Thermal Behaviour of Diclofenac Sodium: Decomposition and Melting Characteristics

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The thermal behaviour and melting characteristics of diclofenac sodium were investigated using various instrumental techniques—differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Fourier-transform infrared (FT-IR) spectroscopy and thin layer chromatography (TLC). DSC analysis of diclofenac sodium performed under dynamic flow of either synthetic air or helium or nitrogen did not produce any sharp endothermic peak characteristic of melting peak of a pure substance. Both the rate of scanning of the sample and the environmental atmospheric condition significantly affected the thermographic profile of diclofenac sodium. An exothermic peak prior to an endothermic peak corresponding to melting of the substance appeared when heated under dynamic flow of synthetic air suggesting oxidation (decomposition) of diclofenac sodium before reaching its melting point. In fact, at a scanning rate of 1 °C/min only the exothermic peak appeared in the thermogram, suggesting complete decomposition prior to melting under the dynamic flow of synthetic air. DSC, FT-IR and TLC data obtained from samples heated under the dynamic flow of either helium or nitrogen revealed formation of a related compound, 1-(2,6-dichlorophenyl)-indolin-2-one, an indol-cyclic amide, as a result of an intramolecular cyclization reaction during the heating process. TGA data demonstrated a loss of 11.4—20.2% of the mass of diclofenac sodium when heated under various environmental conditions, and also supported the oxidative nature of degraded product(s) when the thermal process occurred slowly under a dynamic flow of synthetic air.

Key words diclofenac sodium; thermal decomposition; thermal oxidation; degraded product

Diclofenac sodium is a synthetic compound and therapeutically belongs to the group of non-steroidal anti-inflammatory drugs. Although the drug is well known and commercially available on the market in various pharmaceutical dosage forms (enteric coated oral tablets, sustained release oral tablets, topical preparations, injections and others), literature reports on thermal characterization and melting behaviour of the drug substance are contradictory. Even the melting point (about 280 °C) of diclofenac sodium cited in some reference literature (*e.g.*, European Pharmacopoeia, 3rd edition) does not correspond to the melting point reported in most scientific literature (285—289 °C).[1—3)]

A thorough investigation of the available literature data on thermal behaviour and melting characteristics of diclofenac sodium in our laboratories suggests that the anomalies observed in reported data are due to the fact that most investigators used types of equipment which are not sensitive enough to detect all the phenomena that occur during melting of the substance, and most experiments were not well designed to make comprehensive conclusions possible. It is possible that most of the investigators did not have access to all facilities required for studying the melting and decomposition characteristics of diclofenac sodium. In fact, no differential scanning calorimetric data are available on the influence of scanning rate on the thermal behaviour of diclofenac sodium, and none of the investigators performed differential scanning calorimetry (DSC) on this drug under helium. Therefore, the main objective of our study reported here was to investigate the thermal behaviour of diclofenac sodium under various conditions using a number of techniques—DSC, thermogravimetric analysis (TGA), Fourier-transform infrared (FT-IR) spectroscopy and thin layer chromatography (TLC).

Experimental

Materials Diclofenac sodium (lot 9911010) of British Pharmacopoeia quality was purchased from Sekhsaria Chemicals Ltd. (Mumbai, India). Gases—helium (He), nitrogen (N_2) and synthetic air, were purchased from SOL SPA (Monza, Italy) with stated purity of 99.9996%, 99.999% and 99.995%, respectively. A reference standard of 1-(2,6-dichlorophenyl)-indolin-2-one (Cat. No. 18881; Lot G) was purchased from the USP (Rockville, U.S.A.).

DSC Analysis Perkin Elmer's Pyris 1 equipment was used to analyse the samples under various conditions. Samples weighing 4—6 mg were placed in aluminium pan, sealed and scanned (within the range 50—320 °C) at various rates (1, 5, 10 and 20 °C/min) to see the effect of scanning rate on the thermal behaviour of the studied substance. The scanning runs were repeated under dynamic flow of either helium (He), or nitrogen (N_2) or synthetic air to see the effect of environmental atmospheric condition on the thermal characteristics of the drug substance. The data were analysed using the software package "Pyris for Windows" (version 3.52). Onset temperature was considered as the temperature of the peak (T_o). The equipment was calibrated by scanning indium and zinc before analysing the samples. Maximum temperatures of the peaks (T_m) were also recorded when necessary or if T_o could not be calculated due to the appearance of complex (multiple) peaks. All thermograms have been normalized to give peaks corresponding to 1 mg of the substance.

DSC was also performed on a standard reference sample of 1-(2,6-dichlorophenyl)-indolin-2-one (under dynamic flow of N_2 at 10 °C/min) to characterize its melting behaviour.

TGA Losses of masses that occurred due to heating were determined under conditions that gave maximum noticeable degradation during the DSC studies. About 4—6 mg of the substance was placed in open platinum pan, heated at 1 °C/min within the range of 150—320 °C under the dynamic flow of either He or N_2 or synthetic air (20 ml/min) and the loss of mass recorded.

To study the effect of heating time and temperature about 5—10 mg of the substance was placed in an open platinum pan, heated at either 260 °C or 270 °C or 280 °C under dynamic flow of He (35 ml/min), stabilized for 180 min and the loss of mass recorded.

The effect of scanning rate on the loss of mass due to thermal analysis of diclofenac sodium was also checked by scanning the substance at 10 °C/min and 40 °C/min under the dynamic flow of He.

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The equipment was calibrated by scanning nickel and iron before analysing the samples. Data were analysed using the software package "Pyris for Windows" (version 3.52).

FT-IR Spectroscopy In some cases, following TGA the samples were further subjected to FT-IR analysis after stabilizing them at particular temperatures (either 260 °C or 270 °C) for 30 min to study the nature of any decomposed product produced by thermal reactions.

After DSC scanning, in some cases samples (scanned at 1 °C/min under dynamic flow of He) were scrapped from inside the pans (leftovers at the cover of the pan) and analysed for FT-IR spectra to identify the product(s).

Pure diclofenac sodium and 1-(2,6-dichlorophenyl)-indolin-2-one were also subjected to FT-IR spectroscopic analysis to serve as controls.

FT-IR spectra were obtained on a Perkin Elmer's Spectrum GX FT-IR system using the KBr disc method within the scanning range of 4000—370 cm^{-1}. The resolution used was 4 cm^{-1} (16 scans/spectrum). Data were analysed using the software package "Spectrum" (version 2.0).

TLC After DSC analysis some samples (scanned at 1 °C/min under dynamic flow of He) were analysed by TLC to identify the degraded products and to compare the data with the results obtained from FT-IR spectroscopic analysis.

TLC was performed as described by Gyéresi *et al.*[4] with slight modification. Briefly, methanolic sample solutions were prepared from sublimated products scrapped from the lid of the DSC pan and also residual leftovers in the pan. Both sample and standard solutions [of diclofenac sodium and 1-(2,6-dichlorophenyl)-indolin-2-one] were applied (manually) to the plate and developed using a mobile phase—toluene : *n*-hexane : glacial acetic acid (20 : 2 : 3) and evaluated under UV at λ=254 nm with a Densiometer CD60 (Desaga GmbH Sarstedt-Group, Germany).

Results

DSC Analysis Under dynamic flow of synthetic air, three peaks appeared in the DSC thermograms when scanned at 5, 10 and 20 °C/min (Fig. 1). The first peak was an exothermic one, which was immediately followed by an endothermic and then again exothermic peaks at higher temperatures. But at the lowest scanning rate used, *i.e.*, 1 °C/min, only the exothermic peak appeared (Fig. 1). The location of this exothermic peak was greatly influenced by the scanning rate used (Table 1); the lowest temperature (252—253 °C) being observed for the slowest scanning rate (1 °C/min) and the highest (276—277 °C) for the fastest (20 °C/min) scanning rate. Although the T_o of the endothermic and following exothermic peaks could not be detected due to complexity of the peaks, shift of location of the T_m of the peaks were observed on the basis of the scanning rate used (Fig. 1, Table 1).

Two peaks appeared in the DSC thermograms obtained under the dynamic flow of N_2 at all the scanning rates used, but both peaks were endothermic and the first peak appeared complex (Fig. 2). The rate of scanning greatly influenced the positions of both peaks in the thermograms; an increase in scanning rate increased the temperatures of the peaks (Table 1).

The DSC thermograms obtained under the dynamic flow of He had three endothermic peaks at scanning rates 5, 10 and 20 °C/min (Fig. 3). But the locations of the peaks on the temperature axis were different than those obtained under flow of N_2 when compared on the basis of scanning rate used (Figs. 2, 3, Table 1). Apart from the detectable endothermic peaks, the baseline profiles of the thermograms obtained under N_2 and He were also different.

At lower scanning rates, the differences between thermograms obtained under N_2 and He were more apparent. A broad based peak started to appear at early stages (with slope of the baseline changing within 202—211 °C) giving T_m at 260—288 °C (depending upon the scanning rate used) of the thermograms obtained under He; this was followed by two

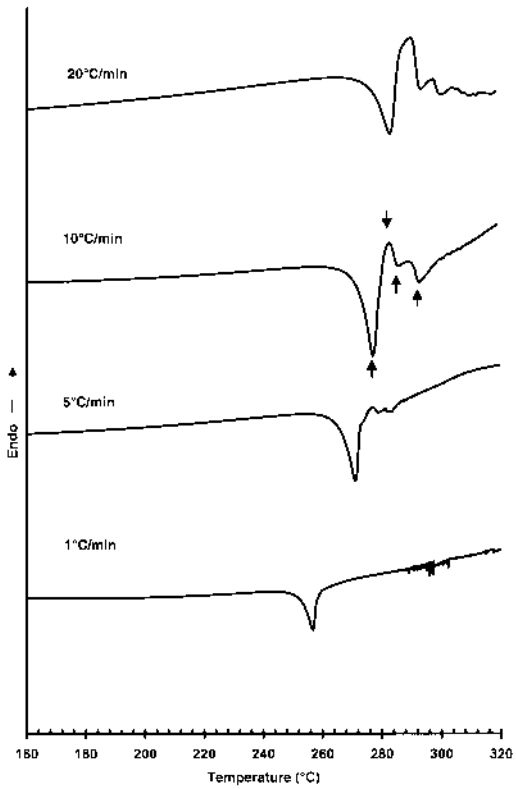

Fig. 1. DSC Thermograms of Diclofenac Sodium Heated at Various Rates under Dynamic Flow of Synthetic Air

Samples were scanned within the temperature range of 50—320 °C, but no changes were observed below 160 °C. The arrows indicate observed peaks in the thermograms.

Table 1. DSC Data Obtained for Diclofenac Sodium Scanned at Various Rates under Dynamic Flow of Either Helium or Nitrogen or Synthetic Air

Heated under dynamic flow of synthetic air

Heating rate (°C/min)	Peak 1		Peak 2	Peak 3	Peak 4
	T_o (°C)	T_m (°C)	T_m (°C)	T_m (°C)	T_m (°C)
1	252—253	257	—	—	—
5	266—267	271	276—277	279	283—286
10	272	277	283—284	285—286	295
20	276—277	283	288—289	292—293	299—304

Heated under dynamic flow of nitrogen

Heating rate (°C/min)	Peak 1		Peak 2	Peak 3	Peak 4
	T_o (°C)	T_m (°C)	T_m (°C)	T_m (°C)	T_m (°C)
1	263	267—268	274—275	—	—
5	275—276	282	289—290	—	—
10	282—283	288—289	299—301	—	—
20	287—291	296—297	302—303	—	—

Heated under dynamic flow of helium

Heating rate (°C/min)	Peak 1		Peak 2	Peak 3	Peak 4
	T_o (°C)	T_m (°C)	T_m (°C)	T_m (°C)	T_m (°C)
1	?	260—261	271	—	—
5	?	272—273	283—284	287—289	—
10	?	282—283	288—291	300—301	—
20	?	288	294—296	301	—

The temperature ranges shown indicate sample to sample variations (n=3).

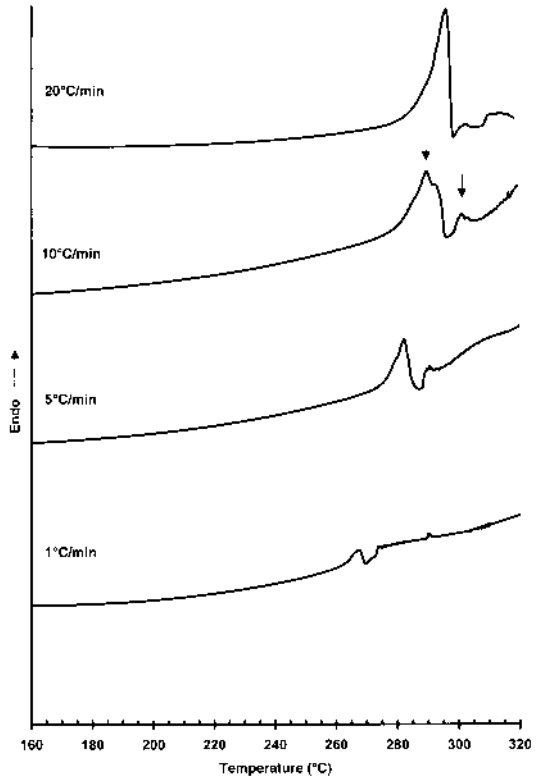

Fig. 2. DSC Thermograms of Diclofenac Sodium Heated at Various Rates under Dynamic Flow of Nitrogen

Samples were scanned within the temperature range of 50—320 °C, but no changes were observed below 160 °C. The arrows indicate observed peaks in the thermograms.

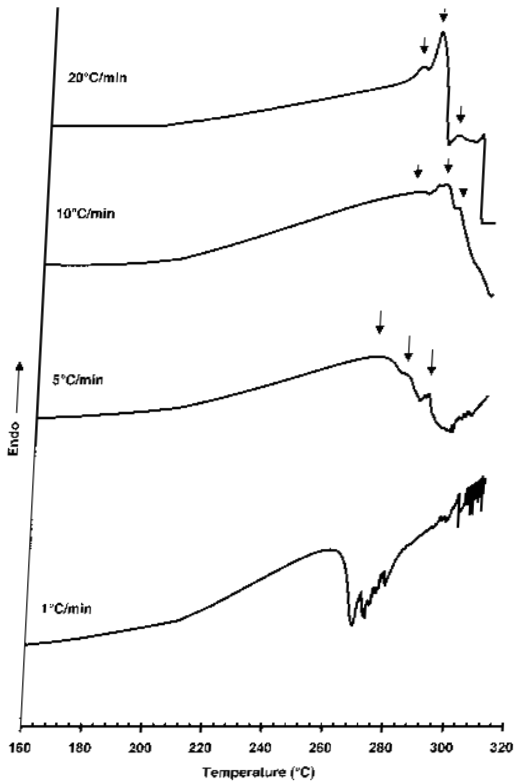

Fig. 3. DSC Thermograms of Diclofenac Sodium Heated at Different Rates under Dynamic Flow of Helium

Samples were scanned within the temperature range of 50—320 °C, but no changes were observed below 160 °C. The arrows indicate observed peaks in the thermograms.

endothermic peaks at higher temperatures. The location of the second peak varied according to the scanning rate used (T_m=271—296 °C). A third peak had T_m value between 287—301 °C at scanning rates of 5—20 °C (Fig. 3, Table 1).

DSC analysis of 1-(2,6-dichlorophenyl)-indolin-2-one produced a sharp endothermic peak at about 126 °C that characterizes melting of the substance (thermogram not shown).

TGA Recorded losses of masses of the samples heated under dynamic flow of synthetic air, N_2 and He were about 14.2%, 19.2% and 20.2%, respectively (Fig. 4). All these samples started losing mass at about 200 °C.

Samples scanned at 10 °C/min and 40 °C/min (under the dynamic flow of He) did not show any loss of mass at temperatures below 290 °C (data not shown). But the samples heated and stabilized at 260, 270 and 280 °C for 180 min under dynamic flow of He recorded losses of mass of 11.4%, 15% and 17.5%, respectively (Fig. 5).

FT-IR Spectroscopy The spectra obtained from the sample heated and stabilized at 260 °C for 30 min are almost comparable to those obtained for untreated diclofenac sodium, although a new peak (at 1732 cm^{-1}) was noticeable in this sample; differences became prominent, however, in the spectra obtained for samples heated and stabilized at 270 °C with appearances of multiple new peaks and disappearances of some peaks characteristics of diclofenac sodium (Fig. 6). The peaks for >NH group (3388, 3260, 1499 cm^{-1}) disappeared in the spectrum of the sample heated (and stabilized) at 270 °C with appearance of new peaks including the one at 1732 cm^{-1} corresponding to the amide group. The FT-IR spectrum obtained for this sample corresponds to a spectrum characteristic of a compound related to diclofenac sodium, [1-(2,6-dichlorophenyl)-indolin-2-one], an intermediate product reportedly obtained during synthesis of diclofenac sodium (Fig. 6).[5)]

The formation of 1-(2,6-dichlorophenyl)-indolin-2-one as a result of heating was further confirmed by the data obtained from FT-IR analysis of sublimated product scrapped from the leftovers inside the DSC pans on the inner side of the lid (Fig. 6).

TLC In line with the FT-IR spectroscopy data, distinct spots corresponding to 1-(2,6-dichlorophenyl)-indolin-2-one were detected in the TLC plates developed from sample solutions prepared both from the sublimated products scrapped from the lid after DSC analysis and from residue of heated diclofenac sodium left in the pan (Fig. 7). Several other spots were also detected in the chromatograms developed from the sample prepared from the residual leftovers in the pan (Fig. 7). Chromatograms developed from the sublimated product produced at least 3 spots, whereas the residual samples produced 4 spots including a weak spot corresponding to a very low concentration of pure diclofenac sodium. This diclofenac sodium spot was absent in the chromatogram developed from samples prepared from the sublimated product.

Discussion

The DSC profile obtained for the sample scanned at 20 °C/min under synthetic air is in agreement with Adeyeye and Li[6)] although we disagree with their conclusions that the exothermic peak represented the melting process, which was followed by an endothermic peak representing decomposition of the substance. In our opinion, it is scientifically im-

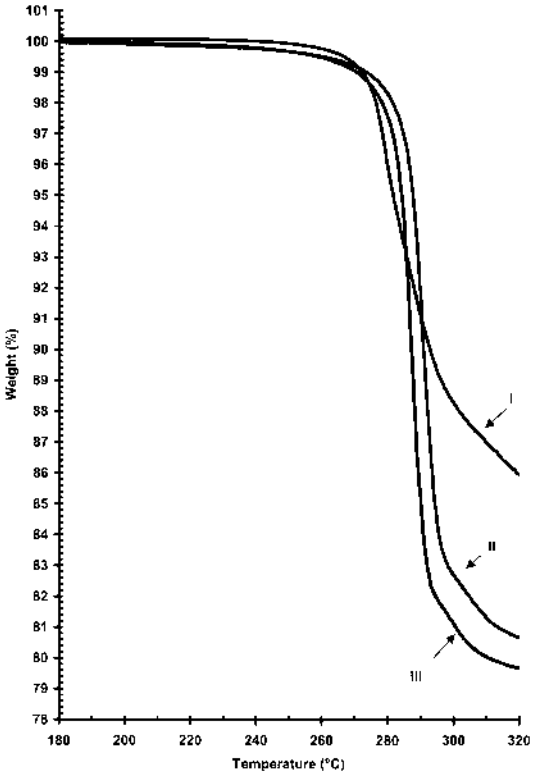

Fig. 4. TGA Thermograms of Diclofenac Sodium Heated at 1 °C/min under the Dynamic Flow of: I, Synthetic Air; II, Nitrogen; and III, Helium

The samples were scanned within the range of 150—320 °C, but no changes were observed below 180 °C.

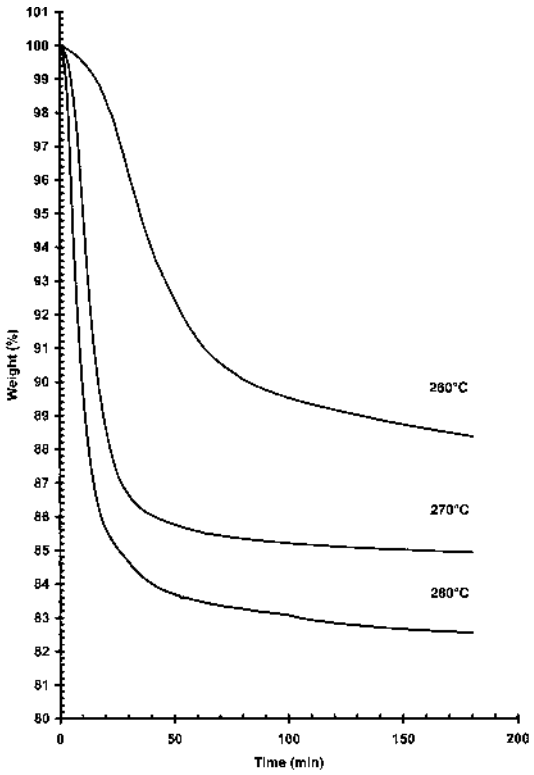

Fig. 5. TGA Profiles (Over Time) of Diclofenac Sodium Heated up to Various Temperatures and Stabilized for 180 min

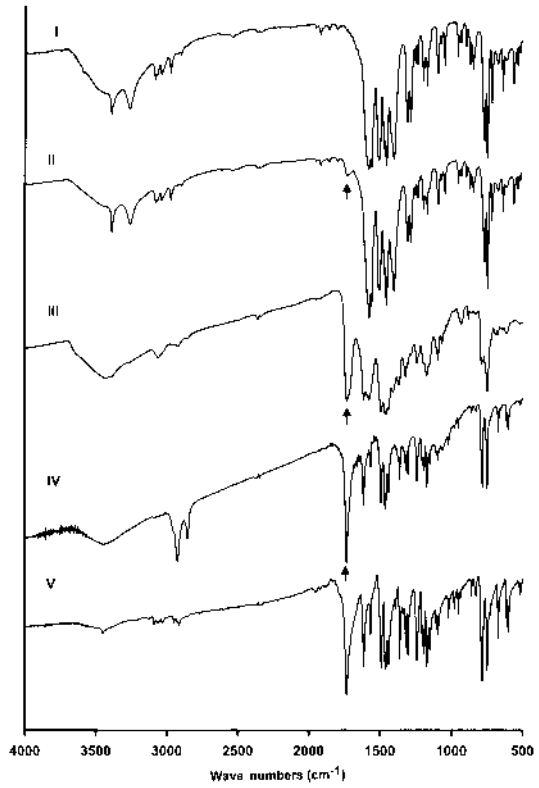

Fig. 6. Comparative FT-IR Spectra of Diclofenac Sodium Treated Differently: I, Untreated (as Control); II, Heated up to 260 °C (under Dynamic Flow of Helium and Isothermally Stabilized for 30 min); III, Heated up to 270 °C (under Dynamic Flow of Helium and Isothermally Stabilized for 30 min); and IV, Sublimated Product Scrapped from the Inner Surface of the Lid of DSC Sample Pan Following DSC Scan under Dynamic Flow of Helium; with V, Spectrum of a Reference Standard of 1-(2,6-Dichlorophenyl)-indolin-2-one

The arrows show notable changes in the spectra of treated diclofenac sodium samples.

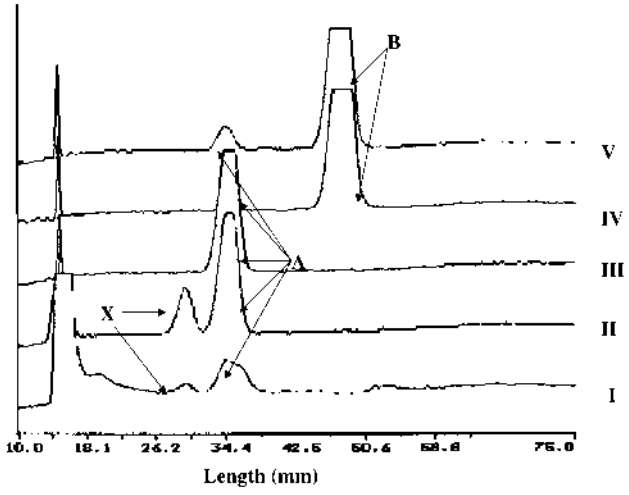

Fig. 7. Chromatograms Obtained from TLC Analysis: I, Sample Prepared from Residual Leftovers in the DSC Pan; II, Sample Prepared from Sublimated Products (Scrapped from Lid of the DSC Pan); III, Standard Solution of 1-(2,6-Dichlorophenyl)-indolin-2-one; IV, Standard Solution of Diclofenac Sodium; and V, Standard Solution of a Mixture of Diclofenac Sodium and 1-(2,6-Dichlorophenyl)-indolin-2-one

Peaks are: A, 1-(2,6-dichlorophenyl)-indolin-2-one; B, diclofenac sodium; and X, unknown degraded product.

possible to obtain an exothermic peak during melting of a substance.[7] Therefore, we suggest that the exothermic peak we obtained for the substance under synthetic air environment prior to the endothermic peak was due to an oxidation reaction between diclofenac sodium and oxygen (decomposition?). It is the following endothermic peak that represents the melting point of the compound and appeared in our thermograms within the temperature range of 276—288 °C (T_m) depending on the scanning rate used. Although changes in positions of melting peaks of substances are not expected to occur due to differences in scanning rates used,[8] in this case it was impossible to accurately detect the T_o of the melting peak of the studied substance due to the complex nature of the peaks and to the fact that more than one phenomenon occurred simultaneously.

The oxidative nature of the process corresponding to the exothermic peak obtained under synthetic air is supported by the TGA data (shown in Fig. 4) which recorded lower loss of mass (about 14.2%) for samples heated under synthetic air than for samples heated under either N_2 or He (19.2—20.2%). It is well known that the oxidation process generally produces products with increased masses.

The shifting of location of the exothermic peak and T_m of the endothermic peak to higher temperatures due to increase in scanning rates is probably attributable to the time required for the oxidation process and equilibrium of the system. The higher the scanning rate is, the lower is the time left for oxidation reaction to occur, contributing to the higher amount of unoxidised substance in the sample pan. This ultimately results in higher temperatures for the exothermic processes and increase in sizes of the peaks.[8] This is supported by the fact that at 1 °C/min scanning rate (slowest) only the exothermic peak appeared (without any endothermic peak) suggesting total decomposition of the substance before reaching its melting point when heated slowly. The T_m temperatures of 283—284 °C and 288—289 °C obtained at scanning rates of 10 °C/min and 20 °C/min, respectively, for the endothermic peak are in close agreement with literature reports for the melting point of diclofenac sodium.[1,6]

The double peak phenomenon observed in the thermograms obtained under both He and N_2 is of specific interest. Ribeiro *et al.*[1] reported that a sharp endothermic peak (at 280 °C) occurred in DSC thermograms for samples of diclofenac sodium under static atmospheric air prior to the melting peak (at 285 °C), and postulated that the peak was due to a polymorphic transition of the material. We were unable to detect such sharp endothermic peaks prior to the melting peak under dynamic flow of neither He nor N_2, and under synthetic air such peak did not appear at all. Our data contradicts the suggestion made by Ribiero *et al.*[1] regarding a polymorphic transition at temperature 280 °C. We hypothesize that this first broad based endothermic peak detected in our DSC thermograms appeared as a result of formation of a new compound during the heating process, and the chances of forming this new compound become higher when slow scanning rates are used due to kinetics of the process. Apparently, the formation of the new compound starts at early stages of heating since changes in slope of the baselines were observed at temperatures 202—211 °C in most cases.

However, the FT-IR data obtained from samples heated and stabilized for 30 min at 260 and 270 °C demonstrate that although trace of the new compound is evident in samples heated and stabilized at 260 °C it becomes prominent only at higher temperature (see Fig. 6). The similarity of the FT-IR spectra of the sample heated and stabilized at 270 °C with the spectra of both diclofenac sodium and 1-(2,6-dichlorophenyl)-indolin-2-one suggest that both these compounds are present in the tested sample. The presence of FT-IR signal of amide group in this sample (heated and stabilized at 270 °C) led us to suggest the occurrence of an intramolecular cyclization reaction between amino and carboxyl group in solid state to form the new compound, 1-(2,6-dichlorophenyl)-indolin-2-one, which is an indol-cyclic amide and an intermediate product reportedly obtained during synthesis of diclofenac sodium.[5] In contrast to diclofenac sodium, our DSC data demonstrate that this indol-cyclic compound melts at 126 °C without any decomposition. The proposed cyclization reaction is shown in Fig. 8. Although such solid state conversion of diclofenac sodium (or diclofenac) to 1-(2,6-dichlorophenyl)-indolin-2-one has not been reported in the literature, cyclization of diclofenac was demonstrated in acidic solution.[9,10]

The presence of 1-(2,6-dichlorophenyl)-indolin-2-one in the TLC chromatograms obtained from the sublimated product (after DSC analysis) and from the residual product supports the FT-IR spectroscopy data and confirms that this 1-(2,6-dichlorophenyl)-indolin-2-one is produced as a result of cyclization of diclofenac sodium during the heating process. The presence of the other degraded products (which have not been identified) further complicates the melting process leading to multiple peaks during DSC analysis instead of a sharp endothermic peak characteristic of melting of a pure substance.

Therefore, it is not surprising that none of the DSC thermograms obtained from diclofenac sodium scanned under all the environmental conditions (He or N_2 or air) produced any sharp endotherm characteristic of melting peak for any pure substance. It is the presence of the indol-cyclic amide [1-(2,6-dichlorophenyl)-indolin-2-one] and other degraded products that created these complex peaks (with shouldering and multiple in nature) characteristic of inhomogeneous samples. This is another reason why the rate of heating of the substance showed such significant effect on position of the peaks along the temperature line.

The different DSC patterns obtained for the substance when the thermal process occurred under the flow of N_2 and He is probably attributable to different thermal conductivity of the two gases, since the recorded loss of mass during TGA for samples heated under these two gases are almost the same (19.2% and 20.2%, respectively).

The TGA data obtained for samples scanned at different rates under dynamic flow of the different gas support the DSC data in terms of roles of the environmental conditions

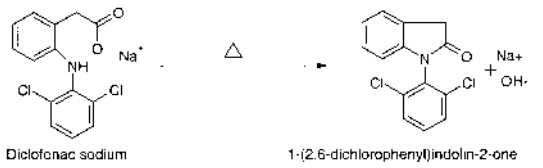

Fig. 8. Schematic Presentation of Solid State Cyclization of Diclofenac Sodium Due to Thermal Reaction

and heating rate of the substance. The losses of mass by 11.4—20.2% obtained during TGA of samples heated under various conditions for different times certainly is not only due to the solid state cyclic reaction and sublimation, but also to simultaneous decomposition of diclofenac sodium into other compounds which was evident from the colour and TLC data of the leftover residue in the sample pan after analysis. Both diclofenac sodium and 1-(2,6-dichlorophenyl)-indolin-2-one are white to off-white, but the heated samples appeared black.

Conclusions

The data presented here clearly demonstrate that diclofenac sodium decomposes and/or undergoes a cyclization reaction before reaching its melting point depending on the environmental atmospheric condition under which the thermal process is carried out. This contradicts previous literature reports (*e.g.*, Cwiertnia *et al.*[3]) on melting behaviour of this compound which advocate that diclofenac sodium melts and decomposes. Apparently the decomposition process is a complex one and the extent of decomposition or conversion to 1-(2,6-dichlorophenyl)-indolin-2-one largely depends on the rate of heating of the substance. In any case, the use of the melting point stated in the literature for diclofenac sodium as a parameter to either identify the material or judge its extent of purity will be misleading.

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