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COMPOUND FORMATION IN PHENOBARBITONE–UREA SYSTEMS

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SUMMARY

Physical and fused mixtures of phenobarbitone and urea have been studied using differential thermal analysis. The physical mixtures show, in addition to the eutectic and liquidus endotherms, a third endotherm which is interpreted as the existence of a weak 1 : 2 phenobarbitone–urea compound. There is further evidence for this in the fused mixtures and changes in infra-red spectra are consistent with this theory.

INTRODUCTION

Over the past 20 years, an extensive literature has been built up on drug–excipient binary systems. Amongst these reports, the phenobarbitone–urea phase diagram has been published twice using different experimental methods. Agrawal et al. (1973) used a cooling curve technique on fused mixtures and found a simple eutectic system with eutectic point at 62.5% phenobarbitone and 106°C. El-Banna et al. (1974) used differential thermal analysis (DTA) for their study. They also found a simple eutectic system but with eutectic point at 52% phenobarbitone and 112°C. In addition, they found some evidence of solid solution formation at 90% phenobarbitone.

It is interesting in view of such differences to know which data are the more reliable. It was decided to study the phenobarbitone–urea system using DTA with both physical and fused mixtures, and to use smaller concentration jumps than in the published work.

MATERIALS AND METHODS

Phenobarbitone B.P. (May and Baker, Lot W1) and urea B.P. (Macarthys, Lot H6201) were used as received, the urea being stored in a desiccator.

DTA thermograms were obtained using a Stanton Redcroft Model 671B instrument and BD9 recorder. The samples, weighing 7–8 mg, were placed in open aluminium crucibles in static air. Alumina was used as reference and heating was at 10°C/min.

Normally, approximately 5% concentration intervals were used, but were reduced to about 1% for areas of particular interest.

Physical mixtures were prepared by grinding together appropriate quantities of phenobarbitone and urea in a glass mortar. Checks were made that this process did not alter the polymorphic form of phenobarbitone.

Fused mixtures were made by heating the materials in a porcelain crucible until melted and then allowing them to cool. From about 60% phenobarbitone upwards a vitreous state was formed which was powdered in a glass mortar for use. Checks were made that fusing time and temperature did not affect the thermogram obtained.

Infra-red spectra were obtained using an Infrascan (Hilger and Watts) using polystyrene to calibrate wavelength. Both physical and fused systems were compressed with KBr in the ratio of about 150 parts KBr to 1 part sample.

RESULTS AND DISCUSSION

The phase diagram for physical mixtures (Fig. 1) was constructed using the extrapolated onset temperature (T_{onset}) of the first endotherm and the peak temperature (T_{peak}) for each subsequent endotherm on the thermogram. The extrapolated onset temperature was chosen as a clearly defined point, particularly useful in systems where the endotherms tend to overlap and merge. With such thermograms, determination of all peak temperatures becomes difficult or impossible. The pure phenobarbitone and urea gave T_{onset} values of 177°C and 134°C, respectively, but the T_{peak} figures were used on the phase diagram to correspond with the T_{peak} data of the mixtures. Simple eutectic systems would be expected to give two endotherms corresponding to the eutectic temperature and the liquidus temperature. All above the 20% phenobarbitone mixture showed at least 3 endotherms (Fig. 2). The lowest temperature endotherm gave a constant T_{onset}, corre-

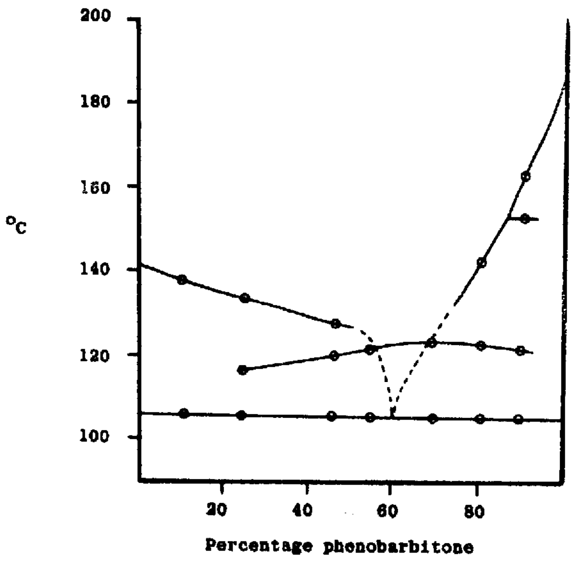

Fig. 1. Phase diagram of phenobarbitone–urea system determined on physical mixtures.

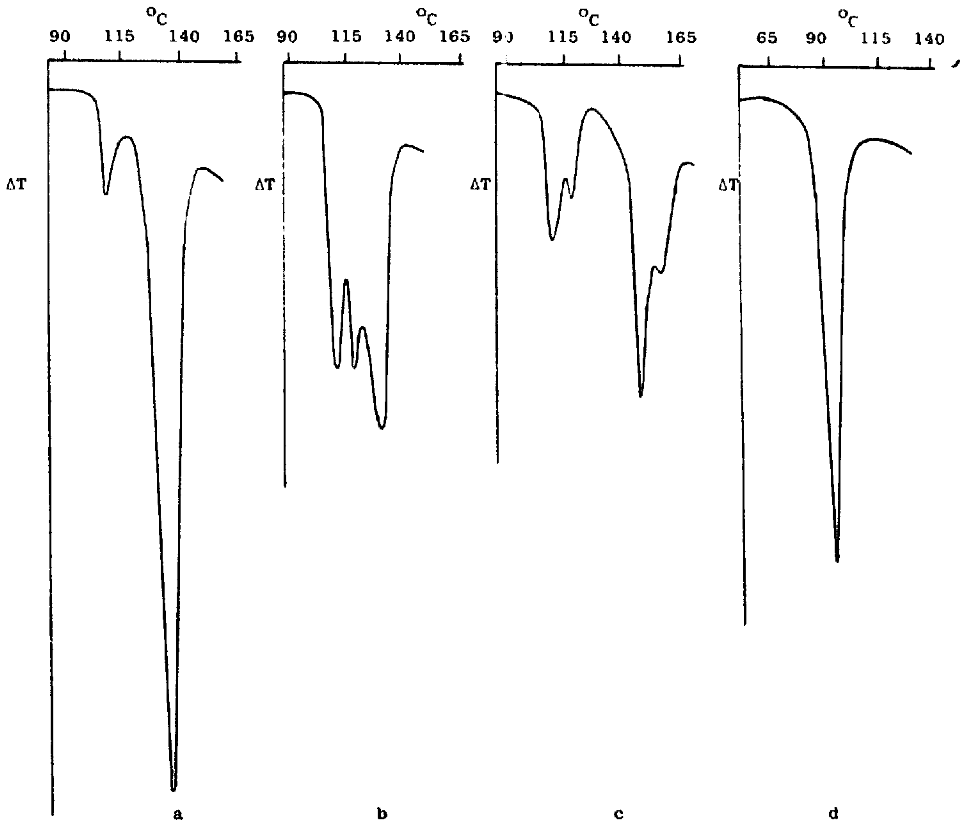

Fig. 2. Thermograms of phenobarbitone–urea mixtures. (a) 10% phenobarbitone, physical mixture; (b) 40% phenobarbitone, physical mixture; (c) 90% phenobarbitone, physical mixture; (d) 61% phenobarbitone, fused mixture.

sponding to the eutectic temperature, at 105°C. The highest temperature endotherm gave a pattern of change in T_{peak} consistent with it being the liquidus temperature. The T_{peak} for the middle endotherm increased to a maximum in the region of 60–70% phenobarbitone and then decreased, over a temperature range 116–122–119°C. There was a corresponding increase in the height of this endotherm and between 55 and 75% phenobarbitone there was a single endotherm with no evidence of a separate liquidus endotherm. From the shape of the phase diagram, this central peak is taken to indicate that an unstable complex is being formed between phenobarbitone and urea. If such a compound is formed, it should be possible to gain further evidence for its existence and to identify it.

If a compound is being formed, the height of the central endotherm relative to the outer endotherms should vary, reaching a maximum or minimum at the composition of the compound. Such a technique has limited accuracy because it does not take into account changes in the thermal properties of the materials and also relies on the extrapolation of the baseline. With DTA, the area under the endotherm is semi-quantitatively related to the quantity of material melting, but could not be used because, with these thermograms, the peaks overlapped. Fig. 3, therefore, shows the relative changes in peak

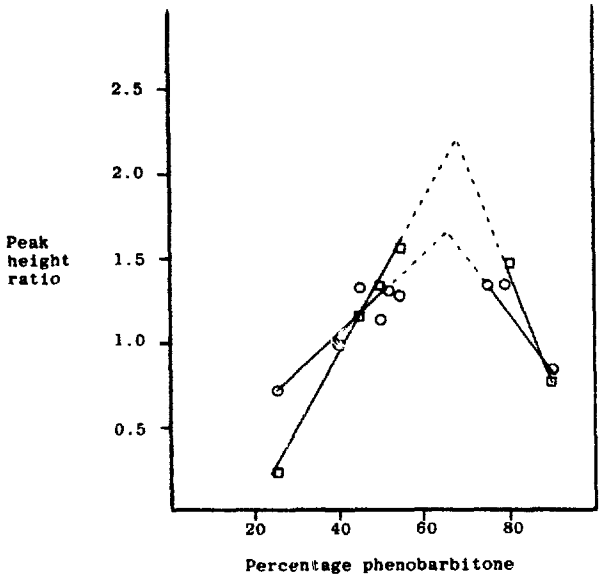

Fig. 3. Endotherm height ratios obtained from thermograms. □, ratio of central endotherm to first endotherm; ○, ratio of central endotherm to third endotherm (or fourth endotherm at 90% phenobarbitone).

height and indicates that the compound is present to the greatest extent in the region of 65% phenobarbitone. This agrees with the phase diagram and with stoichiometry because 65.9% phenobarbitone corresponds to a 1 : 2 phenobarbitone–urea molecular ratio.

Thermograms of mixtures between 87 and 95% phenobarbitone show a fourth endotherm (see Fig. 2c) which has a constant T_{peak} at 152.5°C and shows as a horizontal line in Fig. 1. These compositions do not correspond to a molecular ratio and the peak is

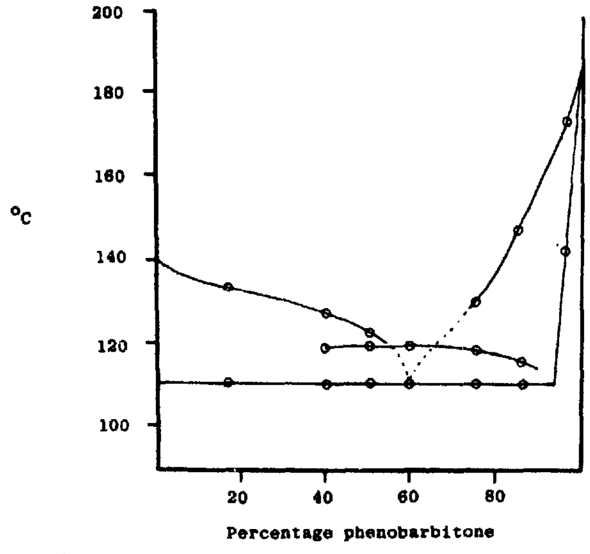

Fig. 4. Phase diagram of phenobarbitone–urea system determined on fused mixtures.

therefore unlikely to indicate the presence of a second compound. The temperature is close to the melting point of phenobarbitone polymorphic form – Form VII as classified by Mesley et al. (1968). Having shown that no polymorphic changes occur in pure phenobarbitone during preparation of samples, it is difficult to derive a mechanism where such a polymorph would be formed in the presence of a small quantity of urea. The significance of this part of the diagram is, therefore, not known.

Thermograms of fused systems generally show a single broad endotherm. The phase diagram (Fig. 4) shows the eutectic temperature at 111°C and normal liquidus lines except in the 55–70% phenobarbitone range. From 40–55% and 70–85% phenobarbitone there is a second peak corresponding to the compound. In the range 55–70% phenobarbitone, however, there is a single peak only (see Fig. 2d). The change in T_{peak} over this concentration range suggests a peritectic system as was found with the physical mixtures. Above 90% phenobarbitone the eutectic temperature rises, indicating the formation of a solid solution. Some of the physical mixtures, after obtaining the thermogram, were cooled rapidly and re-run as fused samples. They did not differ from the corresponding fused samples.

The difference in eutectic temperature between the two methods used may be due in part to the difficulty in measuring T_{onset} for the fused systems. Using T_{peak}, the physical mixtures also show the eutectic temperature to be 111°C. The liquidus lines, however, are virtually superimposable. Extrapolation of the liquidus lines on both phase diagrams indicates a eutectic composition of about 60% phenobarbitone, in good agreement with Agrawal et al. (1973). The presence of the solid solution is in general agreement with El Banna et al. (1974). Neither of these groups of workers reported evidence for a compound. From the published data, it appears that El Banna et al. did not obtain thermograms between 60 and 80% phenobarbitone. This and their use of fused systems make it unlikely that they would detect the presence of the compound. Agrawal et al. used a relatively insensitive technique.

It is reasonable to expect the formation of a 1 : 2 phenobarbitone–urea compound. The barbituric acid nucleus has 5 possible sites for hydrogen bonding, whilst urea has 3. One or two molecules of urea can, therefore, be placed around the barbituric acid nucleus. Thus the possibility exists for 1 : 1 and 1 : 2 phenobarbitone–urea compounds. Courtauld atomic models show phenobarbitone to be a rigid molecule and that two urea molecules can be positioned, one above and one below the barbituric acid nucleus, in a position to form hydrogen bonds. Evidence for such bonding would be expected in the I.R. spectra.

Chang et al. (1975) have studied phenobarbitone and its complex formation with PEG 4000 and were able to allocate some absorption bands in both the N–H and C=O regions of the spectrum. The band at 3310 cm^{-1} is identified as free N–H, not involved in intramolecular hydrogen bonding, whilst bands at 3090 and 3220 cm^{-1} are associated with intramolecular hydrogen bonding. In the present work the 3310 cm^{-1} band is eliminated in mixtures containing 60 and 70% phenobarbitone, whilst the 3090 and 3220 cm^{-1} bands move to a higher frequency. This latter is, according to Chang et al. (1975), consistent with intermolecular as opposed to intramolecular hydrogen bonding. They also allocated the 1780 cm^{-1} band as 2, –C=O stretch and the 1710 cm^{-1} band as 2, 4, 6, –C=O symmetric stretching in phase. Our spectra show the 1780 cm^{-1} band to be eliminated at 60 and 70% phenobarbitone, presumably because the C=O is no longer free with two hydrogen bonds to it. The 1710 cm^{-1} band moves to a lower frequency, also consistent with hydrogen bond formation by all 3 carbonyl groups. The 1680–1670 cm^{-1} bands of phenobarbitone discussed by Chang et al. (1975) are masked by the urea carbonyl absorption in the present work.

The occurrence and extent of these changes in the I.R. spectra vary with composition, reaching their maximum with the 60 and 70% mixtures. Thus the I.R. spectra confirm the formation of the 1 : 2 phenobarbitone–urea compound indicated by the DTA studies.

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