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Phase diagram for the mixtures of ibuprofen and stearic acid

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Abstract

The binary mixtures of ibuprofen and stearic acid have been tested on the DSC at a heating rate of 5°C min^{-1}. All temperatures reported here are for endothermic peak temperatures. The heating curves are employed to construct a phase diagram. The resultant phase diagram shows the existence of a compound formed between the two materials and is essentially two simple eutectic systems compressed into one equilibrium diagram. The component in excess melts at a lower temperature than its single entity. There are two eutectic melting points at 42% ibuprofen and 65% ibuprofen. It would seem probable that the ''condensed phase compound'' has the formula AB_2, where A is stearic acid ($C_{18}H_{36}O_2$) and B is ibuprofen ($C_{13}H_{18}O_2$). A relationship between the enthalpy of melting (ΔH_m) and %composition is found. However, the overlapped endothermic peaks pose difficulty in peak integration resulting in a deviation from a typical plot. DSC is a fast, useful, and reliable analytical tool to detect and investigate the eutectic compound in this study.

Keywords: Phase diagram; Ibuprofen; Stearic acid; Differential scanning calorimetry

1. Introduction

In pharmaceutical formulations, the need to mix or blend thoroughly active ingredient(s) with excipients is a must to obtain uniformity of the formulation. Eutectic compounds may form from the mixtures of one active ingredient and another active ingredient(s), from active ingredient(s) and excipient(s), or from excipients themselves. When eutectic compound(s) are formed, the temperature during drug processing must be kept lower than the eutectic temperature to avoid the eutectic melt. An alternative is an addition of an inert diluent such as $MgCO_3$, light MgO, kaolin, bentonite, or starch to prevent liquefaction or to absorb moist mass. On the contrary, drug-excipient(s) melting as a single phase at a specified temperature, i.e. 37°C, is a favourable suppository formulation. In this case, a phase diagram would be of use to select the ideal excipient(s) in such a formula. DSC is a fast and reliable analytical instrument to detect the eutectic compound formed in such systems. There are various sources of information [1–4] regarding phase diagrams for pharmaceutical materials. These papers investigated racemic species and/or enantiomers of drugs. The present study, however, serves as an example on how DSC helps detect a eutectic compound between drug and excipient and how it can be used in condensed phase rule studies.

2. Materials

Ibuprofen, lot No. 1194F, was supplied by Pharmacia & Upjohn. Stearic acid of 99% purity,

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lot No. 01823EQ, was obtained from Aldrich Chemical. For binary mixtures, certain amounts of ibuprofen and stearic acid were weighed and mixed in 5 dram polystyrene vials with the aid of two Burundum® grinding pebbles (cylindrical shape of 0.5 in. × 0.5 in.) per vial. Two vials of these mixtures were placed in a roller-mixing jar (5.75 in. diameter, 1725 rpm, Paul O. Abbe). The mixing jar was run for 10 min, rested for 10 min, and operated for another 10 min. The total mass of each mixture was about 1 g and the percentage of each material in the mixture was calculated based on the actual mass employed.

3. Equipment and procedure

The binary mixtures of ibuprofen and stearic acid were tested on the Perkin Elmer Pyris 1 DSC. This equipment is operated on the power compensation principle and has separate calorimeters for sample and reference materials. A platinum resistance thermometer is used for linear temperature measurement.

Certified indium wire encapsulated in an aluminium crucible (supplied by instrument manufacturer) was used for temperature and heat flow calibration. A crimped aluminium pan and lid without pinhole were used to contain the sample. An empty container of the same type was employed as a reference. Helium of 99% purity at 20 psi was used as a purge gas for all the experiments performed. The heating and/or cooling rates were 5°C min^{-1}. The temperature range investigated was between 30 and 120°C.

In this equipment, an endothermic peak is shown in an upward direction and vice versa for an exothermic event. All materials and the mixtures were performed in triplicate to ensure the repeatability of the experiments.

4. Results and discussion

Due to the diffusion and/or overlapping of peaks in the binary mixtures, unless specified otherwise, the temperatures reported here are the peak temperatures and are the average values from triplicate runs. Ibuprofen alone gives a single sharp endothermic peak at 80.8°C upon heating as seen in Fig. 1. However, ibuprofen stays as a liquid upon cooling to room

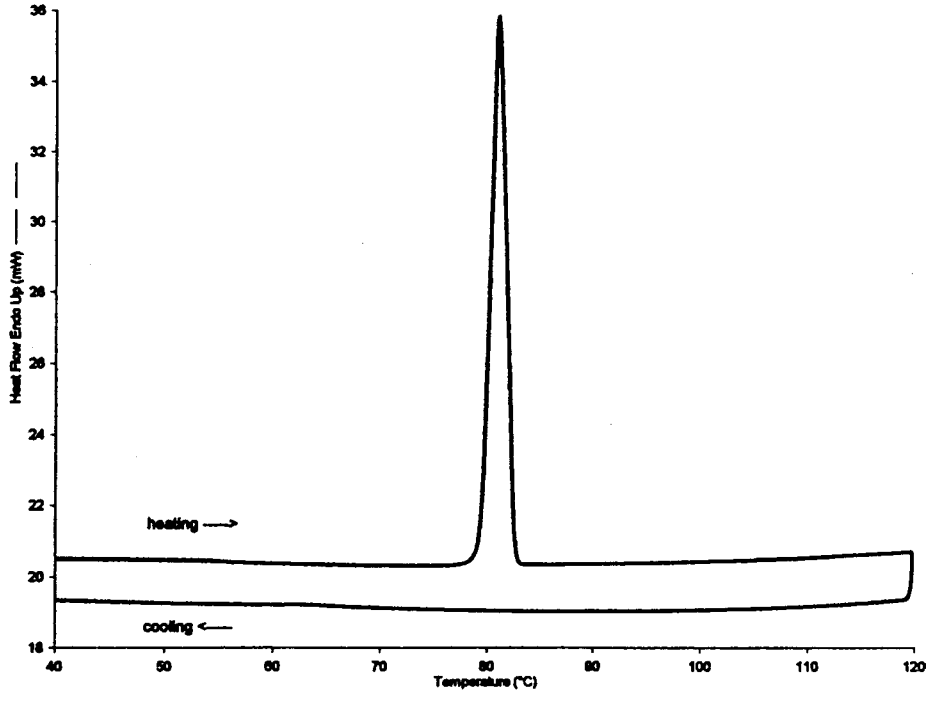

Fig. 1. DSC traces for ibuprofen at the rate of 5°C min^{-1} showing both the heating and cooling step.

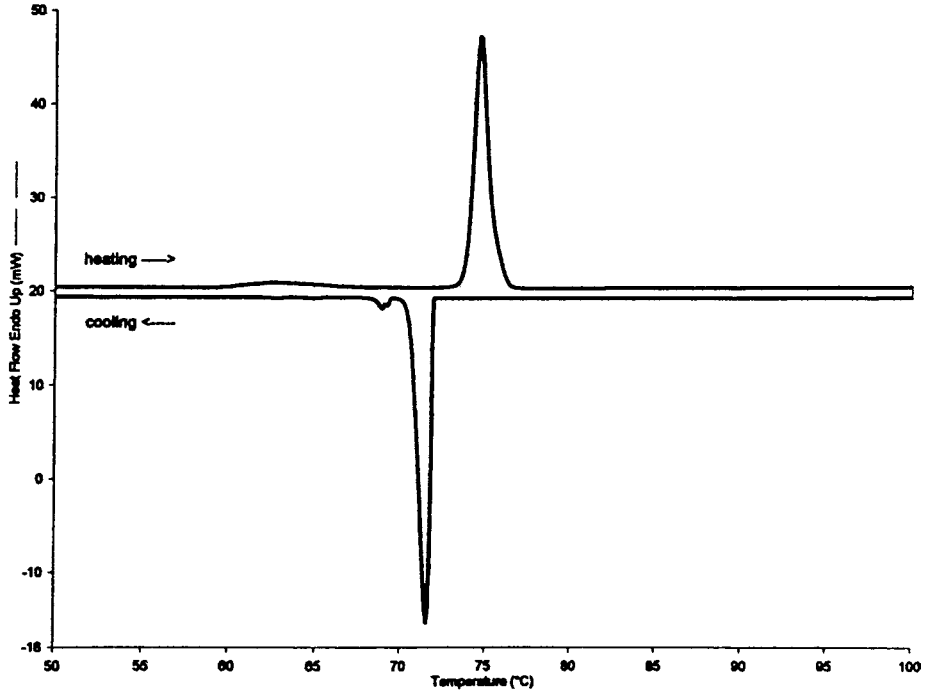

Fig. 2. DSC traces for stearic acid at the rate of 5°C min^{-1} showing both the heating and cooling step.

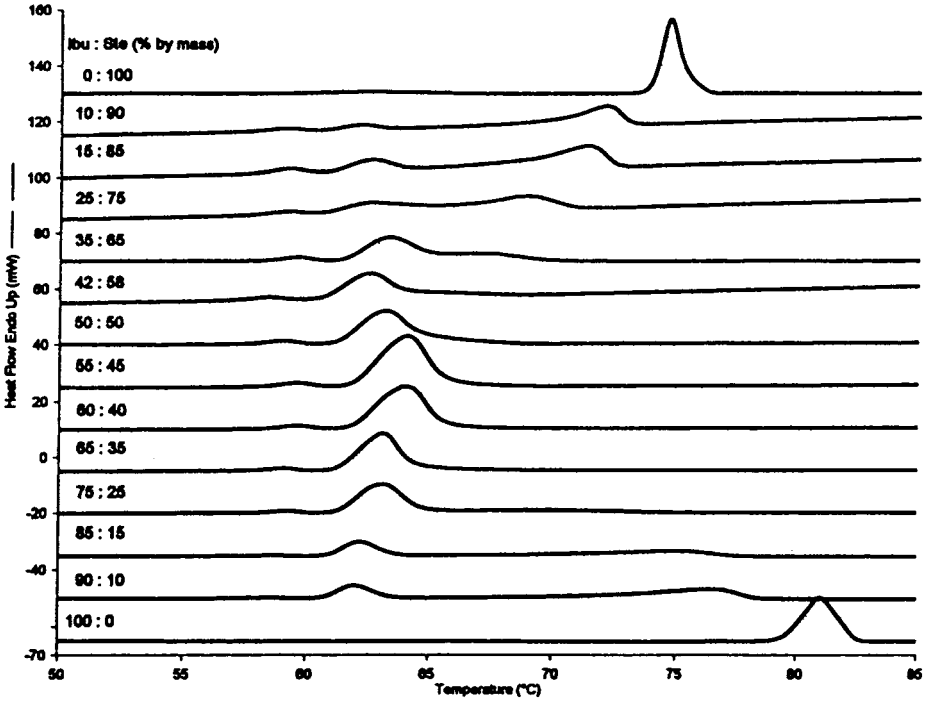

Fig. 3. Superimposed endothermic events for single components and the binary mixtures.

Table 1
Peak temperatures of all endothermic events and enthalpy of melting (ΔH_m) for ibuprofen, stearic acid, and the binary mixtures[a]

Composition (%)		Peak temperature (°C)			Average peak temperature (°C)			ΔH_m (J/g)	Average ΔH_m (J/g)
Ibuprofen	Stearic acid	First	Second	Third	First	Second	Third		
100.0	0.0			81.0			80.8	114.1	114.8
				80.3				114.4	
				81.1				115.9	
89.6	10.4	58.5	62.0	76.4	58.9	62.2	76.4	120.5	121.0
		59.0	62.3	76.1				120.0	
		59.2	62.3	76.6				122.7	
85.0	15.0	58.7	62.2	75.0	59.1	62.4	75.0	124.9	124.1
		58.9	62.1	74.9				123.7	
		59.5	62.8	75.0				123.8	
75.0	25.0	59.2	63.1	69.0	59.3	63.0	69.2	140.7	138.6
		59.1	62.8	69.1				135.1	
		59.5	63.2	69.4				140.0	
65.0	35.0	59.1	63.1		59.2	63.2		151.7	151.1
		59.1	63.0					150.5	
		59.4	63.5					151.2	
60.0	40.0	59.6	64.0		59.3	63.4		156.8	155.1
		58.9	63.0					154.7	
		59.4	63.3					153.8	
55.0	45.0	59.6	64.1		59.2	63.4		166.1	167.1
		58.8	62.9					169.9	
		59.1	63.3					165.2	
49.8	50.2	59.0	63.2		59.1	63.4		175.3	175.4
		59.1	63.1					174.7	
		59.3	64.0					176.1	
42.0	58.0	58.4	62.5		59.3	62.3		171.1	174.0
		57.6	61.7					173.0	
		58.9	62.8					177.9	
35.0	65.0	59.6	63.3	67.0	59.3	62.9	67.0	185.1	188.1
		59.1	62.6	67.1				191.7	
		59.2	62.9	66.9				187.4	
25.0	75.0	59.3	62.7	69.0	59.4	62.7	69.1	184.4	194.6
		59.4	62.7	69.2				199.2	
		59.4	62.7	69.1				200.1	
15.1	84.9	59.3	62.6	71.3	59.3	62.5	71.1	190.1	199.5
		59.3	62.3	70.7				206.0	
		59.5	62.6	71.2				202.0	
10.0	90.0	59.1	62.2	72.0	59.3	62.3	72.0	188.8	201.1
		59.3	62.2	71.9				208.0	
		59.5	62.5	72.1				206.6	
0.0	100.0		62.5	74.6		62.4	74.4	206.1	209.6
			61.9	73.9				214.3	
			62.7	74.8				208.3	

[a] The ΔH values here are the average values given to one decimal point.

temperature or even to −180°C, thus no signal was detected for the ibuprofen at this step. Stearic acid shows signals on both heating and cooling steps. During the heating process, stearic acid gives two well-defined peaks at 62.4 and 74.4°C, while cooled it showed one major exothermic peak at 71.4°C and a various number of small peaks as seen in Fig. 2. This possibly indicates a transformation of stearic acid to various morphological forms during the cooling process.

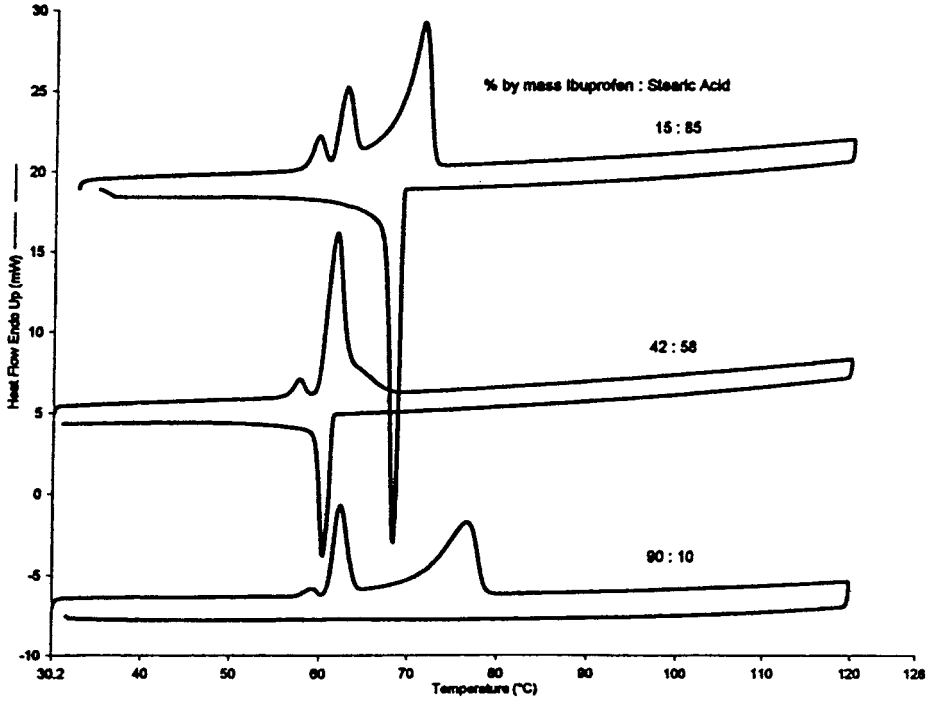

Fig. 4. Superimposed DSC traces for the binary mixtures of 15, 42, and 90% ibuprofen.

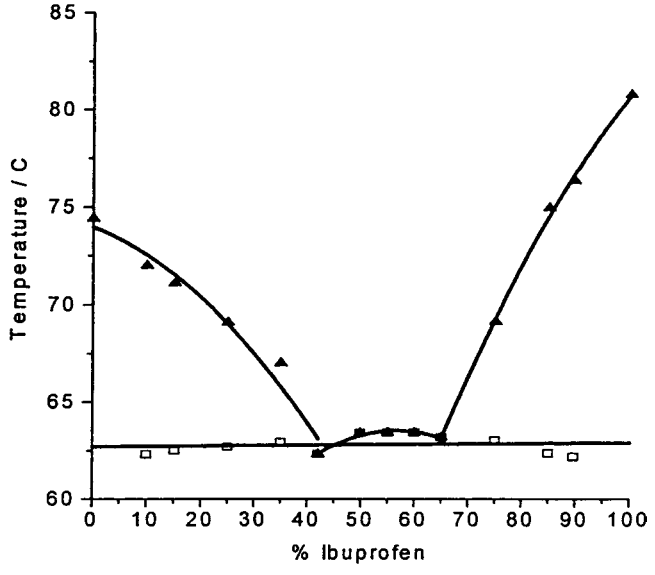

Fig. 5. Phase diagram for the mixtures of ibuprofen and stearic acid.

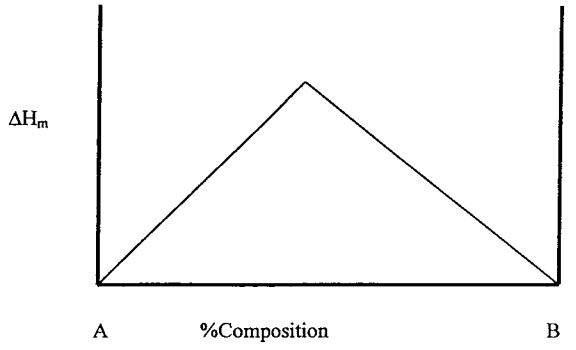

Fig. 6. A typical relationship between the enthalpy of melting (ΔH_m) of the eutectic and %composition.

Only the heating curves of all single components and the binary mixtures were used to construct a phase diagram. Table 1 shows the endothermic peak temperature, ΔH, and their average values for all samples tested. Fig. 3 delineated superimposed endothermic events during heating for these materials. Changes in the melting behaviour with the composition of ibuprofen and stearic acid were investigated leading to the construction of the phase diagram.

The binary mixtures of these materials yield 2–3 endothermic events. The first peak stays approximately at the same temperature (59°C) and this corresponds to the small endothermic peak of stearic acid which is shifted to a few degrees lower than stearic acid per se. The second peak represents the eutectic composition of the binary mixtures. The third peak belongs to either ibuprofen or stearic acid which is melted at a lower temperature compared to its single entity. However, this third peak is absent in certain compositions, i.e. 42–65% ibuprofen in the mixtures. Fig. 4 shows heat flows on both heating and cooling steps for the binary mixtures of 15, 42, and 90% ibuprofen. The phase diagram is constructed from the second and third endothermic peak as seen in Fig. 5.

More information can be extracted from the enthalpy of melting (ΔH_m) and/or recrystallization. Fig. 6 shows the typical relationship of ΔH_m of the eutectic and %composition. A similar pattern is built from the eutectic peak as seen in Fig. 7. A deviation from the "triangle shape" of this figure (compared to Fig. 6) results from the overlapping of the eutectic peak and the component in excess peak. Average ΔH_m values integrated from all endothermic events are plotted against %ibuprofen as seen in Fig. 8. This will show a mirror image if ΔH_m is plotted against %stearic acid. The ΔH of the first peak can also be plotted against %composition as seen in Fig. 9. This possibly indicates the presence of an impurity in stearic acid. In this research, it must also be noted

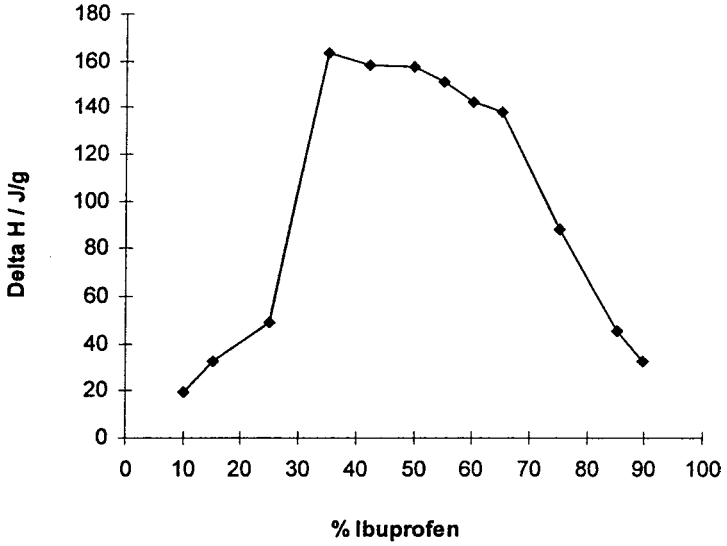

Fig. 7. A relationship between the enthalpy of melting (ΔH_m) of the eutectic and %composition of ibuprofen and stearic acid.

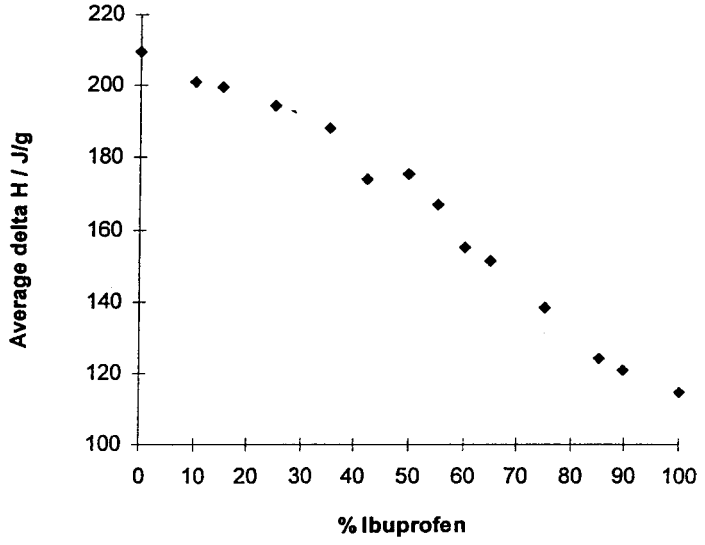

Fig. 8. A plot of ΔH_m for endothermic events vs. %ibuprofen.

that the stearic acid was claimed by the supplier to be 99% pure.

Prausnitz et al. [5] provided a treatment which can be applied to the depression of the melting point in ibuprofen and stearic acid as a colligative property, and where this prediction of two curves intersect on a phase diagram an eutectic might be expected. Without the constraints imposed by fugacity terms, the relationship for the melting point becomes

$$T = \frac{-\Delta H_m/R}{\ln X - (\Delta H_m/RT_m)}$$

where ΔH_m is the enthalpy of melting of the pure compound, T_m the melting point of the pure compound

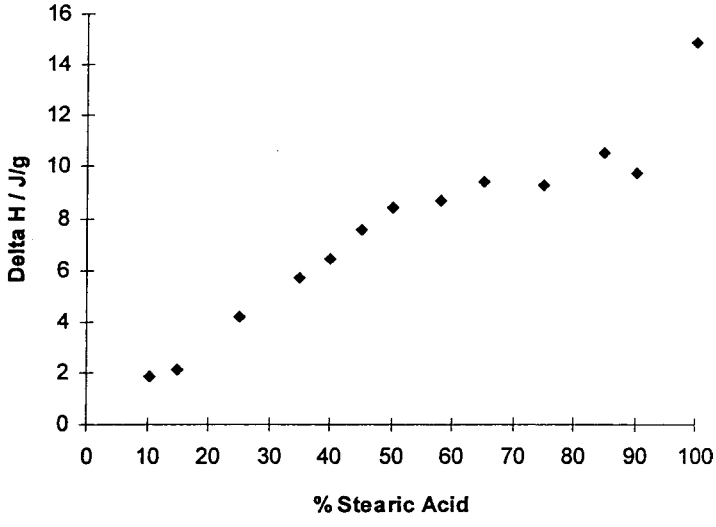

Fig. 9. A plot of ΔH_m for the first endothermic peak vs. %stearic acid.

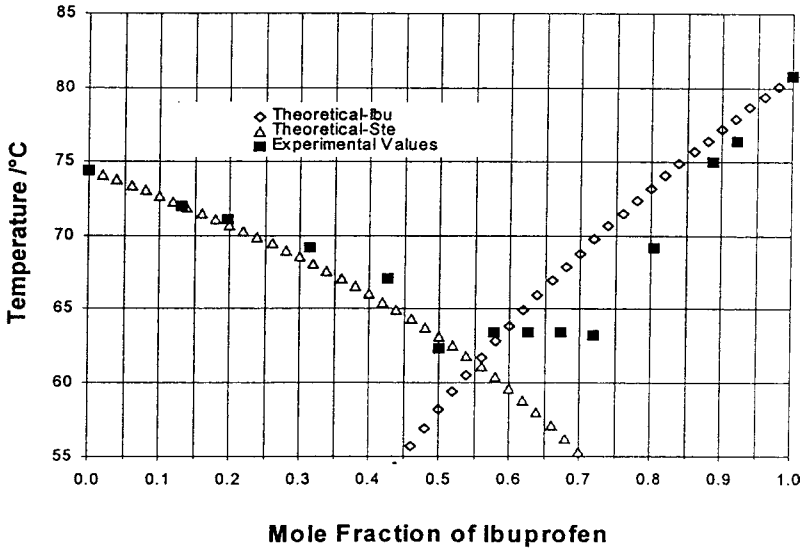

Fig. 10. Superimposed theoretical and experimental phase diagrams of ibuprofen and stearic acid.

in kelvin, T the temperature (variable) in kelvin, R the molar gas constant $= 8.3145\,\mathrm{kJ\,mol^{-1}\,K^{-1}}$, X the mole fraction (from 0 to 1).

A comparison of theoretical and experimental curve for the phase diagram of ibuprofen and stearic acid binary mixtures is shown in Fig. 10. Superficially, the agreement seems reasonable. The presence of the ''almost linear portion'' in the middle of the diagram for the experimental data must be noted. The fact that the experimental depression of the ibuprofen lies below the predicted values while the reverse is true for stearic acid should also be observed. The simplification introduced into the theoretical treatment and the expected departure of the system from ideal behaviour may be due to a large difference in structure between the two components which would possibly lead to some of the divergence noted.

5. Conclusion

Two eutectic melt temperatures (at 62.3 and 63.2°C) are observed for the system ibuprofen and stearic acid at 42 and 65% ibuprofen. The compound formed between these two materials would appear to have the formula AB_2, where A is the molecule of stearic acid and B is the molecule of ibuprofen (40.18% stearic acid and 59.19% ibuprofen). The eutectic point can be discerned in all binary mixtures as the second endothermic peak in the DSC heating curve. DSC proves to be a fast, useful and reliable analytical tool to investigate the eutectic phenomenon. In this investigation, only heating curves yield significant information to construct a phase diagram. However, recrystallization exotherms from the cooling curves can also be used to determine the amount of stearic acid present in the system.

References

[1] S.P. Duddu, A. Khin-Khin, D.J.W. Grant, R. Suryanarayanan, J. Pharm. Sci. 86 (1997) 340.
[2] Z.J. Li, D.J.W. Grant, J. Pharm. Sci. 86 (1997) 1073.
[3] T.R. Kommuru, M.A. Khan, I.K. Reddy, J. Pharm. Sci. 87 (1998) 833.
[4] Z.J. Li, M.T. Zell, E.J. Munson, D.J.W. Grant, J. Pharm. Sci. 88 (1999) 337.
[5] J.M. Prausnitz, R.N. Lichtenthaler, E. Gomes de Azevedo, Molecular Thermodynamics of Fluid-Phase Equilibria, 3rd Edition, Prentice-Hall, Englewood Cliffs, NJ, 1999.