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THERMAL ANALYSIS OF BINARY SYSTEMS OF THE PHARMACEUTICALS TRIMETHOPRIM AND BENZOIC ACID

G. P. Bettinetti, C. Caramella, F. Giordano, A. La Manna,
*C. Margheritis** and *C. Sinistri**

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF PAVIA,
*DEPARTMENT OF PHYSICAL CHEMISTRY, UNIVERSITY OF PAVIA, ITALY

Thermal analysis of the binary system benzoic acid (BA) and trimethoprim (TMP) provided evidence of the formation of two molecular compounds. BA–TMP and two crystalline forms of $(BA)_2$–TMP were characterized on the basis of their thermodynamic parameters as well as of crystallographic and spectroscopic properties. The availability of these compounds (by recrystallization) allowed interpretation of thermal effects in the DSC curves of the mixtures and the theoretical phase diagrams could be drawn. The results are consistent with the model of a very slight dissociation of the molecular compounds in the melt.

Thermal analysis and particularly microcalorimetric differential techniques are widely employed in pharmaceutical technology when interactions between active or inert ingredients of solid (tablets, capsules, powders) or semisolid (suspensions) pharmaceutical forms are concerned. This field of investigation is of practical relevance owing to possible changes in the physical properties and bioavailability of drugs. Microcalorimetric differential techniques allow investigation of the existence and nature of molecular compounds. In addition, on-line control of possible interactions at every stage of the production process (grinding, mixing, sieving, granulation, compression) or after various storage times can be achieved.

In previous papers from our group, investigations on interactions between trimethoprim (TMP) and some organic acids (formic, acetic, propanoic) [1] and between TMP and sulfamethoxazole [2–5] were reported. Investigations were successively extended to binary systems including TMP and some aromatic acids of pharmaceutical interest, such as benzoic, salicylic, acetylsalicylic and nicotinic acids. This paper is concerned with the TMP and benzoic acid (BA) binary system. Different interaction products from TMP and BA were prepared following various procedures, and a comprehensive picture of the thermal properties of this system is reported. IR and X-ray diffraction data were also taken into account when further analytical parameters were required.

Experimental

Apparatus

Thermal analysis was performed with a DSC Mettler TA 3000. Samples (1–4 mg) sealed in Al pans were scanned between 35° and the melt region at heating rates of

5 and 10 degree min^{-1}. Additional information on the thermal behaviour of samples was obtained by visual observation with a heating stage microscope (Kofler).

X-ray diffraction patterns (powder method) were obtained with a Philips PW 1050/25 diffractometer, with CuK_α radiation. X-ray diffraction on a single crystal was performed with a Philips four-circle computer-controlled diffractometer PW 1100, by using CuK_α radiation monochromatized with a graphite crystal.

Samples for IR analysis were prepared as Nujol mulls and examined by means of a Perkin–Elmer 421 dual grating IR spectrophotometer, previously checked with a polystyrene film.

Materials

Commercial trimethoprim (TMP) was purified by recrystallization from water–ethanol mixtures (10/90 v/v) (form I, mp. 199.3°). Benzoic acid (BA) complying with F.U.I. VIII Ed. requirements, mp. 122.0° after recrystallization from water, was used.

Preparation of the molecular compounds

BA–TMP (1:1 complex, $C_{21}H_{24}N_4O_5$)

A mixture containing equimolecular amounts (0.05 mole) of BA and TMP was crystallized from 100 ml of distilled water. The solid was filtered by suction and dried in a drying pistol charged with P_2O_5 (0.1 mm Hg, 90°) to give 0.0475 mole of the title compound, mp. 145.9°.

This compound was also isolated by evaporation in solutions of equimolecular amounts of BA and TMP in methanol or in ethyl acetate.

$(BA)_2$–TMP (2:1 complex, $C_{28}H_{30}N_4O_7$)

A mixture of 0.1 mole of BA and 0.05 mole of TMP was crystallized from 200 ml of distilled water. The solid was filtered by suction, washed with water, and dried under vacuum (P_2O_5) at 0.1 mm Hg and 90° to give 0.048 mole of a 2:1 complex melting at 126.5° (form II). A complex of the same molecular formula, melting at 134.2° (form I), crystallized from the melt on cooling. This latter form of $(BA)_2$–TMP was also isolated by evaporation of a solution containing BA and TMP in 2:1 molar ratio in diethylene glycol.

Preparation of physical mixtures for thermal analysis

Physical mixtures were prepared in a Turbula apparatus by dry-mixing the components, previously powdered by thorough grinding in a china mortar. Table 1 summarizes the mixtures tested in the DSC runs. In particular, BA and TMP mixtures, and mixtures with the same BA content (mole %) containing molecular compound(s), are reported.

Table 1 Physical mixtures scanned in DSC runs

BA content, mole %	BA/TMP mixtures, mole/mole	Equivalent mixtures (mole/mole) or compounds				
		BA/(2:1)*	BA/(1:1)	(2:1)*/(1:1)	(2:1)*/TMP	(1:1)/TMP
95	19/1	17/1	18/1			
90	9/1	7/1	8/1			
85	5.67/1	3.67/1	4.67/1			
80	4/1	2/1	3/1			
75	3/1	1/1	2/1			
70	2.34/1	0.34/1	1.34/1			
67.5	2.08/1	0.08/1	1/08/1			
66.7	2/1	$(BA)_2$–TMP*	1/1			
65	1.86/1		0.86/1	6/1	13/1	
62.5	1.67/1		0.67/1	2/1	5/1	
60	1.5/1		0.5/1	1/1	3/1	
57.5	1.35/1		0.355/1	0.55/1	2.1/1	
57	1.33/1		0.33/1	0.5/1	2/1	
55	1.22/1		0.22/1	0.3/1	1.57/1	
52.5	1.11/1		0.125/1	0.12/1	1/24/1	
50	1/1		BA–TMP		1/1	
47.5	0.91/1				0.826/1	9.7/1
45	0.82/1				0.7/1	4.5/1
43	0.76/1				0.61/1	3.1/1
40	0.67/1				0.5/1	2/1
37.5	0.6/1				0.43/1	1.5/1
35	0.54/1				0.37/1	1.16/1
30	0.43/1				0.275/1	0.75/1
27.5	0.38/1				0.234/1	0.61/1
25	0.33/1				0.2/1	0.5/1
22.5	0.29/1				0.17/1	0.41/1
20	0.25/1				0.144/1	0.335/1
15	0.18/1				0.098/1	0.215/1
10	0.11/1				0.06/1	0.125/1
5	0.053/1				0.027/1	0.056/1

* Both as form I and form II

Results and discussion

The 1:1 complex can be obtained by recrystallization from water as a solvate (trihydrate) which, by loss of water in a desiccator over P_2O_5, becomes amorphous. On heating, the amorphous material is transformed, at about 90°, into a crystalline form of BA–TMP which then melts at 145.9° (Fig. 1a).

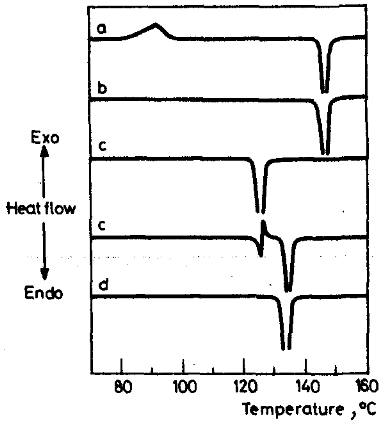

Fig. 1 DSC curves (scan speed 5 degree min^{-1}) of the molecular compounds. a) amorphous BA–TMP; b) crystalline BA–TMP; c) $(BA)_2$–TMP recrystallized from water (form II): non-ground sample (upper curve), ground sample (lower curve); d) $(BA)_2$–TMP obtained by evaporation (solution in diethylene glycol) (form I)

The same crystalline form can be obtained by evaporation of a methanolic solution of stoichiometric amounts of BA and TMP, or obviously by heating the trihydrate in a drying pistol (see Fig. 1b for DSC trace).

The thermal behaviour of the 2:1 complex depends mainly on the sample preparation procedures. Samples not previously ground, isolated by recrystallization from water, melt at 125.6° (Fig. 1c, upper curve). Ground samples, in contrast, show an endothermic effect at the same temperature, immediately followed by an exothermic one, with final fusion at 134.2° (Fig. 1c, lower curve). This exo effect can be ascribed to the formation of the higher-melting $(BA)_2$–TMP modification (form I) within the melt of the lower-melting modification ($(BA)_2$–TMP form II).

Rescanning of samples previously heated up to 125.6° did not show the endo and exo effects described here. The trace thus obtained is of type 1d. The crystal growth of form I can easily be observed with the heating stage microscope. The effect of grinding on the thermal behaviour of polymorphs was earlier reported for sulfamethoxydiazine crystal forms [6]. The slow evaporation of a BA/TMP (2:1 molar ratio) solution in diethylene glycol leaves crystals of a 2:1 complex giving the DSC trace in Fig. 1d, i.e. of the form I of the 2:1 complex.

In Table 2 the fusion temperatures (T_f) and enthalpies (ΔH_f) of the molecular compounds and their constituents are reported.

X-ray diffraction patterns taken on the molecular compounds proved the arrangements of the BA and TMP molecules in new crystal structures, whereas diffractograms of physical mixtures of BA and TMP corresponded (as expected) to the averages of those taken on pure BA and TMP.

The main bands in the IR spectra of the molecular compounds are reported in Fig. 3.

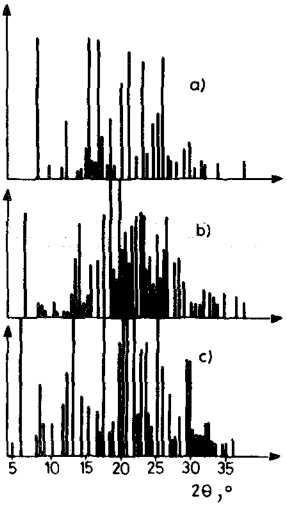

Fig. 2 X-ray diffraction patterns. Unit cell data on the molecular compounds: a) BA–TMP, monoclinic crystalline form: $a = 11.295$, $b = 28.266$, $c = 6.543$ Å, $\beta = 100.97°$, space group $P2_1/N$, $U = 2050.78$ Å^3, $Z = 4$, $M = 412.43$; b) $(BA)_2$–TMP form *I*: X-ray diffraction analysis on a single crystal is in progress; c) $(BA)_2$–TMP form II, triclinic crystalline form: $a = 14.595$, $b = 10.195$, $c = 9.455$ Å, $\alpha = 89.67°$, $\beta = 97.37°$, $\gamma = 104.6°$, space group P_1 or $P\bar{1}$, $U = 1349.95$ Å^3, $Z = 2$, $M = 543.56$

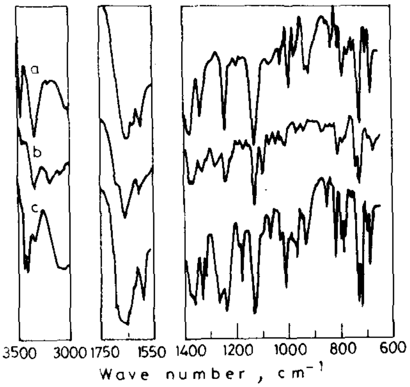

Fig. 3 The main bands in the IR spectra (Nujol mull) of a) BA–TMP; b) $(BA)_2$–TMP form I; c) $(BA)_2$–TMP form II

The IR absorption bands in the 3500–3000 cm^{-1} N–H stretching region, when compared with those of TMP alone and those of the TMP–SMZ molecular compound [2], show that in the solid state the BA molecule(s) is linked to the aminopyrimidine portion(s) of TMP.

The phase diagram of the binary system BA–TMP was studied both by experimental thermal analysis of the mixtures reported in Table 1 and by theoretical calculations on the solid–liquid equilibria using appropriate models of the melt, as in previous work [3]. The overall, and most significant experimental results are reported in Fig. 4: the system presents two intermediate compounds (2:1, 1:1) with congruent melting points, and three simple eutectics: E_1 (at 106.8° and $x_{BA} = 0.86$), E_2 (at 132.5° and $x_{BA} = 0.63$), and E_3 (at 145.0° and $x_{BA} = 0.48$). Moreover, the diagram shows, by a dashed line, the composition range where, at 125.6°, the endo–exothermal effects described in Fig. 1c for the pure form II of the 2:1 compound can be observed for the mixtures containing this crystalline form (Table 1). A dotted line shows the composition range where, at 120.2°, the mixtures of the 2:1 compound and TMP in Table 1 exhibit a thermal effect which could be indicative of the existence of a metastable eutectic between the 2:1 compound and TMP.

In order to study the molecular arrangement of the melt, three different structural models were first developed.

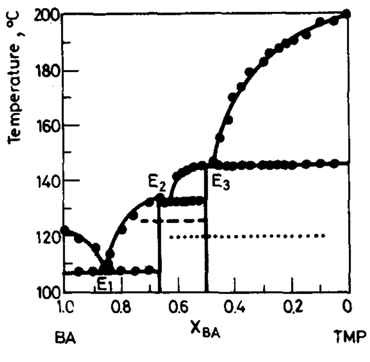

Fig. 4 Experimental phase diagram of the binary system BA/TMP *vs.* mole fraction of BA. The dashed line represents the endo and exo effects of the 2:1 compound (see text), while the dotted line can be ascribed to a metastable eutectic between TMP and the 2:1 compound

1) *A model which assumes total dissociation of the* 2:1 *and* 1:1 *compounds in the melt.*

Curve *a* of Fig. 5 is the geometrical expression of the function $T(x_{BA})$ that can be obtained by using this model along with the methods previously described [3] and the thermal data reported in Table 2.

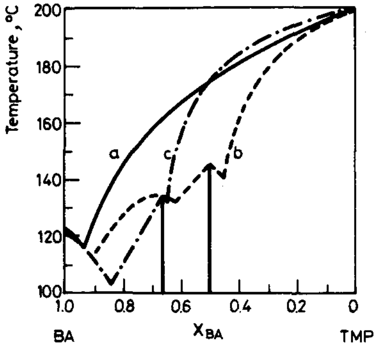

Fig. 5 Phase diagrams calculated by means of the following molecular models of the melt: a) total dissociation of the 2:1 and 1:1 compounds; b) total non-dissociation of the 1:1 compound; c) total non-dissociation of the 2:1 compound

Table 2

Compound		T_f, °C	ΔH_f, kJ mol^{-1}
TMP		199.3	49.4 ± 1.2
BA		122.0	17.2 ± 0.2
BA–TMP		145.9	52.3 ± 0.8
(BA)$_2$–TMP	form I	134.2	56.1 ± 1.2
	form II	126.5	59.0 ± 1.2

A comparison with Fig. 4 shows that this model is totally inconsistent with the experimental results, and particularly with the features of the intermediate compounds: their melting points lie beneath the liquidus curve.

2) *A model which assumes total non-dissociation in the melt only for the* 1:1 *molecular compound.*

Curve *b* of Fig. 5 was obtained with this model. In this case two intermediate compounds are correctly predicted, but the agreement between the experimental equilibrium points and the calculated ones is poor.

3) *A model which assumes total non-dissociation in the melt only for the* 2:1 *molecular compound.*

Curve *c* of Fig. 5 shows the results obtained with this model. The calculated liquidus curve is inconsistent with the experimental thermal parameters of the 1:1 compound.

Following these results, a new and more complex model was developed, which assumes partial dissociation in the melt of the 1:1 and 2:1 molecular compounds. In particular, the equilibrium constant ($k_{1:1}$) of the dissociation:

$$\text{BA–TMP} \rightleftharpoons \text{BA} + \text{TMP}$$

and that ($k_{2:1}$) of the dissociation:

$$(\text{BA})_2\text{–TMP} \rightleftharpoons 2\ \text{BA} + \text{TMP}$$

were taken into account. Their values were chosen by minimizing the difference between the calculated equilibrium curves and the experimental ones.

Figure 6 shows the phase diagram calculated by using $k_{1:1} = 5 \cdot 10^{-3}$ and $k_{2:1} = 5 \cdot 10^{-4}$.

Although these values should be taken as merely indicative, owing to the uncertainties inherent in the experimental solid–liquid equilibrium points, the calculated phase diagram nevertheless now shows a noteworthy agreement with the experimental one. For example, the calculated eutectics E_1 (at 107.0° and $x_{BA} = 0.86$), E_2 (at 131.5° and $x_{BA} = 0.625$) and E_3 (at 145.5° and $x_{BA} = 0.48$) compare very well with the experimental ones.

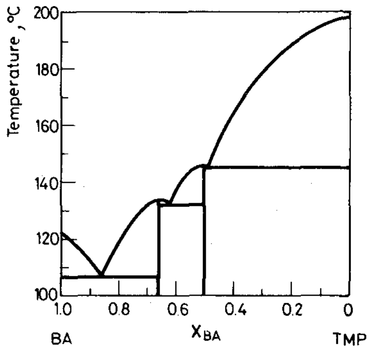

Fig. 6 Phase diagram calculated with a structural model which assumes partial dissociation of the two compounds in the melt ($k_{1:1} = 5 \cdot 10^{-3}$ and $k_{2:1} = 5 \cdot 10^{-4}$)

Conclusions

The availability of pure molecular compounds between BA and TMP allowed interpretation of the thermal effects in the DSC curves of various mixtures (e.g. metastable eutectics, polymorphic transitions, crystallization from the melt) and the construction of theoretical phase diagrams.

In this way it was possible to prove that no total dissociation, as in the case of the binary system TMP/SMZ [3], occurs on melting. The molecular compounds present in the solid phase are also present in the melt. The correlation between the experimental equilibrium diagram and the theoretical diagram, consistent with a very slight dissociation in the melt, confirms the high stability of these molecular compounds. Ion-pair bonds (and not merely hydrogen-bonds as for the TMP–SMZ 1:1 molecular compound [4]), with proton transfer from benzoic acid to the molecular pyrimidinic nitrogen atom(s) of TMP, seem to be the main reason for this behavior.

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Zusammenfassung — Die thermische Analyse des binären Systems Benzoesäure (BA) — Trimethoprim (TMP) erbrachte Hinweise auf die Bildung von zwei Molekülverbindungen. BA–TMP und zwei kristalline Formen von $(BA)_2$–TMP wurden sowohl durch ihre thermodynamischen Parameter als auch durch kristallographische und spektroskopische Eigenschaften charakterisiert. Die Darstellbarkeit dieser Verbindungen (durch Rekristallisation) ermöglichte die Interpretation der thermischen Effekte in den DSC-Kurven der Gemische und die Aufstellung der theoretischen Phasendiagramme. Die Ergebnisse sind vereinbar mit dem Modell einer sehr schwachen Dissoziation der Molekularverbindungen in der Schmelze.

Резюме — Термический анализ двойной системы бензойная кислота (БК) —триметоприм (TMP) показал обращование двух молекулярных соединений. Бинарная система БК—ТМП и две кристаллические формы системы $(БК)_2$—ТМП были охарактеризованы термодинамическими параметрами, кристаллографическими и спектроскопическими характеристиками. Доступность этих соединений, получаемых путем перекристаллизации, позволила интерпретировать термические эффекты, наблюдаемые на ДСК-кривых смесей соединений, и установить теоретические фазовые диаграммы. Полученные результаты согласуются с моделью очень малой диссоциации молекулярных соединений в расплаве.