperature of 25 °C in the cooling cycle. Reheating of the sample obtained after cooling, produced the DSC pattern much different compared to that obtained in the first heating and consisted of a sharp exothermic peak beginning at 81 °C preceding the twin endothermic peak with an onset temperature of 135.3 °C. In addition to these two peaks, a small endothermic peak was also observed around 31 °C, which could be attributed to a glass transition with an associated relaxation. The precise glass transition temperature derived from the data collected from six different independent experiments was found to be (31.67 ± 0.13) °C.

X-ray diffraction pattern of the Fluconazole (I) indicated that the as received sample was crystalline. The molten Fluconazole on cooling, however, produced a glassy amorphous mass. The amorphous product on heating to temperature >81 °C transformed to Fluconazole (II) which subsequently changed to Fluconazole (I) prior to melting. The split endothermic peak beginning at 135.3 °C recorded for the solidified Fluconazole sample is consistent with the observations made by X-ray diffraction.

The observations made by employing DSC and X-ray diffraction were corroborated by FT-IR data on the samples isolated at different stages in the experiments.

Keywords: Fluconazole drug; Differential scanning calorimetry; X-ray; FT-IR

1. Introduction

Fluconazole is an antifungal drug newly manufactured and marketed in India and has been gaining popularity among the medical fraternity. It is essentially an antifungal drug and is related to imidazole derivative.

Drug is often formulated with excipients and additives. It is necessary that the excipients or the additives used in the drug formulation are chemically compatible with the drug. Incompatibility of the excipient with the drug can lead to an accelerated potency loss due to complex formation. Differential scanning calorimetry (DSC) has been successfully employed in recent years in the study of the compatibility of various drugs with excipient with high degree of success [1–5]. The present DSC investigation describes the thermal behaviour of Fluconazole (I) and is a prelude

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to the detailed study of its compatibility with the selected excipients. The results of the compatibility studies will be published separately [6].

2. Experimental

2.1. Materials

Fluconazole (I) used in the present investigation was procured from Dr. Reddy's Laboratories Ltd., India. Its purity was found to be 99.8% as analysed by HPLC. The reverse phase HPLC system (Shimadzu, Model LC 10 AT-vp) consisting of a solvent delivery pump and variable UV detector (set at 261 nm) was used for purity determination. A nonpolar stationary phase (Lichrosphere C18, 10 μm particle size, 4 mm × 250 mm; Merck AG) column was used. The mobile phase consisted of 70% 0.05 M potassium dihydrogen ortho phosphate, 20% acetonitrile and 10% methanol. The flow rate of the mobile phase was maintained at 1.5 ml/min. The injection volume used was 20 μl.

The sample on drying in air oven at 105 °C for 3 h showed a mass loss of 0.3% which could be attributed to the loss of adsorbed moisture.

2.2. Instrumental methods

2.2.1. Differential scanning calorimeter (DSC)

The DSC curves for the samples contained in the sealed aluminum sample holders were recorded in flowing nitrogen atmosphere at the constant heating rate of 5 °C/min employing the heat flux DSC (Shimadzu model DSC-60). The built-in software has been provided with the instrument for the determination of the glass transition and phase transformation temperatures from the recorded curves. About 4 and 8 mg samples were used in the two sets of experiments. Each set consisted of three different DSC scans recorded under identical experimental conditions on 4 and 8 mg sample, respectively. The instrument was calibrated employing the standard reference materials and procedure recommended by Hohne et al. [7].

The sample investigated in the present study was heated up to 160 °C and held at this temperature for 3 min before cooling to room temperature at the same cooling rate of 5 °C/min. The programmed cooling rate in the cooling cycle could be controlled only up to ∼60 °C, below which the system followed the natural cooling rate (Newton's Law of Cooling). The sample cooled to room temperature was reheated up to 160 °C under similar conditions.

2.2.2. X-ray diffraction

The X-ray diffraction patterns for original sample as well as those obtained after thermal cycling were recorded using Philips X-ray diffractometer (Model: PW-1710) at the scanning rate of $2^\circ\ 2\theta\ \mathrm{min}^{-1}$, employing Cu Kα radiation. The diffraction patterns were recorded in the 2θ range of 10–70°.

2.2.3. FT-IR experiments

The FTIR data was recorded on as received sample as well as the samples obtained after thermal cycling, using Shimadzu instrument (Model: 8101A). The patterns were recorded between 4600 and 400 cm^{-1}.

3. Results

The DSC curves recorded for Fluconazole (I) during first heating, first cooling and second heating, second cooling are shown in Figs. 1 and 2, respectively. The DSC pattern for as received Fluconazole (I) (Fig. 1) showed a small deviation from the base line around 27 °C, as soon as the heating was started, and could probably be attributed to the instrumental drift. This was followed by a prominent endothermic peak due to melting of the compound at 138.4 °C which is well within the reported melting range 138–140 °C [8]. Interestingly enough, the DSC curve recorded during first cooling of the sample heated up to 160 °C yielded no peak until 25 °C.

The DSC curve recorded for the sample on second heating was totally different compared to that obtained in the first heating cycle. A small endothermic peak at about 31 °C was found to precede a prominent exothermic peak at 81 °C and a twin endothermic peak at 135.3 °C. Careful analysis of the peak around 31 °C recorded at the increased sensitivity, revealed that this peak was not an instrumental artifact and could be attributed to the glass transition temperature 'T_g', of the product obtained in the first cooling run. This temperature was found to be (31.67 ± 0.13) °C from six

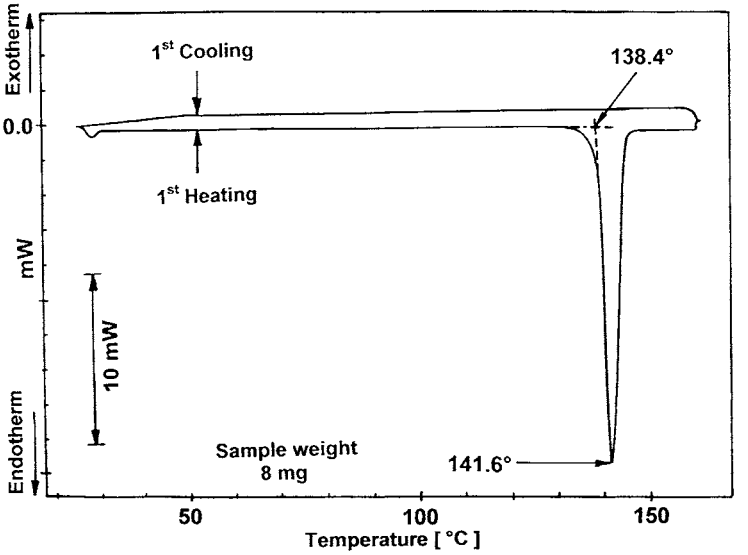

Fig. 1. Differential scanning calorimetric (DSC) traces for as received Fluconazole sample recorded in nitrogen at the heating and cooling rate of 5 °C/min, first heating and first cooling sequence.

independent experiments carried out employing 4 and 8 mg samples, respectively.

A partial superimposition of the instrumental drift and the deviation caused due to glass transition was observed if larger sample size was used in the experiment. This is highlighted in Fig. 3. It can be seen from this figure, that the DSC curve recorded for glass transition on 4 mg sample is better separated from the

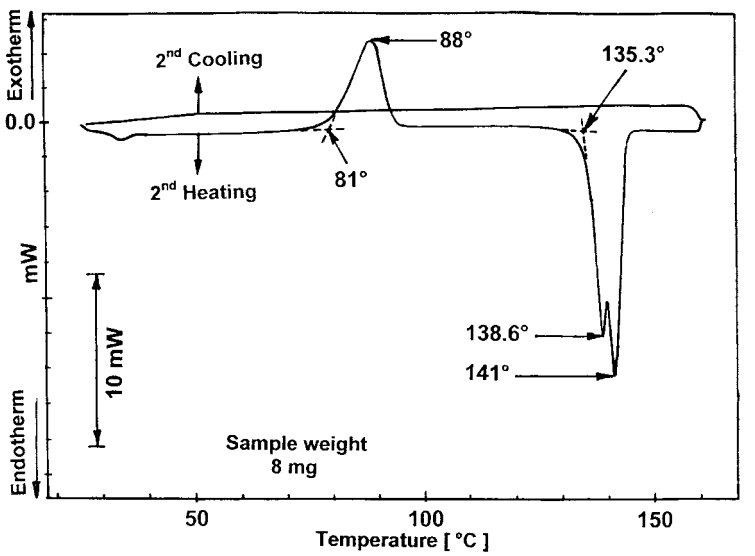

Fig. 2. Differential scanning calorimetric (DSC) traces for Fluconazole sample recorded in nitrogen at the heating and cooling rate of 5 °C/min, for second heating and cooling sequence.

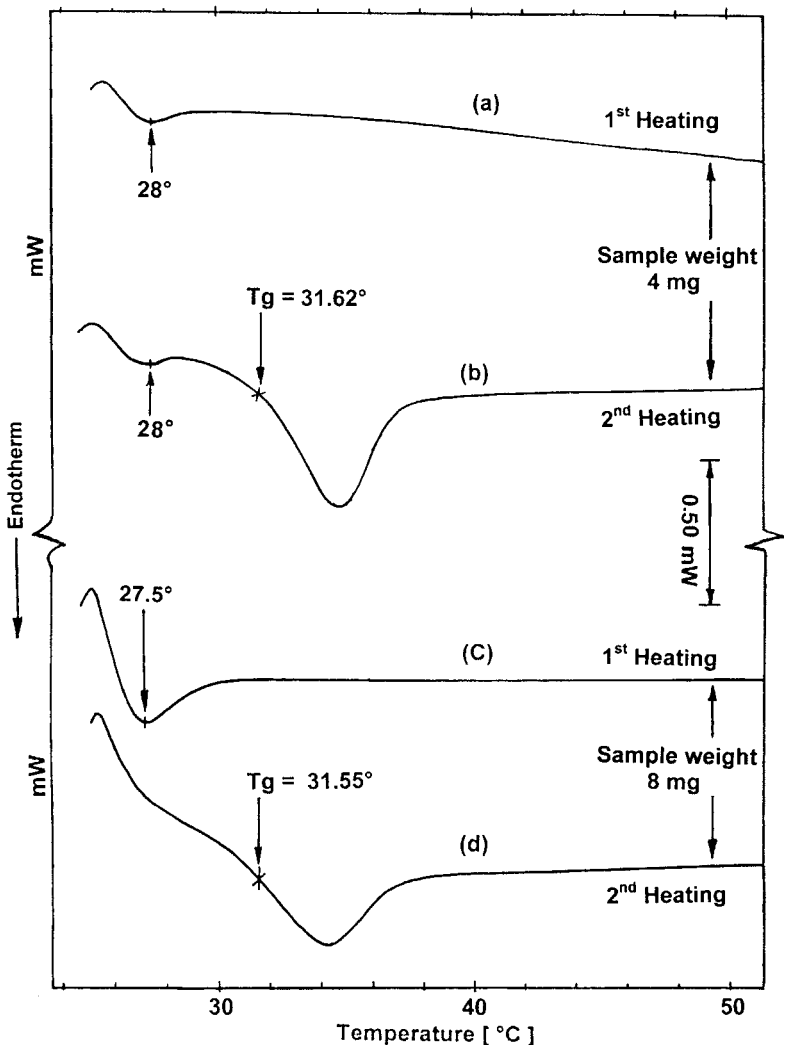

Fig. 3. The influence of sample size on glass transition temperature in the glassy mass obtained from Fluconazole (I) melt. (a) First heat; (b) second heat (with 4 mg sample); (c) first heat and (d) second heat (with 8 mg sample).

instrumental drift compared to that when 8 mg sample was employed.

The DSC curve following the glass transition temperature in Fig. 2, consisted of a prominent exothermic peak beginning at 81 °C, preceding the sharp twin endothermic peak recorded at 135.3 °C. This twin endothermic peak consisted of two partially superimposed peaks with the separation of only 1.5–2.5 °C between them. The initiation temperature of the first endothermic peak was 135.3 °C compared to 138.4 °C obtained for the single peak recorded in the first heating cycle.

The X-ray pattern of moisture free Fluconazole (I) sample obtained by prior drying at 105 °C is shown in Fig. 4a. The absence of DSC peak during cooling in the first cycle and the appearance of strong exothermic peak, after the glass transition temperature, prior to melting in the second heating run followed by a twin endothermic peak suggests that the melt obtained during heating when cooled formed a glass which

re-crystallised in the second heating to a new polymorph, probably Fluconazole (II), which transforms to Fluconazole (I) prior to melting. A separate experiment was carried out to confirm this hypothesis. In this experiment, Fluconazole (I) was melted in a small beaker and the glass slide employed as a sample holder for X-ray diffraction experiments was dipped in to this melt. On withdrawing glass slide from the melt the molten Fluconazole adhering to it in the form of thin layer solidified. The X-ray pattern from molten Fluconazole solidified on the glass slide is shown in Fig. 4b. As expected from DSC results, the solidified melt was found to be amorphous. The XRD data obtained on the original sample and the product obtained after heating the solidified glassy material at 85 °C for 1 h are presented in Fig. 4a and c and listed in Table 1. From all figures presented in Fig. 4a–c and the data presented in Table 1, it can be concluded that the solidified Fluconazole sample is amorphous (Fig. 4b) and it transforms >81 °C to a crystalline phase containing fewer lines (Fig. 4c) compared to that in original Fluconazole (I) sample shown in Fig. 4a.

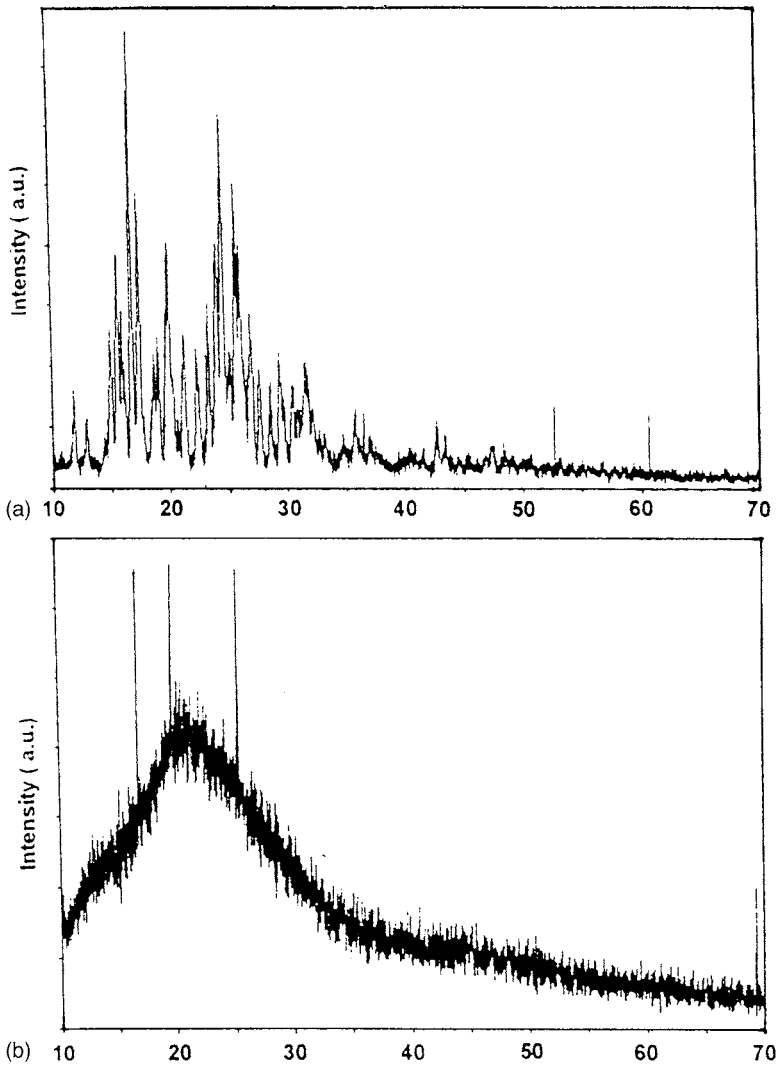

Fig. 4. X-ray diffraction pattern for (a) as received Fluconazole (I) sample; (b) Fluconazole sample obtained from the melt by cooling and (c) Fluconazole sample obtained after heating the solidified material at 85 °C for 1 h.

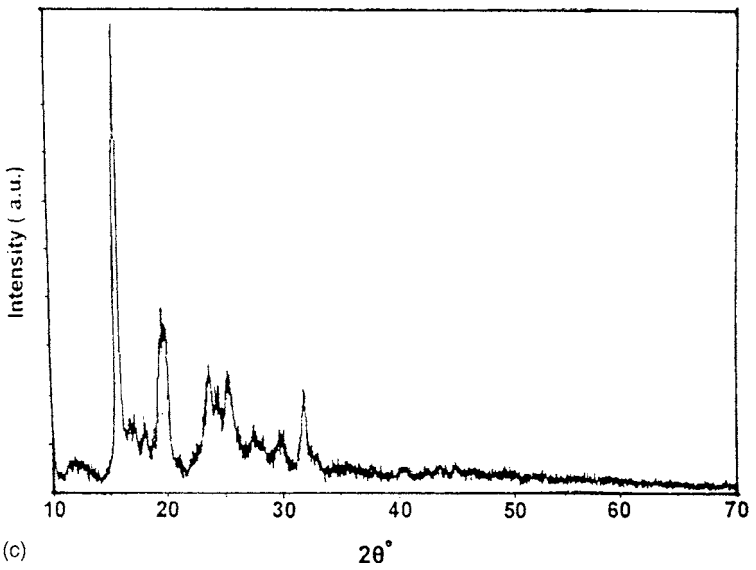

Fig. 4. (*Continued*).

FT-IR patterns for as received Fluconazole (I) sample and the sample obtained after heating amorphous mass at 85 °C for 1 h showed considerable difference. The data presented in Table 2 revealed that wave numbers for several peaks shifted significantly in the case of samples obtained from the solidified melt on heating at 85 °C, compared to that in as received sample. In addition, some new peaks appeared and some of the lines disappeared in the patterns recorded for the sample obtained by heating solidified amorphous mass. This indicated that the original Fluconazole (I) sample and the product obtained by reheating the cooled metastable amorphous mass were distinctly different as observed in X-ray diffraction studies. The FT-IR patterns for the two polymorphic forms of Fluconazole are compared in Fig. 5a and b.

4. Discussion

The DSC curves recorded for Fluconazole (I) sample indicate that the compound has a sharp melting point at 138.4 °C. The molten Fluconazole (I) showed a remarkable undercooling and solidified to a glassy mass on cooling to room temperature. This sample on reheating exhibited a glass transition temperature at (31.67 ± 0.13) °C with an associated relaxation. Generally, a glass transition temperature is obtained from an endothermic step in the DSC curve. In the present case, a peak is observed for glass transition which could be understood only in terms of relaxation of the strain in the material immediately following the glass transition. Such peaks have been reported for glass transition in polymeric materials [9].

The glass transition observed in the second heating was followed by crystallisation of the product at 81 °C prior to the phase transition beginning at 135.3 °C. The peak commencing at 135.3 °C consisted of two overlapping peaks separated only by 1.5–2.5 °C. This twin endothermic peak beginning at 135.3 °C is certainly different from the single endothermic peak at 138.4 °C obtained in the first heating cycle. The peak beginning at 135.3 °C could probably be attributed to the transformation of Fluconazole (II) obtained from the amorphous mass, as concluded from the XRD data, to Fluconazole (I) prior to melting. The superimposition of the two peaks suggests that the melting of Fluconazole (I) begins before the transformation of Fluconazole (II) to Fluconazole (I) is complete.

The DSC results obtained on Fluconazole (I) in the first and second heating cycles, coupled with the X-ray diffraction and FT-IR data on the material obtained after arresting the process at 85 °C, confirms that the glassy or amorphous product obtained from

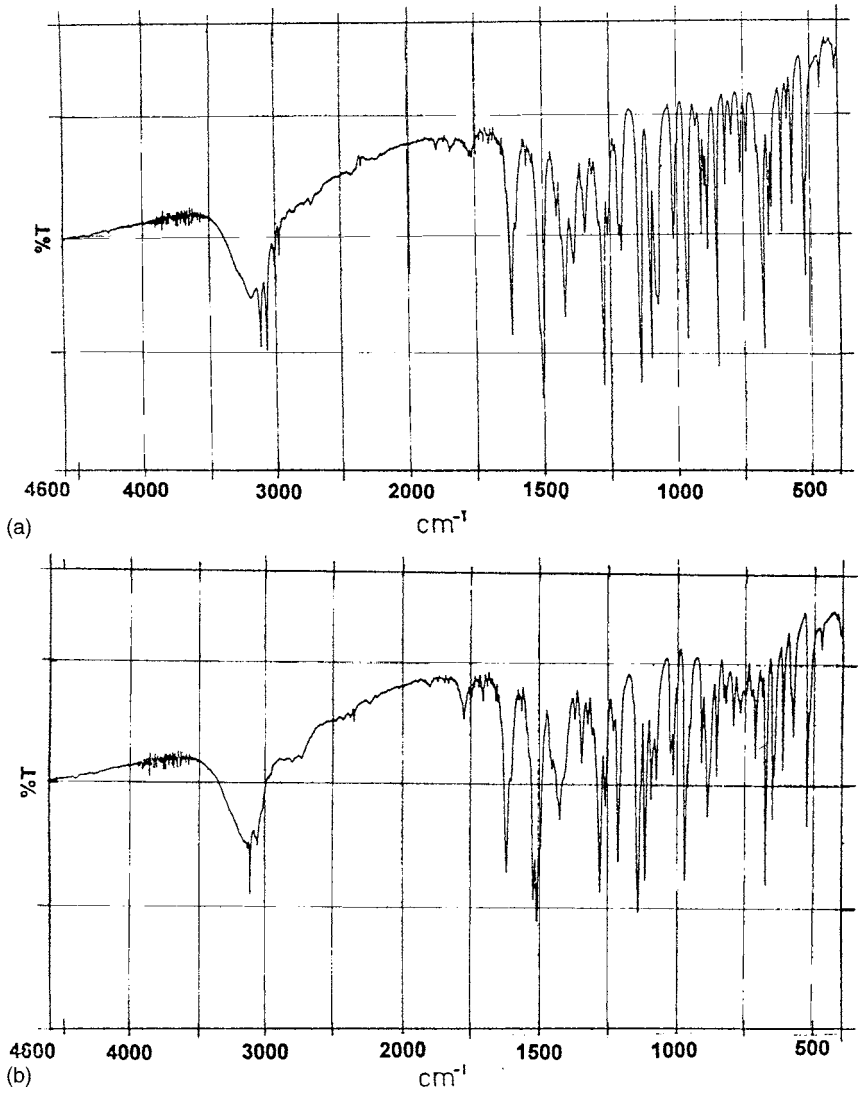

Fig. 5. FT-IR pattern for (a) as received Fluconazole (I) sample and (b) Fluconazole sample obtained by heating the solidified mass to 85 °C for 1 h.

Fluconazole (I) after the first heating run transformed to crystalline polymorphic form (II) after the exothermic process >81 °C.

The X-ray patterns for the two forms of Fluconazole (I and II) are presented in [10]. The as received sample supplied by the vendor in the present study is designated as form (I) and shows only one endothermic DSC peak on heating, in agreement with the observation reported in [10]. The product obtained on transformation of the amorphous mass, in the present case, is termed as form (II) and shows two overlapping endothermic peaks on heating. Gu and Jiang [10] also made similar observation (i.e. two overlapping peaks) in their DSC plot recorded on Fluconazole (II) sample.

The undercooling of molten drug observed in this investigation is quite common. However, the extent of undercooling exhibited by Fluconazole (I) melt is unduly large. Such observations are reported in rare

Table 1
XRD data obtained on the original sample and the product obtained after heating the solidified glassy material at 85 °C for 1 h

2θ	Intensity (%)
XRD data for as received Fluconazole sample	
–	–
11.86	15.50
12.84	11.21
14.95	29.98
15.61	48.56
15.94	37.87
16.84	100.00
17.47	64.87
–	–
18.66	25.68
19.01	28.99
–	–
19.93	52.41
20.29	17.71
21.31	29.98
22.34	26.14
23.37	37.31
–	–
24.16	47.30
24.67	79.46
25.20	23.88
25.72	67.08
25.98	53.07
–	–
26.90	37.87
27.08	24.33
27.61	21.72
28.60	21.72
29.36	28.99
29.73	14.79
30.44	18.09
30.87	14.10
31.53	24.33
31.78	23.44
XRD data for Fluconazole when glassy sample heated at 85 °C for 1 h	
11.62	4.62
–	–
–	–
–	–
–	–
15.94	100.00
–	–
–	–
18.10	12.61
–	–
–	–
19.52	38.05
–	–
20.11	36.90
–	–
–	–
–	–
23.68	28.38
–	–
–	–
25.38	26.90
–	–
–	–
26.14	12.28
–	–
–	–
27.52	9.80
–	–
–	–
–	–
–	–
–	–
–	–
31.96	25.47

Table 2
Wave numbers for several peaks shifted significantly in the case of samples obtained from the solidified melt on heating at 85 °C, compared to that in as received sample

Peak wave numbers (cm^{-1})	
FT-IR data for as received Fluconazole sample	FT-IR data for Fluconazole when glassy sample heated at 85 °C for 1 h
3190.6	3105.5
3119.3	3053.7
3073.0	1655.1
3009.3	1614.6
2968.8	1597.3
1655.1	1560.6
1618.5	1518.2
1601.1	1504.7
1560.6	1458.4
1516.2	1450.6
1506.6	1421.7
1458.4	1367.7
1448.7	1342.6
1433.3	1319.5
1419.8	1304.0
1387.0	1277.0
1342.6	1257.7
1317.5	1230.7
1294.4	1213.4
1279.0	1142.0
1259.7	1132.4
1219.2	1116.9
1211.4	1095.7

Table 2 (*Continued*)

Peak wave numbers (cm^{-1})	
FT-IR data for as received Fluconazole sample	FT-IR data for Fluconazole when glassy sample heated at 85 °C for 1 h
1143.9	1076.4
1103.4	1024.3
1084.1	1014.7
1078.3	1001.2
1016.6	970.3
1010.8	960.7
1001.2	908.6
966.5	887.4
927.9	852.6
908.6	829.5
895.1	819.8
885.4	792.8
850.7	767.8
817.9	748.5
792.8	727.3
762.0	713.7
738.8	688.7
702.2	675.2
679.0	650.1
657.8	644.3
646.2	613.4
609.6	–
–	–

cases; one such case is that of Paracetamol in which the glassy form of Paracetamol obtained from its melt after cooling showed similar crystallisation peak involving the transformation of glassy mass to form II which melted around 157 °C [11].

5. Conclusion

The observations made in this study showed that Flunconazole (I) exhibited remarkable undercooling during cooling cycle. The melt of Fluconazole (I) solidified to a glassy mass. This glassy substance on heating gave Fluconazole (II) which transformed to form (I) prior to melting. The X-ray diffraction studies and FT-IR data have been found to be mutually consistent and lead to the conclusion that the melting of Fluconazole (I) is irreversible leading to metastable solid which subsequently transformed to new stable polymorphic form i.e. Fluconazole (II).

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