A DSC COMPOSITIONAL ANALYSIS OF SOME BINARY ORGANIC MIXTURES OF PHARMACEUTICAL SIGNIFICANCE

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A DSC compositional analysis of 3 model binary systems of pharmaceutical significance has been conducted. Mixtures of known selected composition for each of the systems 3,5-dinitrobenzoic acid/benzoic acid, paracetamol/4-aminobenzoic acid and acetylsalicylic/salicylic acid were prepared and analyzed by DSC. The respective compositions derived from applications of the van't Hoff equation were correlated with the corresponding theoretical values and with the corresponding fusion temperatures and fusion enthalpies, obtained from the relevant DSC profiles.

Linear correlations were found to exist between the theoretical compositions, fusion temperatures and fusion enthalpies for each of these systems and it is apparent that with suitable calibration procedures, the DSC compositional analysis method can be applied to determine the purity at the 90–95 mole% level. This level is of considerable interest in drug stability studies and has real significance in purity assays of commercial pharmaceutical preparations.

Keywords: binary organic mixtures, drug stability, DSC, purity, van't Hoff equation

Introduction

The Thermal Analysis techniques, particularly DSC, have intensive applicability in pharmaceutical science, as detailed in a recent book by Ford and Timmins [1]. Specifically, TG, DTA and DSC are used for the characterisation of pharmaceutical preparations [2–4] and DSC for purity determination [5–7], compatibility and stability studies [8, 9], polymorphism studies [10–12], eutectic melt determination [13, 14], phase diagram determination [15, 16] and drug delivery system analysis [17].

The fundamental purity assay of pharmaceutical compounds is one of the most important aspects of a drug profile. The routine DSC procedure for purity assay is

essentially based on the general method proposed by Watson *et al.* [18], whereby the impurity mole fraction is determined from the DSC profile via application of the van't Hoff relationship. Several assumptions are a prerequisite for this procedure, the most important of which are that the impurities present form an ideal eutectic mixture with the principal component and that no chemical interaction occurs between components. Two variations of this basic method are available, which have been concisely reviewed [5]. Both of these demand specific sample presentation procedures and careful selection of instrumental conditions.

The objectives of the present project are to apply the DSC purity determination procedures to assay drug composition, using model systems for preliminary study and thence to investigate relationships of fusion temperatures and fusion enthalpies to drug composition, thereby using these thermodynamic data for analytical purposes.

Experimental

Chemicals

Benzoic acid (Ministry of Health, Singapore), 3.5-dinitrobenzoic acid (BDH), 4'-hydroxyacetanilide (Paracetamol) (Merck), 4-aminobenzoic acid (Merck), salicylic acid (Merck) and acetylsalicylic acid (Merck) were purified by recrystallisation from suitable solvents, dried at 80°C to constant mass and lightly ground to remove aggregates.

Instrumental

DSC data were obtained using a Perkin-Elmer DSC-4 Thermal Analysis System, coupled to a Perkin-Elmer (Model 3600) Thermal Analysis Data Station (TADS). Samples, in the mass range 2.5–3.5 mg were heated in hermetically sealed aluminium crucibles at a rate of 1.5 deg·min^{-1} in a dynamic nitrogen atmosphere with a purge flow rate of 50 cm^3·min^{-1}. Temperature and Heat Flux rate calibrations of the DSC were effected using indium metal as the Certified Reference Material [19], using the same instrumental conditions as for the other samples studied.

Sample presentation procedures

3 model systems were investigated: 3,5-dinitrobenzoic acid – doped with benzoic acid: 4'-hydroxyacetanilide – doped with 4-aminobenzoic acid and acetylsalicylic acid – doped with salicylic acid. For each of these systems, a series of binary mixtures, in the 90–100 mole % (main component) range were prepared 'in situ' by direct weighing into the aluminium crucibles. For the

paracetamol/4-aminobenzoic acid system, a 'bulk mixing' sampling technique was also employed.

Data analysis procedures

DSC curves for the binary systems studied were analyzed in terms of the onset and peak temperatures of the fusion peak and in terms of the fusion enthalpy. The melt temperature was taken as the onset temperature of the fusion peak. For van't Hoff analysis of the DSC data, the fusion peak was arbitrarily subdivided into several sections and the area of each section was determined to give the fraction melted (F_s) as a function of the melt temperature (T_s). The former was corrected for 'undetected sample melting' and the latter for 'instrumental thermal resistance'. The required peak area correction for 'undetected sample melting' was determined by a least squares analysis of the T_s *vs.* $1/F_s$ plot or by application of the Sondack equation [20].

Based on the indium calibration data, the overall reproducibility of the DSC data in terms of temperature averages to $\pm 0.01°C$ and in terms of heat flux, averages to ± 0.2 J·g^{-1}.

Results and discussion

The experimental and calculated data for the 3 systems studied are collected in Table 1. The first column of data gives the mole% of the main component, as determined by the measured masses of the 2 components: the second column gives the mole% of the main component, as determined by a van't Hoff analysis of the corresponding DSC data: the third and fourth columns give the onset and peak temperatures, as related to the observed fusion peak of the system and the final column gives the fusion enthalpy, as determined directly from the DSC data.

For each system, 4 different correlations were assessed: mole% (van't Hoff) *vs.* mole% (by mass): fusion peak onset temperature *vs.* mole% (by mass): fusion peak temperature *vs.* mole% (by mass) and fusion enthalpy *vs.* mole% (by mass). For all systems, an excellent linear correlation is found for fusion peak onset temperature *vs.* mole% (by mass) and these are shown in Fig. 1. The regression analysis data are (r^2): A, 0.955: B, 0.979 and C, 0.987. These excellent correlations in the 90% main component range indicate the superiority of this data analysis procedure over mole% (van't Hoff) *vs.* mole% (by mass), which exhibit a linearity cut-off at about 96% main component. The lower dilution limit is of pharmaceutical significance.

Table 1

Binary system code	Mole% (main component) (by mass)	Mole% (main component) (by calculation)	Fusion peak definition temperatures/$^{\circ}$C		Fusion enthalpy $\Delta_{fus}H$ /J·g^{-1}
			Onset	Peak	
A	90	89.9	195.2	200.4	95.8
	91	91.4	195.4	199.1	–
	92	92.3	196.1	200.2	–
	93	93.2	196.6	201.8	–
	94	94.2	197.2	200.9	103.8
	95	94.9	198.9	202.9	111.7
	96	96.2	201.2	204.7	120.5
	97	97.1	202.3	205.6	125.9
	98	98.2	203.4	206.2	131.0
	99	99.1	206.0	207.4	146.9
	100	99.6	206.9	208.5	159.8
B	90	93.4	–	–	96.7
	91	93.8	156.5	161.0	106.7
	92	94.5	157.8	163.1	113.8
	93	95.0	159.1	163.4	121.8
	94	95.4	161.0	165.5	140.2
	95	95.9	162.9	165.7	136.8
	96	96.4	163.5	166.0	146.4
	97	97.2	164.2	166.7	154.8
	98	97.5	165.0	166.5	142.7
	99	98.0	166.3	168.5	162.3
	100	98.8	168.7	169.7	179.9
C	90	91.2	121.3	130.1	101.3
	91	91.5	122.3	129.0	104.6
	92	91.7	123.2	131.3	116.3
	93	93.0	124.5	131.5	126.8
	94	93.5	126.3	132.4	129.3
	95	94.9	127.0	133.8	146.0
	96	95.4	128.7	133.7	137.7
	97	95.3	128.8	133.9	151.0
	98	96.9	131.0	134.2	155.6
	99	97.1	132.8	135.2	176.1
	100	–	–	–	–

A = 3,5-dinitrobenzoic acid/benzoic acid; B = 4'-hydroxyacetanilide/4-aminobenzoic acid;
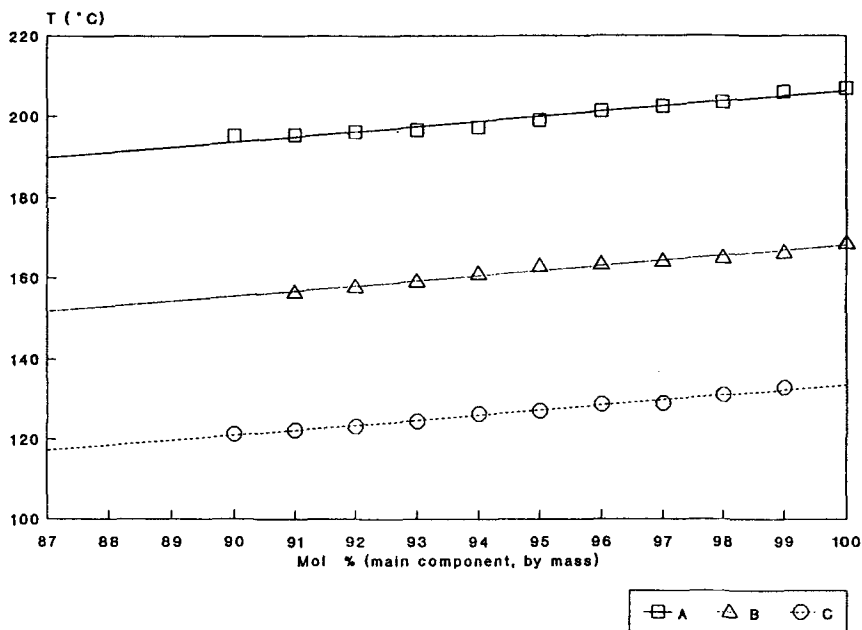C = acetylsalicylic acid/salicylic acid

Fig. 1 Fusion peak onset temperature *vs.* concentration of main component

Conclusion

The excellent fusion peak onset temperature *vs.* mole% (by mass) linear correlations suggest a general procedure for the routine analysis of binary organic mixtures by a dilution (standard addition) method. This procedure has the advantage that complex corrections for non-ideal behaviour are not required and that the composition of an unknown sample can be determined directly from the fusion peak onset temperature *vs.* mole% (by mass) − calibration plot. Further, fusion peak onset temperatures are easy to determine from the DSC profiles, either graphically or via the DSC data analysis software package. These onset temperatures are less effected by weighing errors than enthalpy data and are also less effected by DSC calibration errors and base-line deviations. The problems with this procedure are associated with the mixing technique − the 'in-situ' method leads to weighing inaccuracies and 'bulk-mixing' leads to non-homogeneous mixing. However, a 'line of best fit' approach in the derivation of the calibration profile tends to 'smooth out' these deficiencies.

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Zusammenfassung Es wurde eine DSC-Untersuchung der Zusammensetzung von 3 binären Modellsystemen pharmazeutischer Bedeutung durchgeführt. Gemische bekannter Zusammensetzung für jedes der folgenden Systeme wurden gefertigt und mittels DSC analysiert: 3,5-Dinitrobenzoesäure/ Benzoesäure, Paracetamol/4-Aminobenzoesäure und Acetylsalicylsäure/Salicylsäure. Die durch Anwendung der van't Hoffschen Gleichung erhaltenen entsprechenden Zusammensetzungen wurden mit den entsprechenden theoretischen Werten und den anhand der relevanten DSC-Kurven ermittelten Schmelztemperaturen und Schmelzenthalpien verglichen.

Für jedes dieser Systeme wurde eine lineare Korrelation zwischen theoretischer Zusammensetzung, Schmelztemperatur und Schmelzenthalpie gefunden und es ergab sich, daß die DSC-Untersuchung der Zusammensetzung zur Bestimmung der Reinheit im Bereich 90–95 mol% angewendet werden kann. Dieser Bereich ist besonders in Stabilitätstests von pharmazeutischen Wirkstoffen von Interesse und hat eine reelle Bedeutung bei der Reinheitsprüfung von kommerziellen pharmazeutischen Herstellungen.