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THERMAL BEHAVIOUR OF DICLOFENAC, DICLOFENAC SODIUM AND SODIUM BICARBONATE COMPOSITIONS

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This work aims to investigate the thermal behaviour of diclofenac, diclofenac sodium, and $NaHCO_3$ both as single components and binary mixtures. In particular, the melting point and latent heat of fusion binary diagrams of the diclofenac sodium/diclofenac mixtures at different mole fraction compositions were investigated in order to gain information about the thermal behaviour of their solid mixtures. A good agreement between liquidus curves, calculated by the Schroeder–Van Laar equation from fusion enthalpies and temperatures, and the experimental results was found. For all binary compositions, an endothermic effect at 153°C, probably due to the eutectic fusion, is present.

Keywords: *binary melting point diagram, diclofenac, diclofenac sodium, eutectics*

Introduction

Diclofenac, 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid (DCLH), is a non-steroidal anti-inflammatory drug with analgesic properties. DCLH (pK_a 3.80 at 25°C) shows very low aqueous solubility ($6\cdot10^{-5}$ M at 25°C) [1]. Salts from a variety of inorganic and organic bases [2, 3] (in particular the sodium salt, DCLNa) are commonly used to improve solubility and, consequently, the dissolution rate of the drug.

In a previous work [4], DCLNa was chosen as model drug to study the solubility in supercritical carbon dioxide (SC–CO_2) of the tetrahydrate form in comparison with the anhydrous form. Solid-state modifications due to the interaction of DCLNa with SC–CO_2 were also investigated by differential scanning calorimetry (DSC), thermogravimetric analysis (TG), hot stage microscopy (HSM), Fourier transform infrared spectroscopy (FTIR) and Karl Fischer titrimetry. The DSC trace of untreated DCLNa (Fig. 1a) showed an endothermic peak in the 40–60°C temperature range (assigned to water removal, TG), followed, above 260°C, by complex endo–exo phenomena mainly due to decomposition; on the other hand, the DSC patterns of the solid phase recovered after SC–CO_2 treatment evidenced a series of thermal events between 100 and 170°C (Fig. 1b). This peculiar behaviour was attributed to possible reaction of DCLNa with the supercritical fluid, mediated by crystal water (in the case of DCLNa·$4H_2O$) or surfacial moisture with anhydrous DCLNa. DCLNa, in the presence of SC–CO_2 and water, generated solid residues whose thermal behaviour was difficult to interpret, owing to the formation of mixtures containing different proportions of unreacted DCLNa, DCLH and $NaHCO_3$.

To achieve a better interpretation of the thermal phenomena shown by these multicomponent systems, DSC analyses of the single components and of possible binary mixtures were carried out and the results are reported in this paper, along with the corresponding binary melting point and the heat of fusion diagrams [5].

Experimental

Materials

DCLNa (Lisapharma, Como, Italy) and sodium bicarbonate (Carlo Erba, Milan, Italy) were used as purchased.

Preparation of DCLH

A DCLNa solution in water (10 g L^{-1}) was acidified with 0.1 N HCl until a pH value of 3–4 was reached to achieve the complete precipitation of DCLH. The precipitate was filtered, thoroughly washed with distilled water, air dried and stored in a desiccator. The formation of DCLH was confirmed by Fourier transform infrared spectroscopy.

Preparation of binary mixtures

Binary physical mixtures of DCLH/DCLNa, DCLNa/$NaHCO_3$, DCLH/$NaHCO_3$ in different mole fraction compositions (ranging from 0.1 to 0.9) were prepared by simple gentle mixing in a mortar to achieve a randomly even distribution of components prior to scanning.

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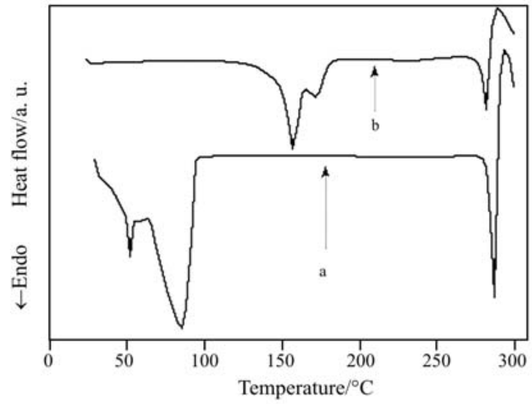

Fig. 1 DSC traces of DCLNa a – before and b – after supercritical treatment [4]

Methods

Differential scanning calorimetry was performed with a Mettler DSC 821e (Mettler Toledo, USA) driven by STARe software (Mettler Toledo) on 4–5 mg samples (Microbalance MT5 Mettler Toledo) placed in sealed and pierced 40 μL aluminium pans. Scans of each component and the binary mixtures were carried out under a flux of dry nitrogen (100 mL min^{-1}) between 30–290°C at 10 K min^{-1}. Calibration of temperature and enthalpy values was performed with indium.

Thermogravimetric analyses (TG50, Mettler Toledo, USA) were carried out on samples placed in 70 μL alumina pans with a pierced cover. The samples were heated under a flux of nitrogen (200 mL min^{-1}) at 10 K min^{-1} in the 30–290°C temperature range.

Each sample was analysed at least in triplicate. All data are expressed as mean value.

Only first heating DSC and TG scans were considered owing to massive decomposition of DCLH, DCLNa and $NaHCO_3$ on heating.

Results and discussion

As mentioned above, the treatment of DCLNa with SC–CO_2, in presence of water, both in the case of crystal water and surfacial moisture, generated inside the vessel of the supercritical fluids apparatus, mixtures of unreacted DCLNa, DCLH and $NaHCO_3$ in different proportions depending on the experimental conditions, according to the following reaction:

$$DCLNa+H_2O+CO_2 \leftrightarrow DCLH+NaHCO_3 \quad (1)$$

The broad double peak recorded between 158 and 175°C (Fig. 1b), therefore, includes all thermal events due to the complex mixture of chemicals present inside the vessel [4]. In particular, the in situ reactions are mainly responsible for the thermal behaviour. The TG reported in our previous work [4], associated to the broad double peak, showed a mass loss of 25% in the 90–200°C interval.

Thermal behaviour of single components

Diclofenac

TG and DSC traces of DCLH are reported in Fig. 2. The DSC pattern of DCLH shows a sharp endothermic peak at 181°C, corresponding to fusion [6]. The latent heat of fusion, ΔH= –133 J g^{-1} was calculated as the area under the peak by numerical integration. DCLH mass loss under dynamic flow of dry nitrogen was below 10% before fusion, while massive degradation of the compound after fusion was evidenced by TG.

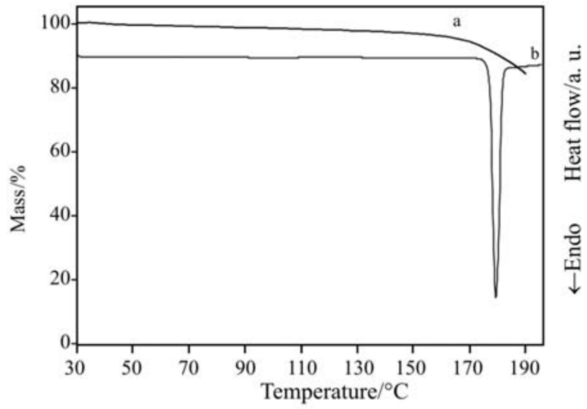

Fig. 2 a – TG and b – DSC traces of DCLH

Diclofenac sodium

The DSC trace of DCLNa (Fig. 3) shows an endotherm at 280°C, followed by an exotherm. This result is indicative of melting followed by decomposition. The melting point of the drug was 287°C with an enthalpy variation (ΔH) of –85.9 J g^{-1} (within the 265–295°C range).

$NaHCO_3$

The DSC trace of $NaHCO_3$ (Fig. 4c) shows two endothermic events at 96°C (ΔH= –27.3 J g^{-1}) and at 150°C (ΔH= –717.2 J g^{-1}). TG (Fig. 4a) evidences the thermal decomposition of $NaHCO_3$, that occurs generating H_2O and CO_2 and sodium carbonate, which starts approximately at 50°C ending at 170°C with a measured mass loss of 36.8% (calculated 36.9%). The agreement between the DSC (Fig. 4c) and 1st derivative of the TG (Fig. 4b) traces is a further confirmation of the decomposition of the salt.

Thermal behaviour of binary systems

DCLNa/DCLH mixtures

The thermal traces of the DCLNa/DCLH mixtures at different mole fraction compositions are reported in

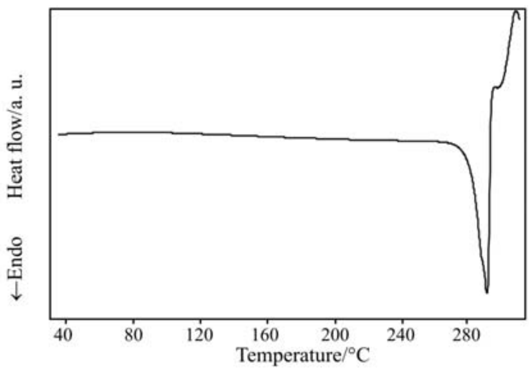

Fig. 3 DSC trace of anhydrous DCLNa

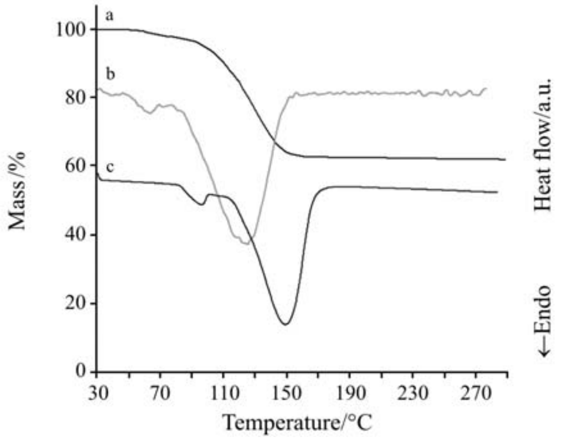

Fig. 4 a – TG, b – DTG and c – DSC of $NaHCO_3$

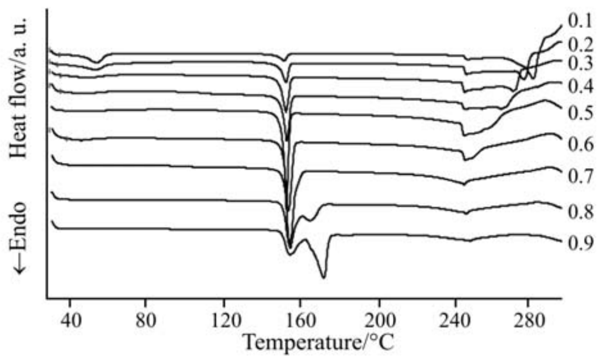

Fig. 5 DSC traces of the mixtures DCLH/DCLNa at different mole fractions

Fig. 5. Samples from 0.1 to 0.7 DCLNa mole fraction exhibited two endothermic peaks around 153 and 250°C. A further endothermic event around 170°C (Fig. 1b) was present in the DSC trace of the 0.8 and 0.9 mole fractions. All samples exhibited several endo-exothermic events above 250°C. Thermal data measured from the DSC traces of samples having different compositions were used to draw the binary melting point diagram (Fig. 6). In the same diagram the experimental data are reported along with the data

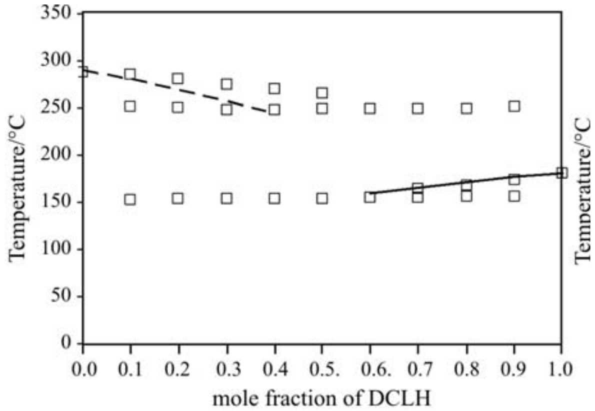

Fig. 6 Phase diagram of the DCLH/DCLNa binary system (empty squares: experimental data obtained from DSC curves; see Fig. 7 — and - - - calculated temperature composition curve)

calculated using the Schroeder–Van Laar equation in its simplified form [7]:

$$\ln x = \frac{\Delta H_f^A}{R}\left(\frac{1}{T_f^A} - \frac{1}{T_f}\right) \tag{2}$$

where x is the mole fraction of the more abundant component of a mixture whose melting terminates at T_f (K); ΔH_f^A (cal mol^{-1}) and T_f^A (K) are the enthalpy of fusion and melting point of the pure component, respectively, and R is the gas constant, 1.9869 cal mol^{-1} K^{-1}. For mixtures that form a true eutectic (i.e., complete miscibility of the liquid phases and immiscibility of the solid phases) the melting point of each component is lowered by the presence of the other component and, therefore, the melting point decreases from both sides of the diagram. A satisfactory agreement between theoretical and experimental liquidus curves could be found only regarding binaries with x_{DCLH}>0.6 (150–181°C temperature range). For mixtures with x_{DCLH}<0.6, it was practically impossible to evaluate accurately the thermal parameters due to extensive decomposition of both components, thus leading to a clearly unsatisfactory agreement between calculated (dashed line) and experimental values (above 180°C). All binary compositions show at 153°C an endothermic effect, probably due to the eutectic fusion.

A second endothermic effect at constant temperature was also observed experimentally at higher temperature (250°C). Unfortunately, the extensive decomposition undergone by DCLH above its melting point makes quite difficult to give a convincing explanation of this phenomenon.

Aiming to demonstrate the presence of a true eutectic between DCLH and DCLNa at 153°C, data obtained from DSC analyses were used to draw the latent heat of fusion diagram (Fig. 7). The theoretical

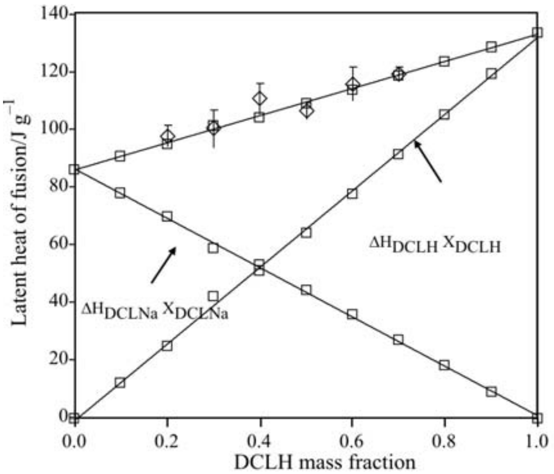

Fig. 7 Latent heat of fusion diagram at 153°C of the binary mixture DCLH/DCLNa (empty squares: calculated data, empty diamonds: experimental data; bars represent the standard deviation, *n*=3)

heat of fusion at 153°C for each DCLNa/DCLH mixture was calculated with the following equation:

$$\Delta H_{\text{fus (mixt)}} = \Sigma \Delta H_{\text{fusx}} X_{\text{x}} \quad (3)$$

where, $\Delta H_{\text{fus (mixt)}}$ (J g^{-1}) is the heat of fusion at 153°C for the mixture, ΔH_{fusx} and X_{x} denote the specific heat of fusion and the mole fraction of each component *x* in the mixture. As shown in the relevant diagram, the latent heat of fusion at 153°C of the mixture increases with increasing the amount of DCLH. Discrepancies between calculated and measured latent heats of fusion were found, due to intrinsic difficulties of peak integration (mixtures 0.8 and 0.9, Fig. 5) or dishomogeneity of the sample (mixture 0.1). For all other mole fraction compositions there is a good agreement between experimental and calculated data.

DCLH/$NaHCO_3$ mixtures

The DSC scans of DCLH/$NaHCO_3$ mixtures are reported in Fig. 8. For all samples, an endothermic event between 80 and 100°C, reasonably due to initial thermal decomposition of $NaHCO_3$, is present. In addition, several endothermic effects, between 140 and 280°C, depending on the composition of the mixture, are present. In particular, all mixtures within the 0.1–0.5 DCLH mole fraction interval show an analogous trend, characterised by peaks at 153, 180 and 285°C. The peak at higher temperature (285°C) can be attributed to the decomposition of DCLNa formed by reaction of DCLH with $NaHCO_3$ or its decomposition product, Na_2CO_3. This is further confirmed by the similar patterns shown by DCLH/DCLNa and DCLH/$NaHCO_3$ mixtures with compositions ≥0.6 DCLH mole fraction (Figs 5 and 8).

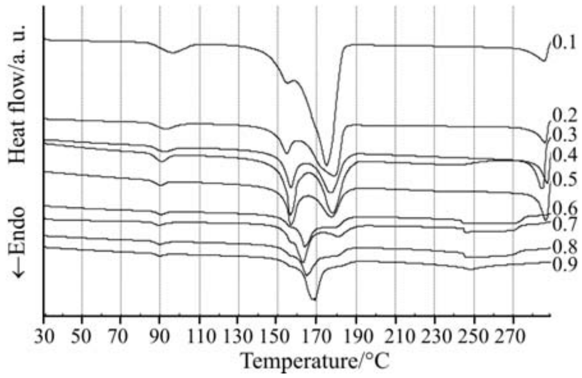

Fig. 8 DSC traces of the DCLH/$NaHCO_3$ mixtures at different mole fractions

It may be useful to recall the following reactions which can take place when DCLH and $NaHCO_3$ are heated together,

$$\text{DCLH}+NaHCO_3 \leftrightarrow \text{DCLNa}+H_2O+CO_2 \quad (4a)$$

$$2NaHCO_3 \rightarrow Na_2CO_3+H_2O+CO_2 \quad (4b)$$

$$2\text{DCLH}+Na_2CO_3 \leftrightarrow 2\ \text{DCLNa}+H_2O+CO_2 \quad (4c)$$

It should be stressed that the reaction (4a) in the experimental conditions is not quantitative, i.e., although an excess $NaHCO_3$ or DCLH is present, mixtures of the solid products and reactants are formed. The overall composition, therefore, progressively changes on heating due to the formation and decomposition phenomena. To demonstrate this assumption, mixtures of DCLH and $NaHCO_3$ were treated in aqueous medium in order to achieve a complete reaction. After water removal, the DSC scan of the solid residue showed the pattern reported in Fig. 9 (trace b) in comparison with the trace obtained before the treatment with water (trace a). As can be seen, the same DSC trace of pure anhydrous DCLNa (Fig. 3) was obtained.

The DSC traces of 0.1–0.5 DCLH mole fraction compositions show (Fig. 8) the $NaHCO_3$ decomposition with two peaks in the 90 and 150°C range, the melting of DCLH around 180°C and the DCLNa de-

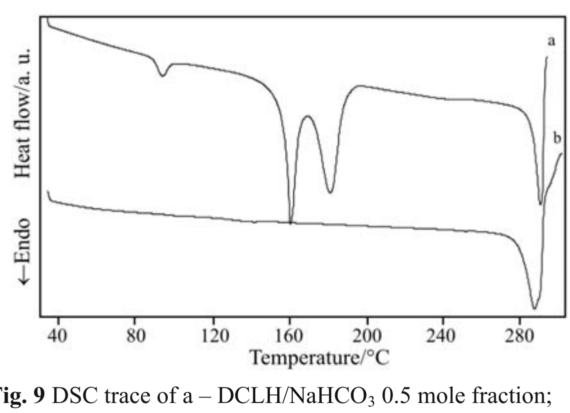

Fig. 9 DSC trace of a – DCLH/$NaHCO_3$ 0.5 mole fraction; b – the same after complete reaction (see text)

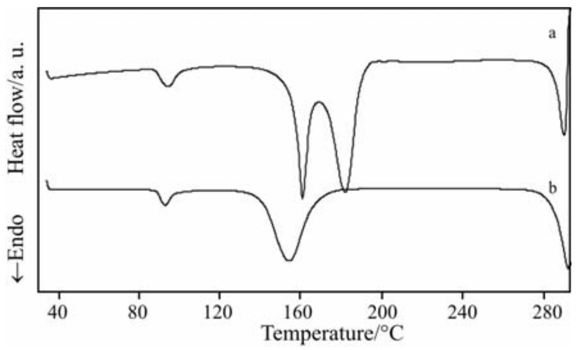

Fig. 10 DSC traces of the mixture DCLH/$NaHCO_3$ a – 0.33 and b – 0.5 mole fraction composition

composition at 280°C. It was not possible to put into evidence the eutectic fusion for two reasons: *i*) the temperature very close to the decomposition temperature of $NaHCO_3$, *ii*) the small amount of the eutectic mixture. Within the 0.6–0.9 DCLH mole fraction range, the two peaks at 150 and 180°C tend to overlap, and a broad peak between 170–180°C is evident.

A further final demonstration of the non-quantitative reaction between DCLH and $NaHCO_3$ was achieved by comparing the DSC trace of DCLH/$NaHCO_3$ mixture at 0.33 mole fraction composition with the DSC trace of the DCLNa/$NaHCO_3$ at 0.5 mixture composition (Figs 10a and b, respectively). A quantitative reaction between 1 mole of DCLH and 2 mole of $NaHCO_3$ would theoretically lead to the 1:1 DCLNa/$NaHCO_3$ mixture reported in Fig. 10b, where, however, it is still clearly visible the melting peak of unreacted DCLH (around 180°C).

Conclusions

Pharmaceutical formulations are multi-component systems which are influenced by possible physico-chemical interactions. The prediction and comprehension of such interactions are therefore of particular interest. Thermal analysis methods can commonly be utilized to obtain information concerning such interactions [8]. To overcome the intrinsic difficulties when investigating pharmaceutical products, the simplification of the multi-component systems as binaries is sometimes necessary.

In this work, a good agreement between liquidus curves calculated by the Schroeder–Van Laar equation from fusion enthalpies and temperatures, and the experimental results obtained by first heating runs was found. For all binary compositions, an endothermic effect at 153°C, probably due to the eutectic fusion, is present. The presence of a true eutectic between DCLH and DCLNa at 153°C, was further demonstrated by drawing the latent heat of fusion diagram at the same temperature.

References

1 A. Chiarini, A. Tartarici and A. Fini, Arch. Pharm., 317 (1984) 268.
2 A. Fini, G. Fazio and I. Rapaport, Drug Exp. Clin. Res., 19 (1993) 81.
3 K. M. O'Connor and O. I. Corrigan, Int. J. Pharm., 226 (2001) 163.
4 R. Bettini, G. Bertolini, E. Frigo, A. Rossi, I. Casini, I. Pasquali and F. Giordano, J. Therm. Anal. Cal., 77 (2004) 625.
5 A. K. Galvey, J. Therm. Anal. Cal., 82 (2005) 423.
6 F. Giordano, A. Rossi, I. Pasquali, R. Bettini, E. Frigo, A Gazzaniga, M. E. Sangalli, V. Mileo and S. Catinella, J. Therm. Anal. Cal., 73 (2003) 509.
7 J. T. Carstensen, Advanced Pharmaceutical Solids, Marcel Dekker, New York 2001, p. 171.
8 K. Khimeche and A. Dahmani, J. Therm. Anal. Cal., 84 (2006) 47.

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