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Compatibility of paroxetine hydrochloride and GW597599B

A physico-chemical approach

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Abstract In this study, we present a full thermal characterization of antidepressant paroxetine and summarize the results for another drug which treats depression: GW597599B. The main aim is to analyze how the thermodynamic and structural properties of these compounds are modified when the two drugs are mixed in the solid state. We begin by putting into evidence how dehydration and melting concur in shaping the calorimetric curves of paroxetine under different experimental conditions. Equipped with this knowledge, we are able to interpret the thermal response of the physical mixtures paroxetine:GW597599B, in terms of partial eutectic formation and simple superposition of contribution from the two compounds.

Keywords Hydrate · Interaction · Physico-chemical properties · Pseudo-polymorphism · Solid state · Thermal analysis

Introduction

Paroxetine hydrochloride, (3S-trans)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl) piperidinium chloride hemihydrate (MW = 365.82), is a drug belonging to a family of antidepressant [1] called selective serotonin reuptake inhibitor (SSRI). It is prescribed in many pathologies, such as generalized anxiety disorder, social anxiety disorder, obsessive–compulsive disorder, and depression [2–4].

Paroxetine hydrochloride is a typical pseudo-polymorphic compound. Polymorphism is the property of a solid which may be found, over a range of temperatures, in different crystalline forms but with the same chemical composition [5]. A solvated/hydrated compound, in which two or more crystalline forms which differ as regards the number of solvent/water molecules in the unit cell exist, is usually called pseudo-polymorphic. Actually, a hydrated crystal may dehydrate either (a) maintaining the original crystal lattice; or, (b) transforming into an amorphous substance, or, (c) yielding a new crystal with fewer or no solvent/water molecules [6–13].

At room temperature (r.t.), paroxetine hydrochloride can be obtained (with different synthesis procedures) in two crystalline forms, called pseudo-polymorphs I and II, having different hydration levels [14–16]. Form I is an hemihydrate, with a reported melting temperature of 143 °C, which thermally dehydrates above 100 °C [16]. Form II is a hygroscopic substance which melts at 118 °C and has an equilibrium water content which depends upon temperature and vapor partial pressure.

Here, we study the compatibility of paroxetine hydrochloride form I with a new antidepressant drug, GW597599B [17], recently developed by GlaxoSmithKline, which is a NK1 receptor antagonist particularly successful in the treatment of unipolar depression. The two drugs have different action mechanisms so that their association in a single dosage form can produce a synergetic effect [18].

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We will analyze the physico-chemical properties of the pure compounds and their mixtures. In particular, we need to discuss in deeper details, relative to the published article [16], the thermal response of paroxetine form I. For GW597599B, we will just summarize the main properties, since its full characterization has been given elsewhere [19].

Experimental

Paroxetine hydrochloride hemihydrate (form I) and GW597599B come from batches of industrial production (GlaxoSmithKline, Verona, Italy) characterized by HPLC. About 1 g of physical mixtures of paroxetine hydrochloride hemihydrate and GW597599B (in ratios ranging from 10:90 to 90:10 by mass) were prepared by mixing properly weighted amounts of the drugs using a Turbula (W.A. Bachofen) at 96 rpm for 10 min.

SEM microphotographs were collected on gold-sputtered samples at r.t. with a Cambridge Stereoscan 200 (UK) Scanning Electron Microscopy.

X-ray diffraction patterns were recorded at r.t. using a powder diffractometer Bruker D5005 (Siemens, Germany) using the CuKα radiation from a bent graphite monochromator.

Thermogravimetric (TG) measurements at various heating rates (β, $1 \div 20$ °C min^{-1}) were performed under a flow of nitrogen using a TGA 2950 apparatus (TA Instruments, USA), calibrated using a 100 mg standard and interfaced with a TA 5000 data station. Most of the TG data were acquired as usual, i.e., with sample in a standard open platinum holder. We also ran TG experiments with sealed DSC pans on the same Pt-holder. Calorimetric data were collected under a flow of nitrogen with a DSC TA2920 apparatus interfaced with the TA 5000 data station. Calibration of temperature and enthalpy scales was achieved by running ultrapure (99.999%) indium samples (m.p. = 156.6 °C). Standard aluminum pans were used in three different configurations: open, fully sealed, and with a pierced cover. Cyclic thermal treatments were applied directly in the DSC apparatus with a 10 °C min^{-1} heating rate and the following protocol: (i) first heating up to 133 °C or 160 °C; (ii) cooling to r.t. at different rates ($1 \div 20$ °C min^{-1}); and (iii) second heating to 180 °C.

All experimental data from thermal measurements are averages of three or more experiments. Typically, temperatures are reproduced within 1 °C.

Results and discussion

Paroxetine hydrochloride

Original samples

SEM pictures of as-received paroxetine HCl, form I, are shown in Fig. 1. The powder consists of irregular platelets up to 200 μm in size. Micron-sized particles are seen over the surface of the platelets.

The water content of the as-received sample was determined with many TG runs in static air at 2 °C min^{-1}. Typical TG and derivative TG (DTG) plots are shown in Fig. 2. Below 50 °C, we observe a small water loss ($\sim$0.1%), which is likely due to removal of surface water. Two distinct dehydration steps follow: one below 120 °C, and one above. The overall water loss of these two steps is about 2.3%, as predicted for the hemihydrate form (2.4%).

DSC traces of paroxetine HCl are strongly dependent upon the experimental conditions. In Fig. 3, we compare the DSC traces obtained at 10 °C min^{-1} with sealed, pierced and open pans.

With the experiments performed in a sealed pan (a), a single peak is observed with an onset temperature of $\sim$143 °C, i.e., the melting temperature of the hemihydrate reported in the literature [14]. In a pierced pan (b), melting begins at a much lower temperature, and the endothermic effect is spread over two poorly resolved peaks. In open pans (c), the onset temperature is further decreased ($T_{onset} \sim 117$ °C), and the overall shift of the peaks to lower

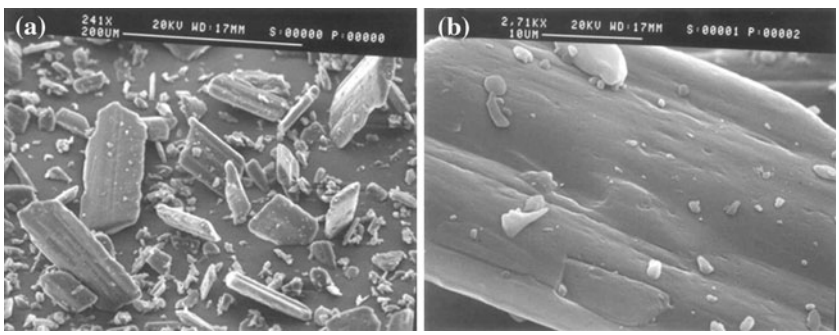

Fig. 1 SEM micrographs of a paroxetine HCl sample at two different magnifications

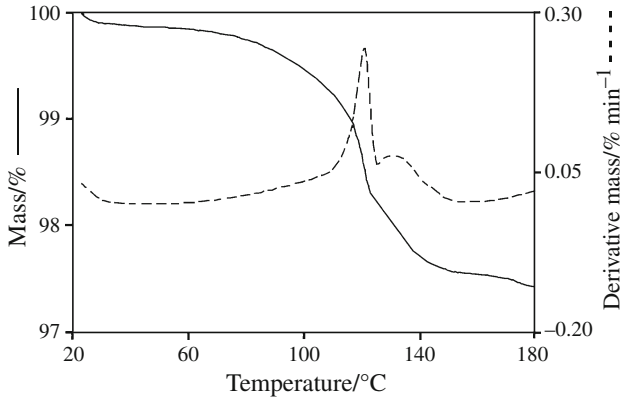

Fig. 2 TG and DTG curves recorded with paroxetine HCl in static air at 2 °C min^{-1}

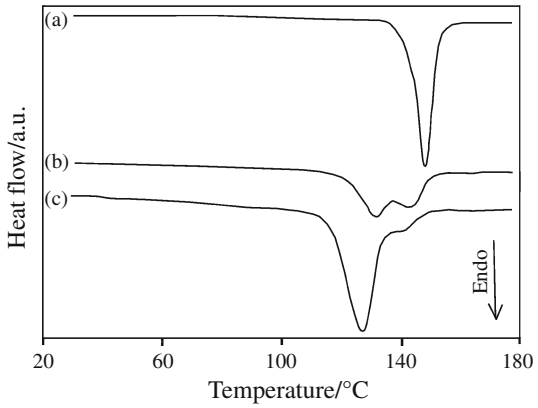

Fig. 3 DSC traces recorded with paroxetine HCl samples at 10 °C min^{-1} under nitrogen flux: sealed pan (**a**); pierced pan (**b**); and open pan (**c**)

Table 1 T_{onset} and ΔH enthalpy change values of paroxetine HCl samples measured at 10 °C min^{-1} (dry nitrogen) under different experimental configurations

Experimental configuration	T_{onset}/°C	ΔH/J/g
Open pan	116.9	87.4 ± 1.3
Pierced pan	121.8	94.5 ± 1.8
Sealed pan	143.8	93.0 ± 1.6

temperatures leaves only a shoulder where melting started in sealed pans. Table 1 lists the average T_{onset} and change of enthalpy ΔH measured with the three types of pan.

Figure 4 compares the DSC traces obtained at different heating rates in open pans. At low rates (1 ÷ 2 °C min^{-1}), the high-temperature shoulder disappears, the endothermic peak shifts further to lower temperatures, and its enthalpy change ΔH decreases (see Table 2).

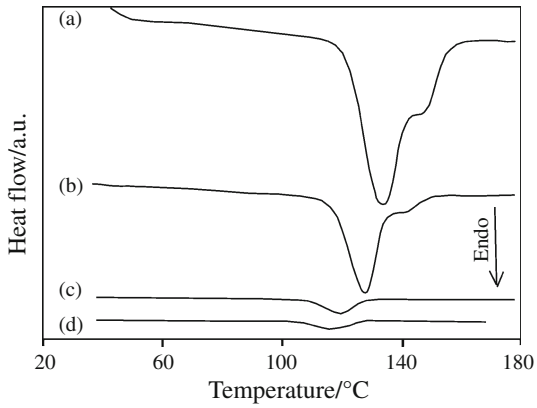

Fig. 4 DSC traces recorded with paroxetine HCl in open pan (flux of dry nitrogen): 20 °C min^{-1} (**a**); 10 °C min^{-1} (**b**); 2 °C min^{-1} (**c**); and 1 °C min^{-1} (**d**)

Table 2 T_{onset} and ΔH of paroxetine HCl in open pan at different heating rates

β/°C/min	T_{onset}/°C	ΔH/J/g
1	108.3	71.3 ± 1.1
2	109.9	75.3 ± 1.6
10	116.9	87.4 ± 1.3
20	121.3	85.6 ± 1.5

Table 3 T_{onset} and ΔH of paroxetine in sealed pans and different heating rates

β/°C/min	T_{onset}/°C	ΔH/J/g
1	140.6	89.7 ± 2.1
10	143.8	93.0 ± 1.6

The strong dependence of T_{onset} upon the heating rate suggests that melting is not the only cause of the endothermic effect, since we would have expected a true melting process to be little influenced by a change of the heating rate in the 1 ÷ 20 °C min^{-1} range. The large variability discussed above is certainly associated with the dehydration process. If we avoid/reduce this phenomenon with experiments in sealed pans, then the dependence upon the heating rate nearly disappears, as expected (see Table 3), and the measured enthalpies are roughly those of melting.

To make sure that the last experiment actually controls water release, TG experiments were performed at 10 °C min^{-1} with the sealed pans used by DSC. The mass loss is now only 0.3% before the endothermic peak, and

~0.6% in the peak region, corresponding to 25% of the water content of the hemihydrate. This fact suggests that the sample pan is not perfectly hermetic, and the water released from the crystal lattice causes an high vapor pressure which makes the seal weaker. However, it is reasonable to say that, with sealed pans, the endothermic peak is essentially due to melting of the form I.

Figure 5 superimposes the previous TG and DSC experiments performed with open pans. The DSC peak begins at 110 °C, where we have already lost about 0.7% of mass. The endothermic effect is largest where the dehydration rate is highest, between 110 and 130 °C (1.1% loss). Water loss continues also at higher temperatures, where the endothermic phenomenon exhibits a shoulder.

With slower heating rates (2 °C min^{-1}) in open pans, thermal dehydration occurs earlier, with about 1.1% of mass being lost below 100 °C. Notice (Fig. 6) that the high temperature DSC shoulder has now disappeared.

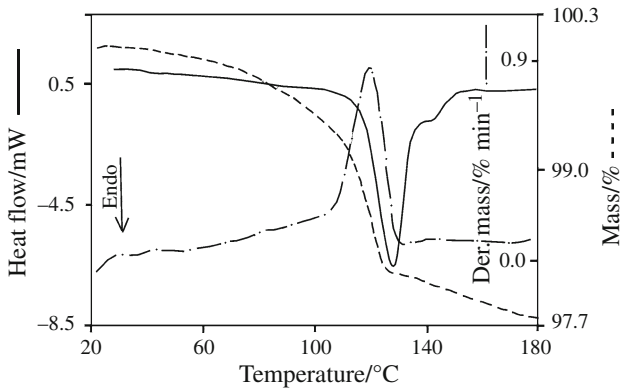

Fig. 5 DSC (*solid line*), TG (*dash*), and e DTG (dash dot) curves recorded with paroxetine HCl in open pans at 10 °C min^{-1}

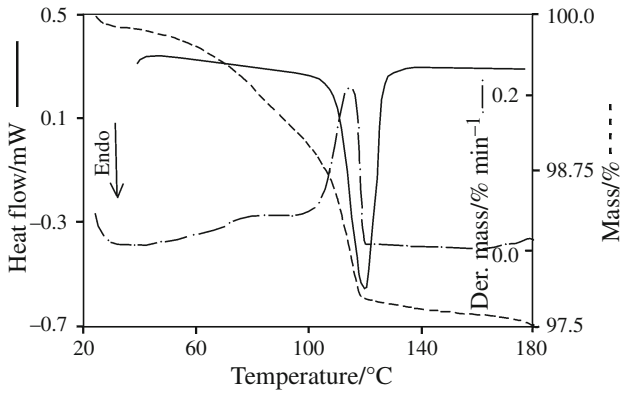

Fig. 6 DSC (*solid line*), TG (*dash*) e DTG (*dash dot*) curves recorded with paroxetine HCl in open pans at 2 °C min^{-1}

Thermally treated samples

The protocol described in the experimental section was applied to deepen and understand the melting behavior of paroxetine HCl.

Cooling a sample from 160 °C (i.e., above the melting of the hemihydrate) at every cooling rate yields a glass which, upon reheating, shows only a characteristic glass transition beginning at 73 °C. On the other hand, reheating a sample cycled to 133 °C in open pan (partially melted and dehydrated) gives both a glass transition (at 66 °C), and a melting peak at 137 °C (beginning at 127 °C) where only the shoulder attributed to melting of the hemihydrate in a partially dehydrated sample occurs.

Figures 7 and 8 compare SEM pictures and X-ray patterns of samples annealed to different temperatures with heating rates at 10 °C min^{-1} in open pans. In the SEM Fig. 7a, b, the top temperature was 115 °C (where overall water loss was ~0.7%); the platelets are better aggregated, with small particles strongly bonded to their surfaces and occasional openings due to the released water. The corresponding X-Ray pattern (Fig. 8, curve a) is similar to that of an original sample, with reduced intensities and broadened peaks. Figures 7c, d, and 8b refer to a sample heated to 122 °C in open pan, with an estimated water loss of 1.1%. Partial melting has rounded the edges of the platelets with a glassy cover; the intensity of the Bragg peaks are further reduced. At 130 °C, the mass loss is 1.9%; crystalline grains are now embedded in a glassy matrix, where holes due to water vapor escaped from the sample are evident (Fig. 7e, f); the XRPD pattern (Fig. 8c) shows an increase of the peak at $2\vartheta = 22°$ and a decrease of the one at 14°, both relative to the spectrum of the sample annealed to 122 °C. Heating up to 160 °C produces a sample with smooth glassy surfaces broken by sharp holes (Fig. 7g, h). The XRPD peaks have disappeared.

Comments on the melting behavior of paroxetine HCl

Our thermal, microscopic, and diffractometric characterizations makes it evident that the melting behavior of paroxetine HCl form I is not a simple one.

The "true" temperature and enthalpy of melting for the hemihydrate can be determined only with sealed pans, when dehydration is effectively hindered. However, water loss is not fully avoided, and the true enthalpy of melting is somewhat lower than the experimental value of 93 J g^{-1}. On the other hand, dehydration seems to trigger melting, most likely through formation of an anhydrous compound which may be easily created either below or above its melting temperature. In the case of runs in open pans and low heating rates, a single DSC peak is observed which is due to two processes occurring in sequence:

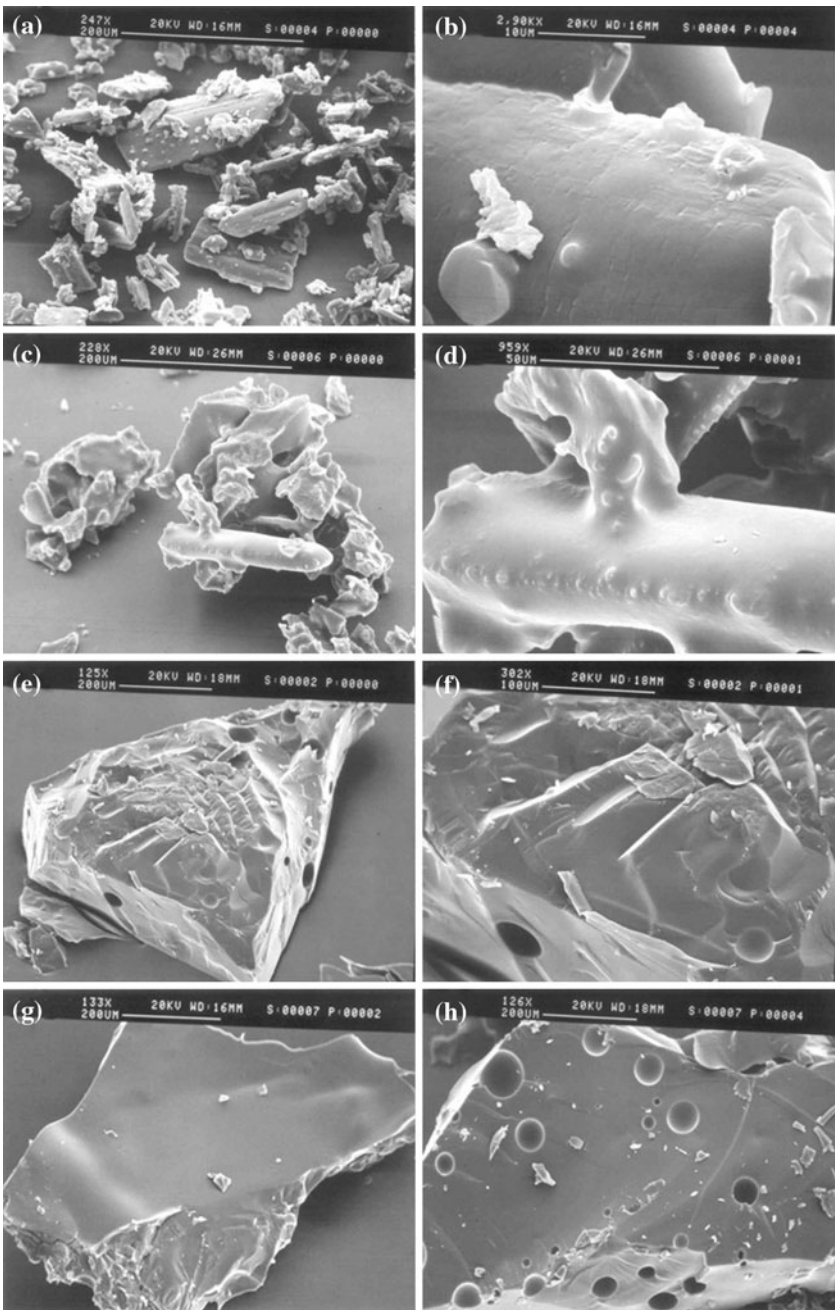

Fig. 7 SEM photographs of paroxetine HCl heated (10 °C min^{-1}) up to 115 °C (**a**, **b**), 122 °C (**c**, **d**), 130 °C (**e**, **f**), and 160 °C (**g**, **h**)

(a) dehydration of the hemihydrate, (b) melting of the dehydrated. At high heating rates, dehydration shifts to higher temperatures along with the entire endothermic peak, at least as long as the melting temperature of the hemihydrate is not attained. Reaching this temperature region with some water left in the sample is what contributes most to the high temperature shoulder of the endothermic peak. However, here we have three simultaneous processes: dehydration, melting of the hemihydrate, and melting of the anhydrous form.

The enthalpy changes in open pans at low and high temperature rates (see Table 2) strongly imply that the melting enthalpy of the hemihydrate is appreciably higher than that of the anhydrous form, even if the difficult-to-quantify contribution of dehydration makes a quantitative evaluation uncertain.

GW597599B

The sample is not hygroscopic and loses mass only above 190 °C when it decomposes. Below this temperature, the thermal behavior does not depend upon the open/sealed-pan conditions. The DSC curve at slow temperature rates (Fig. 9a) has a first endothermic peak at 150 °C followed

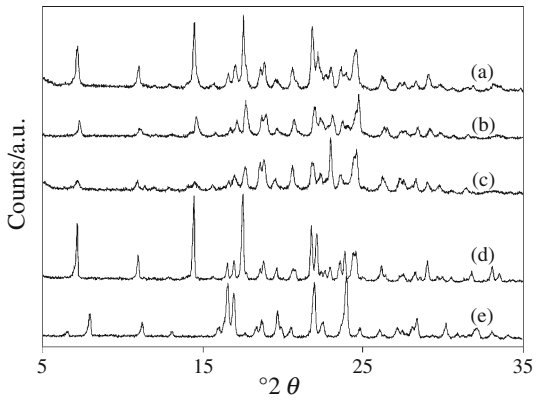

Fig. 8 X-ray patterns of paroxetine HCl hemihydrate heated to 115 °C (**a**), 122 °C (**b**), 130 °C (**c**), as received (**d**), and anhydrous paroxetine HCl (**e**)

by an exothermic effect and by a second endothermic phenomenon. The first peak is attributed to melting of metastable polymorph 1, which quickly yields polymorph 2 by exothermic crystallization. The second endothermic peak is due to melting of polymorph 2.

The shape of DSC curves shows a strong dependence upon the heating rate (but it is independent of the pan configuration). With increasing this rate, the intensity of the first endothermic peak increases, while the exothermic phenomenon becomes smaller (see Fig. 9; Table 4); the effect is due to kinetic reasons, and has been discussed in detail by other authors [19].

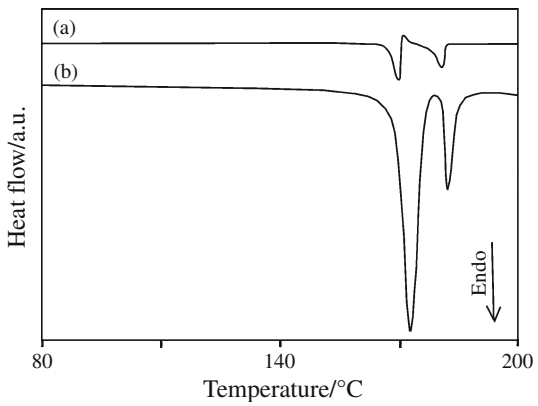

Fig. 9 DSC curves recorded with GW597599B at 2 °C min^{-1} (**a**) and 20 °C min^{-1} (**b**)

Table 4 Enthalpy changes measured for peaks 1 (ΔH_1) and 2 (ΔH_2) at different heating rates

β/ °C/min	ΔH_1/J/g	ΔH_2/J/g
1	31.4 ± 0.8	25.4 ± 0.4
10	45.1 ± 1.1	10.5 ± 0.2

Physical mixtures GW597599B:paroxetine HCl

TG measurements

The TG traces of all mixtures follow those of paroxetine under the same experimental conditions (see Fig. 2), as expected by addition of a component that does not have mass losses below 190 °C (decomposition temperature).

DSC measurements in sealed pan

In the DSC traces recorded in sealed pan with the mixtures in different mass ratios (ranging from 10:90 to 90:10 GW597599B:Paroxetine HCl), we consistently observe the disappearance of GW5975599 melting and a peak at T_{onset} = 124 °C, i.e., below that of paroxetine HCl hemihydrate melting. The shape of this peak changes with the mass ratio of the mixture: for the mixtures rich in paroxetine HCl, it is a double peak and the second maximum is very near to the pure paroxetine HCl melting, while for the mixtures rich in GW597599B, the thermal phenomenon is very broad and is over just before the maximum of the first endothermic peak in pure GW597599B. The overall enthaply changes of all mixtures agree with those computed as the weighted averages of the enthalpies of GW597599 (ΔH = 55.6 J g^{-1}) and paroxetine (ΔH = 93.0 J g^{-1}) under the same experimental conditions (Table 5). Figure 10 reports the DSC curves recorded in sealed pans at 10 °C min^{-1} with pure GW597599B, pure paroxetine and their mixtures in the ratios 20:80 and 80:20. The same conclusion holds when comparing DSC traces collected at 1 °C min^{-1}.

DSC measurements in open pan

When the DSC experiment is performed in open pans at 10 °C min^{-1}, the shape and position of the endothermic

Table 5 Enthalpies of the GW597599B:paroxetine HCl physical mixtures, measured in sealed pan at 10 °C min^{-1}, compared with the corresponding weighted averages of the enthalpies of the components

Mass ratio GW597599: paroxetine HCl	ΔH_{meas} J per g of mix	ΔH_{calc} J per g of mix
10:90	91.7 ± 1.1	89.3
20:80	83.5 ± 2.7	85.5
30:70	82.6 ± 1.5	81.8
40:60	78.3 ± 0.5	78.0
50:50	72.2 ± 2.1	74.3
60:40	69.3 ± 1.9	70.6
70:30	65.1 ± 1.9	66.8
80:20	58.6 ± 2.3	63.1
90:10	58.1 ± 2.3	59.3

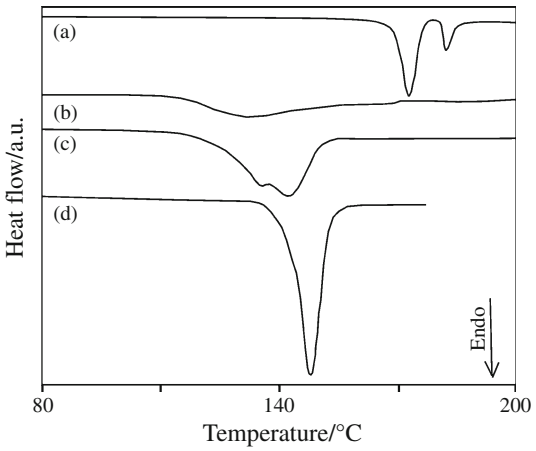

Fig. 10 DSC curves of GW597599B (**a**), physical mixture GW597599B:paroxetine HCl = 80:20 (**b**), physical mixture GW597599B:paroxetine HCl = 20:80 (**c**), and pure paroxetine HCl (**d**) in sealed pan (10 °C min^{-1}, nitrogen flux)

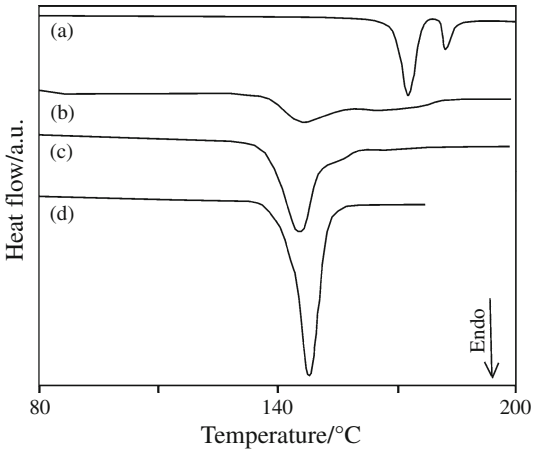

Fig. 11 DSC curves of GW597599B (**a**), physical mixture GW597599B:paroxetine HCl = 80:20 (**b**), physical mixture GW597599B:paroxetine HCl = 20:80 (**c**); and pure paroxetine HCl (**d**) in open pan (10 °C min^{-1}, nitrogen flux)

phenomenon are very similar in paroxetine and in its mixtures with GW597599B (Fig. 11). However, unlike pure paroxetine HCl, it seems that the DSC peak of the mixture is not completely over just after the high temperature shoulder and that a low enthalpy intake continues up to the temperature of the first endothermic peak in pure GW597599B. This behavior is much more evident with increasing relative amount of GW597599B in the mixture. Also with the measurements in open pan, the observed enthalpy for the mixtures agree with the one calculated as weighted average (see Table 6).

XRPD measurements

The XRPD patterns of all physical mixtures are roughly a weighted average of the patterns of their pure components,

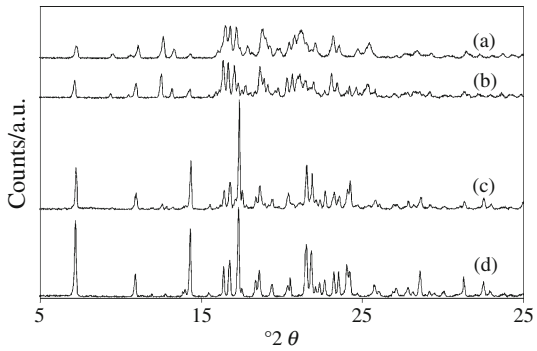

Fig. 12 XRPD patterns: GW597599B (**a**), physical mixture GW597599B:paroxetine HCl = 80:20 (**b**), physical mixture GW597599B:paroxetine HCl = 20:80 (**c**), and paroxetine (**d**)

Table 6 Enthalpies of the GW597599B:paroxetine HCl physical mixtures, measured in open pan at 10 °C min^{-1}, compared with the corresponding weighted averages of the enthalpies of the components

Mass ratio GW597599:paroxetine HCl	ΔH_{meas} J per g of mix	ΔH_{calc} J per g of mix
10:90	86.1 ± 2.2	84.2
20:80	78.2 ± 1.8	81.0
30:70	81.5 ± 0.9	77.9
40:60	74.2 ± 0.2	74.7
50:50	70.1 ± 1.3	71.5
60:40	66.3 ± 2.5	68.3
70:30	62.9 ± 1.7	65.1
80:20	54.8 ± 2.5	62.0
90:10	55.0 ± 2.7	58.8

as expected when no complex formation has taken place. In Fig. 12, the X-ray patterns of the pure components and of the mixtures with GW597599B/paroxetine HCl in 20:80 and 80.20 mass ratios are reported for comparison. This suggests that no solid-state interaction takes place in the mixtures.

Conclusions

The melting behavior of the hemihydrate form of paroxetine HCl is substantially more complicated than described in the literature [16], being also very much dependent upon experimental details. We argue that a reliable estimate of its melting enthalpy requires sealed pans and rather high heating rates (10 °C min^{-1}) to minimize contributions from dehydration, and formation of a different pseudo-polymorph. When DSC measurements are performed in open pans, a strong dependence upon the heating rate is observed due to variously overlapping processes which, in sequence, are

- dehydration;
- melting of the anhydrate form;
- melting of the (residual) hemihydrate form.

These processes cannot be fully separated nor can their characteristic enthalpies be determined. Therefore, in this article, we have been dealing with the effects of mixing, where only the overall thermal response of the ingredients matters.

The XRPD patterns seem to rule out any interaction among components and, accordingly, the thermal data with sealed pans display the behavior expected for a system with simple eutectic phase diagram. The eutectic mixture paroxetine hemihydrate-GW597599B melts around 120 °C, much below the melting of paroxetine form I.

On the other hand, when the measurements are performed in open pans, the dehydration of paroxetine form I to paroxetine form II can be observed because the process occurs below the eutectic temperature. Paroxetine form II and GW597599B do not form any eutectic mixture as it can be seen from the DSC thermograms that show that thermal response is not affected by mixing. The final result is that paroxetine form II melts at its own temperature, completely unaffected by the presence of GW597599B. Furthermore, it can be noted (Fig. 11) that a very broad peak is present spanning a temperature range between the melting temperature of paroxetine and GW597599B. At the same time the melting peak of GW597599B does not appear. This can be tentatively explained by the dissolution of GW597599B into liquid paroxetine Table 6.

The authors have proposed, in previous articles [20–23], the use of physico-chemical techniques to approach in a non-conventional way compatibility studies. The results discussed in this article confirm that thermal analysis constitutes the first choice between the physico-chemical techniques suited for compatibility studies.

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