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An experimental and theoretical approach to the analysis of pharmaceutical binary systems*

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Introduction

Drug formulation often implies the preparation of multicomponent systems based both on drug–drug and drug–excipient combinations. Differential microcalorimetry allows the rapid and reliable determination of fundamental thermodynamic parameters such as enthalpies of fusion, specific heats, phase transition temperatures, etc., with milligram quantities of substance. As for binary systems, the drawing of phase diagrams from these data is of great interest when investigating stable and metastable eutectics, addition compounds, solid solutions, etc., to be taken into account for stability, formulation and bioavailability problems. The use of structural models of the melt permits us to trace, from a restricted number of carefully chosen experimental measurements, the theoretical solid–liquid equilibria curves and therefore the overall phase diagram of the system [1, 2]. Some examples of calculated and experimentally determined phase diagrams concerning systems showing simple eutectic and addition compound formation are reported here.

Experimental

Materials

Trimethoprim (TMP), sulphamethoxypyridazine (SMPD), sulphadiazine (SFD), and sulphamethoxazole (SMZ) of pharmacopoeial (F.U. 9th Edn.) purity grade were used. Pure TMP-SMPD and TMP-SMZ (both 1:1 mol:mol) addition compounds were prepared by recrystallization from solutions in methanol of stoichiometric quantities of

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components [3]. Table 1 reports the relevant thermal parameters of the substances tested.

Apparatus

A Mettler TA3000 DSC thermal analysis system equipped with a DSC 20 cell and a Mettler M3 microbalance were used. Samples (2–5 mg, sealed in A1 pans) were scanned between ambient temperature and the melt region at 5K min^{-1}.

Table 1

Compound*	Melting point (°C) (S.D.)	Enthalpy of fusion (kJ mol^{-1}) (S.D.)
TMP	199.4 (0.3)	49.4 (1.3)
SFD	257.6 (0.4)	43.7 (0.6)
SMPD	180.9 (0.3)	32.6 (0.3)
SMZ	170.3 (0.5)	32.2 (0.8)
TMP-SMZ	180.3 (0.4)	41.4 (0.8)
TMP-SMPD	169.5 (0.2)	72.3 (0.5)

*See text for symbols.

Discussion

When complete immiscibility in the solid state and ideality of mixtures in the liquid state can be assumed, the fusion temperature of the component in a mixture of given composition can be calculated from the fusion temperature and enthalpy of the same component, according to the following equation:

$$T_f = \frac{\Delta H_f}{\Delta S_f - \mathrm{R}\ \ln(a/a^*)}, \tag{1}$$

where T_f is the solid–liquid equilibrium temperature (in K), i.e. the final fusion temperature of the mixture; R is the gas constant; a is the activity of the component in the melt; a^* is the activity of pure molten component; ΔH_f is the enthalpy of fusion of the component (assumed independent of temperature); ΔS_f is the molar fusion entropy of the component at its fusion temperature (T_c) i.e. $\Delta H_f/T_c$.

(a) *Simple eutectic systems*

The activity term a^*_A is equal to 1 while a_A represents the mole fraction of the component A (x_A). By introducing in the above equation different values of a_A ($0 < a_A < 1$), the solid–liquid equilibrium curve is obtained. The same procedure is used for the second component, B. In this way two curves are obtained, one for each component, and by expressing on the abscissa the composition as a function of the mole fraction of one component ($x_A + x_B = 1$), the intersection point of these curves will give the composition and temperature of the eutectic.

An example of a simple eutectic is reported in Fig. 1 and it is related to the TMP and SFD system.

(b) *Systems forming AB 1:1 (mol:mol) addition compounds*

The drawing of this theoretical phase diagram needs, of course, also the determination of fusion enthalpy and temperature of the pure addition compound (prepared from

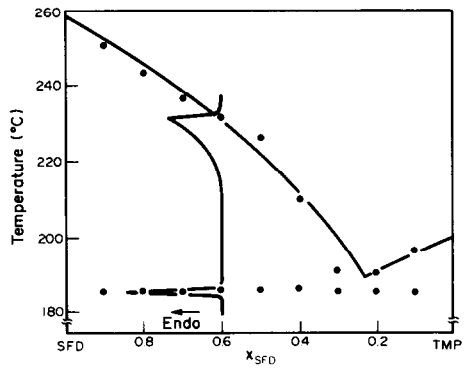

Figure 1
Phase diagram of the TMP and SFD binary system. The continuous line was calculated from equation (1) (T_e = 189.4°C, x = 0.23); dots represent experimentally determined points (T_e = 189.5 (0.4) °C, x_e 0.25). The DSC trace of a mixture (x_{SFD} = 0.6) is also shown.

mixtures of A and B by common procedures of recrystallization, evaporation, fusion, precipitation, etc.). The behaviour of AB in the melt can be assumed to fall into the following cases:

(1) *Complete dissociation (AB → A + B)*

The considerations which hold for simple eutectic systems are still valid for the single components (A and B) equilibrium curves. The activity term of the addition compound (a_{AB}/a^*_{AB}) is $x_A \,.\, x_B/(0.5 \,.\, 0.5)$, i.e. $4x_A.x_B$: the symmetrical bell-shaped equilibrium curve of AB is obtained by inserting different mole fraction values in equation (1). The intersection points of this curve with the curves relative to pure A and B allow the determination of fusion temperatures and compositions of both eutectics. A phase diagram consistent with this structural model related to the TMP and SMZ binary system is reported in ref. 4 and discussed in ref. 5.

(2) *Complete undissociation (A + B → AB)*

The solid–liquid equilibrium curves of A and B can be easily calculated through equation (1) using $(x_A - x_B)/x_A$ or $(x_B - x_A)/x_B$ as the respective activity terms. As for the calculation of the activity term of AB, when excess A or B (with respect to the addition compound composition) is present its value is x_B/x_A or x_A/x_B, respectively. The activities of pure molten compounds (A, B, AB) are taken as unity. The intersection points of the symmetric equilibrium curve of AB with the curves of A and B give the same informations outlined above. No experimental phase diagrams of binary systems fitting this structural model are up-to-date available. It represents however the other limiting situation with respect to the case of complete dissociation in the melt.

(3) *Partial dissociation in the melt (AB = A + B)*

A structural model implying partial dissociation of the addition compound in the melt has to be considered when experimental data fail to fit those already discussed. A practical approach to calculate the activities of molecular species present in the melt consists, as suggested by Sinistri and Margheritis, in selecting a value of the formation constant, K_{AB}, (here assumed independent of temperature for simplification), and calculating from this the number of moles of each component (n_A, n_B, n_{AB}) for each molar fraction. If the equilibrium A + B = AB is assumed, the respective formation constant is expressed by equation:

$$K_{AB} = \frac{n_{AB}}{n_A \cdot n_B} N, \tag{2}$$

where $N = n_A + n_B + n_{AB}$ is the sum of all particles in the system, i.e. of the true number of moles of A, B and AB in the mixture. Considering that $x_A = n_A + n_{AB}$, $x_B = n_B + n_{AB}$ and $N = 1 - n_{AB}$, equation (3) can be used to calculate the value of n_{AB} for the given formation constant and mixture composition:

$$n_{AB} = \frac{(K_{AB} + 1) - \sqrt{(K_{AB} + 1)^2 - 4(K_{AB} + 1)K_{AB} \cdot x_A \cdot x_B}}{2(K_{AB} + 1)} \tag{3}$$

In Table 2 the values obtained for a series of mixtures for $K_{AB} = 1$ are reported. The relative activities of A, B and AB are determined from the ratio between the respective number of moles and N. Since the activity coefficients of pure A and B in the molten state can be assumed as unity, the activity values of A and B can be fed into equation (1) to calculate their solid–liquid equilibrium curves. The activity coefficient of the pure addition compound, a^*_{AB}, for a given K_{AB} value, is obtained through equation (3) for $x_A = 0.5$. The symmetrical bell-shaped equilibrium curve of AB is drawn by inserting into equation (1) the values of the ratios (a_{AB}/a^*_{AB}) corresponding to different compositions. Its intersections with the curves of A and B define eutectic temperatures and compositions, for a given K_{AB} value. The same procedure is repeated for different K_{AB} values until the best fitting with the theoretical phase diagram is reached. A practical case of a binary system whose experimentally determined phase diagram was found to match a structural model of partial dissociation ($K_{AB} = 1$) in the melt is reported in Fig. 2 and it concerns TMP, SMPD and their 1:1 mol:mol addition compound.

Table 2†

x_A	n_A	n_B	n_{AB}	N	a_A	a_B	a_{AB}
0.9	0.85	0.053	0.047	0.95	0.895	0.055	0.0496
0.8	0.71	0.11	0.088	0.91	0.78	0.12	0.096
0.7	0.58	0.18	0.12	0.88	0.66	0.21	0.135
0.6	0.46	0.26	0.14	0.86	0.54	0.30	0.162
0.5	0.35	0.35	0.15	0.85	0.41	0.41	0.172‡

†See text for symbols; ‡$a_{AB} = a^*_{AB}$.

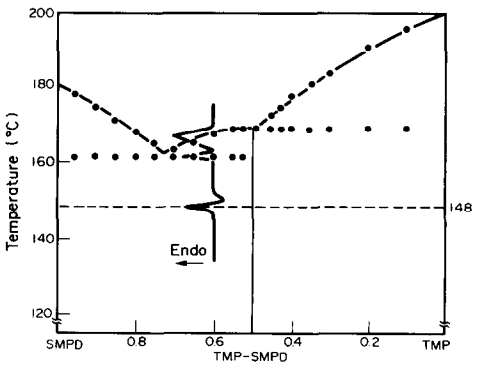

Figure 2
Phase diagram of the TMP and SMPD binary system. The continuous line was calculated on the assumption of partial dissociation in the melt ($K_{AB} = 1$) ($T_{e1} = 162.2$°C, $x_{e1} = 0.73$; $T_{e2} = 169.3$°C, $x_{e2} = 0.49$); dots represent experimentally determined points ($T_{e1} = 162.0\,(0.8)$ °C, $x_{e1} = 0.71$; $T_{e2} = 168.8\,(0.5)$ °C, $x_{e2} = 0.49$); dashed line refers to eutectic metastable fusion. The DSC trace of a mixture ($x_{SMPD} = 0.6$) is also shown.

Conclusions

From a practical point of view thermal analysis offers the possibility of a rapid screening of the behaviour of solid mixtures. All the calculations reported can be easily handled by means of a microcomputer program with graphic facilities. Moreover, readily available thermodynamic parameters allow the comparison between experimental and theoretical phase diagrams. In this way information about the ideality of the mixture under examination can be achieved giving useful indications about the stability of the system under examination. It seems worthwhile to add that the binary systems here reported include therapeutic combinations of relevant interest, whose composition (e.g. Co-trimazine, Co-trimoxazole [6]) is dictated only by pharmacokinetic considerations. While in the case of the binary system between TMP and SFD a simple eutectic system was found with no solid state interaction, TMP interacts both with SMZ and SMPD giving 1:1 addition compounds. This was proved to significantly affect physical and technological properties of suspensions [7], tablets [8] and suppositories [9].

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