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Utilization of differential scanning calorimetry in the compatibility screening of ibuprofen with the stearate lubricants and construction of phase diagrams

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Summary

Differential Scanning Calorimetry (DSC) was employed to identify and define the interaction between ibuprofen and stearic acid, stearyl alcohol, calcium stearate and magnesium stearate. All stearates were found to form simple eutectics with ibuprofen, and phase diagrams for each system were constructed.

Introduction

During the formulation of new drug candidates or the reformulation of existing products, it is advantageous for the pharmaceutical formulator to have readily available knowledge of any drug–excipient interactions which might affect the stability of the final dosage form. Since tablet formulations typically contain diluents, binders and lubricants, compatibility screening must be considered with selected excipients from each class and in a ratio which approximates the proportions expected in the final dosage form.

In a series of articles, Gluzman et al. (1954, 1956a, 1956b, 1958) determined that typically solid–solid interactions result in a lowering of the melting point or points of the substances being investigated. This characteristic lowering of the melting

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point lends itself to the study of solid–solid interactions with thermal analysis — DTA or DSC; thus, the recent widespread acceptance of this method as a tool for excipient screening during preformulation studies is not unanticipated. However, the interpretation of the thermal data is not always straightforward; i.e. when two substances are mixed, the purity of each may be reduced and generally slightly lower melting points result. Nevertheless, if the solid–solid interaction is extremely weak or non-existent, the reduction of the melting point is usually inconsequential. On the other hand, any large shift in melting point signifies that a strong solid–solid interaction has occurred. The presence of a strong solid–solid interaction, nevertheless, does not necessarily indicate that stability problems will result. Nonetheless, utilizing the DSC for compatibility screening does provide a method for selecting the most favorable direction to pursue in the initial formulation development stages.

Since historically the stearates have been shown to influence the stability of selected active ingredients (Jacobson et al., 1969; Lee et al., 1977), the current study will examine the compatibility of ibuprofen with a variety of stearates and describe the use of a DuPont 910 DSC in the elucidation of ibuprofen-stearate phase diagrams.

Experimental

Supplies of ibuprofen USP, magnesium stearate NF Powder Food Grade, calcium stearate NF Impalpable Powder Food Grade, stearic acid NF Powder Food Grade, and stearyl alcohol NF as received from the manufacturer were employed in this study.

Ibuprofen and one of the aforementioned lubricants were weighed out, sieved through a 30-mesh screen, and then the two ingredients were mixed for 3 min in a Hobart mixer. From this final mixture, approximately 5–15 mg of powder was weighed directly into a DSC sample pan and subjeted to a heat flux over a temperature range of 30–110 °C at a rate of 1.5 °C/min under an atmosphere of flowing dry nitrogen. The temperature and corresponding heat flux data were sampled at a rate of 0.6 s per point and permanently stored on a floppy disk via the DuPont 1090 data station. Irrespective of the sample being investigated, all DSC runs were performed precisely as described above, and the following calorimetric determinations were performed: (a) the active drug substance and the lubricants individually; and (b) the following mixtures of the active drug and lubricant immediately after mixing, respectively: 99.9/0.1, 99.5/0.5, 99.0/1.0, 95.0/5.0, 90.0/10.0, 80.0/20.0, 70.0/30.0, 60.0/40.0, 50.0/50.0, 40.0/60.0, 30.0/70.0, 20.0/80.0, 10.0/90.0.

Results and Discussion

Figs. 1–4 illustrate selected thermograms of the various systems investigated. Trace 1 in these figures corresponds to the thermogram of pure ibuprofen. A single

Fig. 1.

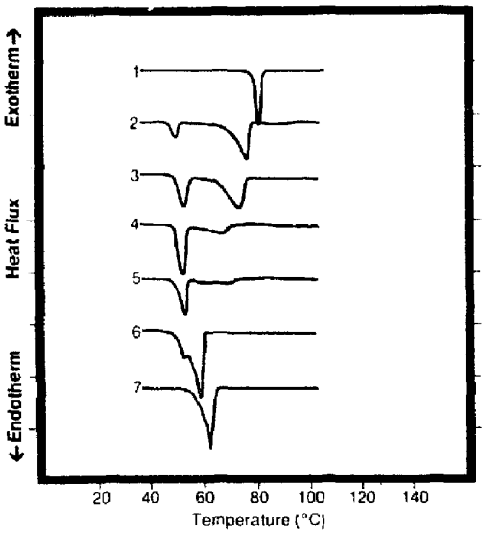

Fig. 2.

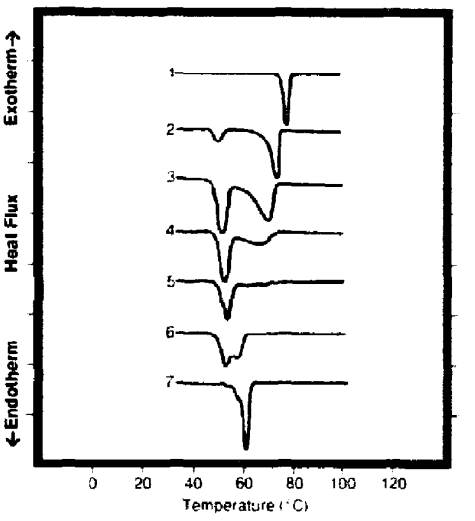

Fig. 1. Thermograms of the ibuprofen–stearic acid System. Key: (1) ibuprofen USP; (2) = 90% ibuprofen + 10% stearic acid; (3) = 80% ibuprofen + 20% stearic acid; (4) = 70% ibuprofen + 30% stearic acid; (5) = 60% ibuprofen + 40% stearic acid; (6) = 10% ibuprofen + 90% stearic acid; (7) = stearic acid.

Fig. 2. Thermograms of the ibuprofen–stearyl alcohol system. Key: (1) ibuprofen USP; (2) 90% ibuprofen + 10% stearyl alcohol; (3) 80% ibuprofen + 20% stearyl alcohol; (4) 70% ibuprofen + 30% stearyl alcohol; (5) 60% ibuprofen + 40% stearyl alcohol; (6) 20% ibuprofen + 80% stearyl alcohol; (7) stearyl alcohol.

Fig. 3.

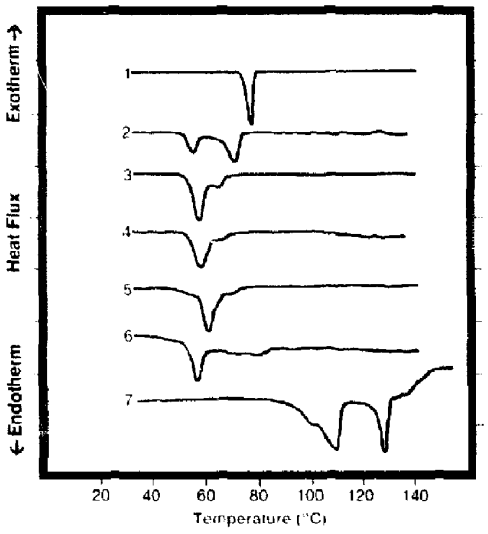

Fig. 4.

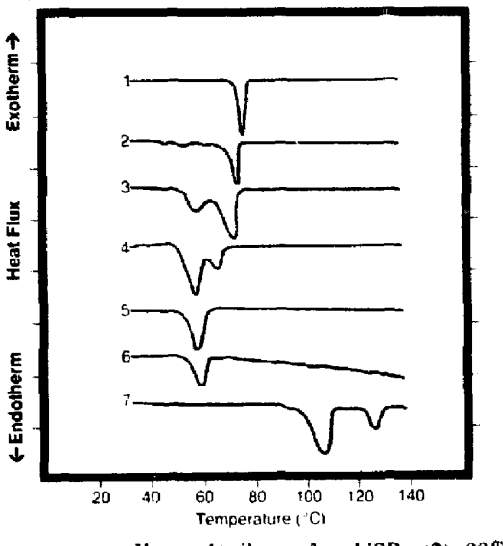

Fig. 3. Thermograms of the ibuprofen–calcium stearate system. Key: (1) ibuprofen USP; (2) 90% ibuprofen + 10% calcium stearate; (3) 80% ibuprofen + 20% calcium stearate; (4) 70% ibuprofen + 30% calcium stearate; (5) 50% ibuprofen + 50% calcium stearate; (6) 30% ibuprofen + 70% calcium stearate; (7) calcium stearate.

Fig. 4. Thermograms of the ibuprofen–magnesium stearate system Key: (1) ibuprofen USP; (2) 95% ibuprofen + 5% magnesium stearate; (3) 90% ibuprofen + 10% magnesium stearate; (4) 80% ibuprofen + 20% magnesium stearate; (5) 70% ibuprofen + 30% magnesium stearate; (6) 30% ibuprofen + 70% magnesium stearate; (7) magnesium stearate.

endothermic peak is observed around 77°C which represents ibuprofen's solid-to-liquid phase transition. Trace 7 represents the thermograms of the pure lubricants investigated: Fig. 1—stearic acid; Fig. 2—stearyl alcohol; Fig. 3—calcium stearate; and Fig. 4—magnesium stearate. Stearic acid and stearyl alcohol, like ibuprofen, have a single phase transition (fusion) in the region of 59°C (Figs. 1 and 2). Magnesium stearate and calcium stearate, on the other hand, display two distinct endothermic phase transitions. The first endothermic peak corresponds to the fusion of the calcium or magnesium stearate, while the second endothermic peak is due to the presence of the corresponding palmitate salt impurity.

Since the principles applied in analyzing these thermograms can be reciprocated to the other ibuprofen–lubricant systems investigated, only one ibuprofen–lubricant system (ibuprofen–stearic acid) will be described in detail. In Fig. 1, Traces 2, 3, 4, 5 and 6 reveal the appearance of two endothermic peaks. The first peak around 49°C was initially believed to be the melting of either a compound formation between ibuprofen and stearic acid or a degradation by-product of this interaction because of the loss of stearic acid's endotherm around 59°C. However, the continual shift of ibuprofen's melting endotherm towards this lower peak as the weight percent of stearic acid was increased indicates ibuprofen and stearic acid, when mixed, form a simple eutectic mixture. Evidence further supporting this opinion is the eutectic's sharp melting endotherm and its invariant nature. The second endothermic peak is the result of fusion of either ibuprofen or stearic acid.

Ideally, the general method employed in the construction of phase diagrams utilizes data from cooling curves. However, since a cooling or refrigerant system was not available to cool the liquid mixtures down at regulated rates, heating curves were employed. Therefore, the phase diagrams were constructed for each ibuprofen–lubricant system by plotting the temperature of fusion of the two components versus the weight fraction of the lubricants as shown in Figs. 5–8. In Fig. 5, the different regions in equilibrium are labeled: L signifies liquid and Ib or StAc signifies pure solid ibuprofen or pure solid stearic acid. While Figs. 5–8 denote phase separations

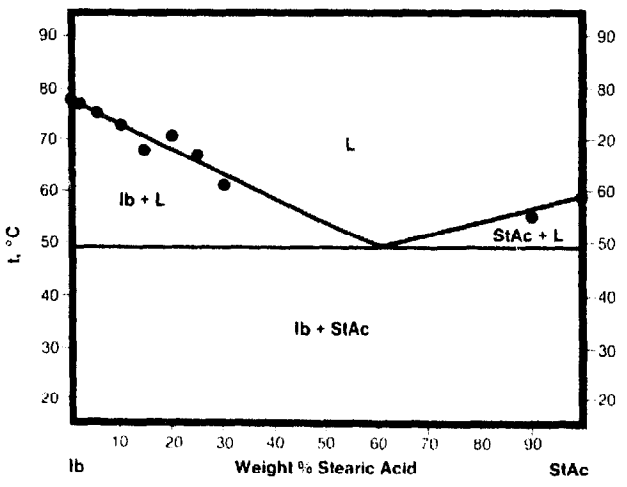

Fig. 5. Phase diagram of the ibuprofen–stearic acid system.

by a straight line extrapolation of the data, theoretically the line should be curved. This curvature is the result of the freezing-point depression or colligative properties of the system and can be mathematically expressed by:

$$\ln X_i = -\frac{\Delta H_{fusion,i}}{R}\left(\frac{1}{T} - \frac{1}{T_{m,i}}\right) \quad (1)$$

where X_i = the mole fraction of the i component, $\Delta H_{fusion,i}$ = the heat of the fusion of the i component, T = the temperature of the system expressed in degrees Kelvin, and $T_{m,i}$ = the melting point of the i^{th}, pure compound in degrees Kelvin. Nonetheless, Eqn. 1 was derived for ideal liquid systems. Therefore, since the objective of this study was not the investigation of ideallity or lack thereof, least-squares lines were fitted to the data.

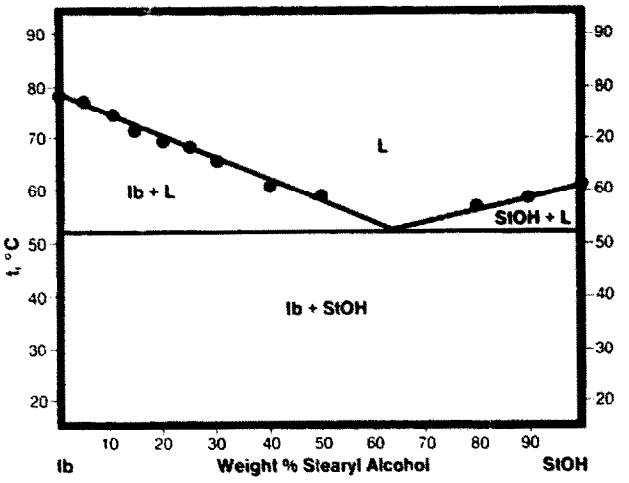

Fig. 6. Phase diagram of the ibuprofen–stearyl alcohol system.

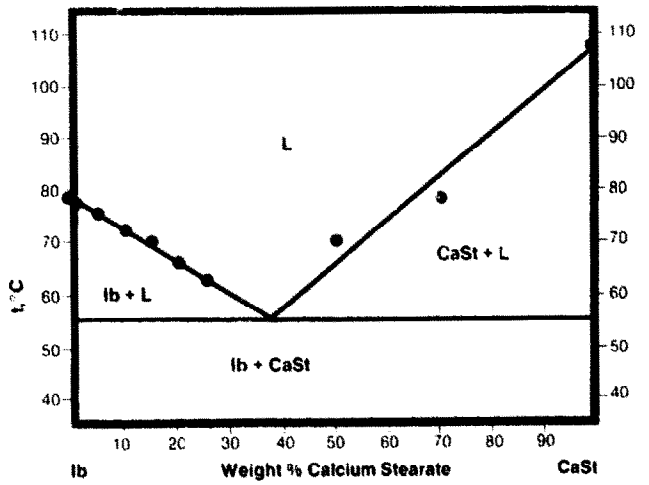

Fig. 7. Phase diagram of the ibuprofen–calcium stearate system.

Also, close inspection of all the phase diagrams reveals a variability in the number of data points included (range 8–12 points) while the experimental procedure called for 15 runs. The discrepancy in the number of data points is due to overlapping peaks and the resulting additivity of the combined profiles, thus complicating the interpretation and location of the true maximum deflection in each component's fusion peak. As a result, these data were excluded from the phase diagram. The data so excluded primarily occurred as the amount of stearic acid approaches the eutectic point from both phase directions. This required an extrapolation of the data for each phase separation line to a point of intersection for the location of the eutectic point. The eutectic temperature for this system is then 49 °C (this temperature corresponds to the maximum deflection in the thermogram), and the eutectic composition is 56 weight-percent stearic acid. The numerical information from the other phase diagrams is summarized in Table 1.

These results demonstrate the utility of differential scanning calorimetry as a method of ascertaining excipient compatibility or incompatibility and a means of constructing phase diagrams when simple eutectics are formed. While the stearates

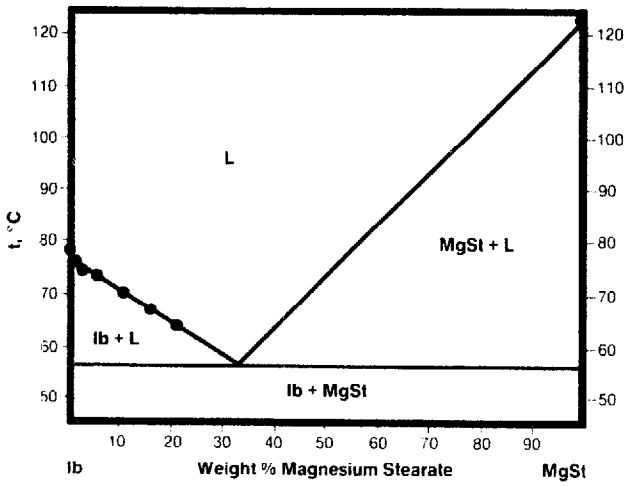

Fig. 8. Phase diagram of the ibuprofen–magnesium stearate system.

TABLE 1

NUMERICAL SUMMARY OF THE LUBRICANT-IBUPROFEN PHASE DIAGRAM SYSTEMS

System	Eutectic point [a]	Eutectic melting point [b] (°C)
Ibuprofen–stearic acid	56.0	49
Ibuprofen–stearyl alcohol	64.2	51
Ibuprofen–calcium stearate	37.5	55
Ibuprofen–magnesium stearate	32.6	56

[a] Expressed in weight-% of lubricant.

[b] This is the temperature of maximum deflection in the thermograms. Melting, as indicated by deviation of the baseline, started in all systems 3 °C lower than the temperature stated above.

have been shown to be incompatible with ibuprofen by forming simple eutectics, a classical stability program needs to be followed to determine if chemical instability of ibuprofen results from these interactions.

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