International Journal of Pharmaceutics, 5 (1980) 109–116

PHASES IN THE PARACETAMOL–PHENAZONE SYSTEM

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(Received October 29th, 1979)
(Revised version received January 12th, 1980)
(Accepted January 29th, 1980)

SUMMARY

The phase diagram of the paracetamol–phenazone system has been determined by differential thermal analysis with the aid of hot-stage microscopy. As paracetamol (m.p. 169.5°C) is doped with phenazone (m.p. 111°C), three endotherms are observed up to 40 mole % phenazone. One endotherm represents the depressed melting point of impure paracetamol and its temperature varies inversely with the concentration of phenazone; another endotherm is observed at 107°C and represents the decomposition of a 1 : 1 complex between paracetamol and phenazone; the third endotherm is that of the eutectic and occurs at 83°C. For fused mixtures containing between about 40 and 70 mole % phenazone, two endotherms are observed, one at 107°C due to the melting of the complex, and one at 83°C representing the eutectic. At the eutectic composition, 76 mole % phenazone (24 mole % paracetamol), only one endotherm at 83°C is present. Above 76 mole % two endotherms are again observed, viz. that of the eutectic at 83°C and that representing the melting of doped phenazone. The temperature of the latter endotherm increases as the composition approaches pure phenazone.

Physical mixtures of phenazone and paracetamol give behaviour similar to that of fused mixtures, but the eutectic occurs at 70 mole % phenazone (30 mole % paracetamol) and, for compositions containing up to 50 mole % phenazone, an exotherm is observed at 90°C which is ascribed to the formation of the 1 : 1 complex in the melt.

INTRODUCTION

Phenazone (antipyrine) forms complexes with many compounds, particularly phenols (e.g. Kremann and Haas, 1919; Cagnoli, 1958; Krupatkin and Medvedeva, 1964). Simi-

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larly, paracetamol (reviewed by Fairbrother, 1974) forms complexes with compounds containing hydroxyl groups, such as chloral (Hinsberg, 1917) and possibly sorbitol (Sterwin, 1962; Winternitz, 1965) and with compounds containing amino groups, such as caffeine and theophilline (Chow and Repta, 1972). The complexes of phenazone and paracetamol appear to involve hydrogen bonding.

The 1 : 1 complex that can be formed between paracetamol (p-acetamidophenol, p-hydroxyacetanilide, acetaminophen) and phenazone has been patented (Ridgway and Johnson, 1970) for its analgesic and antipyretic properties. In a spectroscopic study of the nature of the complex Dearden (1972) has shown that it is stabilized by hydrogen bonding involving both the –NH and –OH groups of paracetamol and the carbonyl groups of phenazone but not the carbonyl group of paracetamol. The present communication reports the changes which take place and the phase diagram obtained, when the complex is formed by fusion of paracetamol and phenazone and decomposes on further heating. This system provides a good example of the use of differential thermal analysis for studying interactions between drugs.

MATERIALS AND METHODS

Materials

Paracetamol was B.P. grade purchased from the Boots Company Ltd. Phenazone, not less than 99% pure, was purchased from B.D.H. Laboratories Ltd. The purity of the materials was checked by means of a Perkin Elmer DSC-2 differential scanning calorimeter and found to be better than 99.5%, as evidenced by analysis of the very sharp, well-defined melting transitions. Fig. 1 shows the DTA peaks of paracetamol (A) and of phenazone (Z).

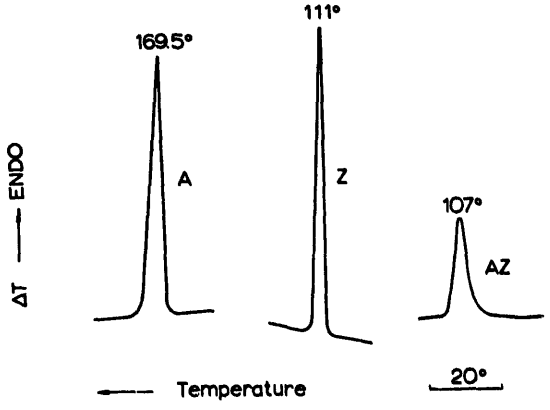

Fig. 1. DTA thermograms of: A, paracetamol; Z, phenazone; AZ, 1 : 1 complex between paracetamol and phenazone.

Methods

Preparation of mixtures

Physical mixtures of paracetamol and phenazone were prepared by grinding the components by hand in an agate mortar. This procedure ensured that the minimum amount of energy was imparted to the solid phases during the process of intimate mixing.

Each fused-cooled mixture was prepared by heating a sample of the corresponding physical mixture in a small test tube in an oil bath to a temperature 2°C above that of complete fusion, stirring for a few seconds, then pouring onto a glass Petri dish at room temperature and finally grinding the solidified cake by hand in an agate mortar.

The 1 : 1 complex (m.p. 107°C) was prepared from an equimolar physical mixture either by the process of fusion followed by cooling just described or by crystallisation from an aqueous solution. After two consecutive crystallisations from water the DTA of the complex (AZ in Fig. 1) showed a significantly broader peak than for paracetamol (A) or phenazone (Z), which suggests that the complex is somewhat unstable near its melting point.

Differential thermal analysis (DTA)

Eight mg of ground sample was heated at a rate of 5°C per min from room temperature to 210°C in a Stanton–Redcroft model 671 differential thermal analyser coupled to a Servoscribe two-channel potentiometric recorder. Static air was the gas phase and alumina was employed as the reference material.

The data were confirmed by means of a DuPont Model 900 apparatus using capillary melting point tubes, a heating rate of 15°C per min, glass beads as the reference material and static air as the gas phase.

Each instrument was calibrated using highly purified benzoic acid (m.p. 122°C).

Hot stage microscopy (HSM)

A fraction of a mg of ground sample was placed between a microscope slide and cover slip in a Köfler hot stage microscope. The heating rate was 5°C per min from room temperature to 70°C and thereafter 1°C per min until the sample had melted completely. This technique provided valuable complementary evidence for DTA but yielded little additional information. Since the sample for microscopy was so small and appeared highly magnified, individual crystals of two components could be seen and these melted above the range of the DTA transitions. Thus, whereas DTA represents the statistical mean behaviour, HSM shows transitory effects which DTA does not record.

RESULTS AND DISCUSSION

DTA of pure paracetamol (A in Fig. 1) or of pure phenazone (Z in Fig. 1) gave a sharp endothermic peak at 169.5°C (A) or at 111°C (Z), respectively, and HSM confirmed these data.

Physical mixtures of paracetamol and phenazone will now be considered in detail. All showed an endotherm at 83°C (a throughout Fig. 2). This corresponds to the eutectic temperature, since HSM showed fusion of both components at 83°C. This transition was that of lowest temperature.

Physical mixtures containing 5–50 mole % phenazone gave an exotherm at 90°C (b shown at 20 and 40 mole % phenazone in Fig. 2). This peak could either result from an exothermic chemical reaction in the liquid state or from a release of crystal energy, such as lattice strain, in the solid state. The latter suggestion is unlikely in view of the fact that little energy was imparted to the samples on grinding and that release of crystal energy, if it occurred, would not be restricted to 5–50 mole % phenazone. The former possibility is consistent with the formation of a 1 : 1 complex by an exothermic chemical reaction in the liquid state. This interpretation is supported by the fact that the area of the exothermic peak increases progressively from 5 to 50 mole % phenazone, being difficult to discern at less than 5 mole % phenazone and greatest near to the equimolar composition. The endotherm b was not detected beyond 50 mole % phenazone, presumably because it is so broad and weak (Fig. 2) that DTA was unable to detect it as endotherm a grew larger on approaching the eutectic composition (cf. the DTA thermograms at 40 and 60 mole % Z in Fig. 2).

Physical mixtures containing 2–60 mole % phenazone gave an endotherm (c shown at 20, 40 and 60 mole % phenazone in Fig. 2) at a constant temperature (107°C). At this point HSM showed that a considerable fraction of the solid melted from 104 to 108°C to give globules. Evidently, peak c in DTA corresponds to fusion of the 1 : 1 complex and this is supported by the value of 108°C found by Dearden (1972) to be the melting point

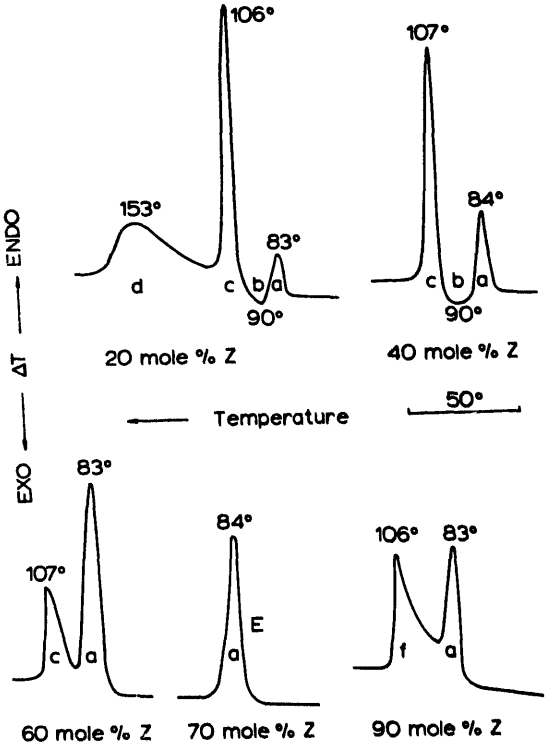

Fig. 2. DTA thermograms of physical mixtures of paracetamol (A) and phenazone (Z). E refers to the eutectic mixture. The letters a, b, c, d and f refer to the peaks discussed in the text.

of the purified complex and by the value of 107°C deduced from DTA of the complex prepared by fusion-cooling or crystallisation. Over the range 55–70 mole % phenazone the temperature and area of endotherm c decreased while the eutectic endotherm grew relatively larger. Endotherm c disappeared at the eutectic composition (70% phenazone, 30% paracetamol) leaving only endotherm a (E in Fig. 2).

Physical mixtures containing 2–35 mole % phenazone gave a second endotherm (d shown at 20 mole % phenazone in Fig. 2) which was rather wedge-shaped and is due to the melting of paracetamol at a temperature that is depressed by the presence of phenazone. The higher the proportion of phenazone, the lower the melting point of paracetamol present in the mixture and the smaller the relative area of peak d.

Physical mixtures containing 40 mole % or more phenazone (Fig. 2) did not show peak d, suggesting that the presence of the 1 : 1 complex was dominating the behaviour of the mixture. For compositions between about 60 and 70 mole % phenazone, however, the melting point of the complex (c in Fig. 2) and the area of the corresponding endotherm were being depressed by the presence of excess of phenazone.

Physical mixtures containing 75–98 mole % phenazone gave two endotherms (a and f shown at 90% phenazone). This behaviour is similar to that for mixtures containing 55–65 mole % phenazone (endotherms a and c shown at 60 mole % phenazone in Fig. 2). The paracetamol 'doped' the phenazone which was present at 75–98 mole % and depressed the melting point (f shown at 90 mole % phenazone in Fig. 2), whereas the presence of excess of phenazone with the 1 : 1 complex similarly 'doped' that species and depressed its melting point (e.g. c at 60 mole % phenazone in Fig. 2). Seventy mole % phenazone represents the composition of the eutectic formed between paracetamol and phenazone, the eutectic temperature being 83°C (E in Fig. 2). HSM confirmed that both components melted simultaneously and completely at this temperature.

Combination of the data presented here affords the overall phase diagram in Fig. 3. Physical mixtures of paracetamol and phenazone partially melt together at the eutectic temperature of 83°C. If paracetamol is in excess, the 1 : 1 complex is formed exothermically at 90°C and melts or dissociates at 107°C. Point m in Fig. 3 is the actual congruent melting point of the complex (AZ). The flatness of the melting point composition curve from 40 to 50 mole % phenazone indicates that the complex dissociates near its melting point (Bowden, 1938; Reisman, 1970) and is therefore not very stable to heat. In samples containing between 2 and 40 mole % phenazone, the solid complex (AZ) dissociates, or interacts with the liquid, to produce solid paracetamol (A) which itself melts at a higher temperature. Point p in Fig. 3 has the properties of a 'peritectic point' (Bowden, 1938). The present system, however, gives no evidence of solid solution formation (within the range 2–98 mole % phenazone). From 2 to 40 mole % phenazone the system therefore more closely resembles that described by Reisman (1970). Since the solid–solid phase transition at 107°C between 2 and 40 mole % phenazone represents a change in the chemical species, i.e. from the solid complex (AZ) to solid paracetamol (A), point p resembles a meritectic point (Bowden, 1938). Since, however, the complex melts congruently at point m, then p is not a true meritectic point. Point P is also atypical of a peritectic point, since peritectic transitions are normally characterised by a change from one solid solution to another solid solution.

The right hand side of the phase diagram in Fig. 3 corresponds to a simple eutectic

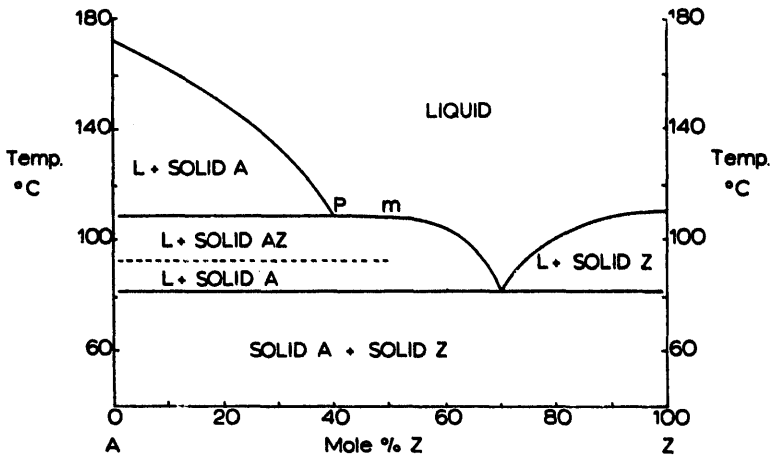

Fig. 3. Phase diagram obtained on heating physical mixtures of paracetamol (A) and phenazone (Z). AZ, 1 : 1 complex; L, liquid; p, peritectic point; – – –, exothermic change; m, congruent melting point of AZ.

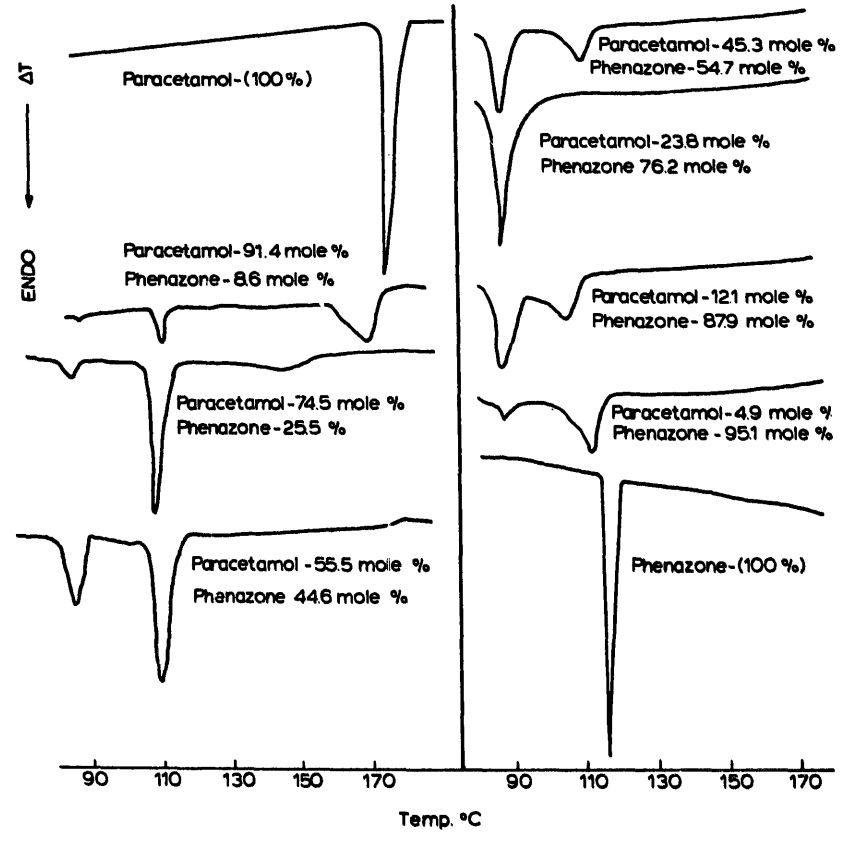

Fig. 4. DTA thermograms of fused-cooled mixtures of paracetamol and phenazone.

system formed between the 1 : 1 complex (at 50 mole % phenazone) and phenazone itself. Again, no formation of solid solutions was observed.

The fused-cooled samples afforded DTA curves (Fig. 4) similar to those given by the physical mixtures but without the exothermic transition c near 90°C, presumably because the complex has already been formed in the fusion process. The resulting phase diagram shown in Fig. 5 is almost identical with Fig. 3 but does not have the exothermic transition b. The eutectic temperature is still 83°C for all the samples, but the eutectic composition is now 76 mole % phenazone (24 mole % paracetamol) and consists of a mixture of the complex and phenazone. The reason for the differences between Fig. 5 and Fig. 3, including differences of eutectic composition, is that Fig. 5 is the true equilibrium phase diagram of the paracetamol–phenazone system, whereas Fig. 3 is the apparent diagram which reflects the artifact of insufficient mixing at the molecular level. Endotherm a at 83°C is the eutectic temperature for paracetamol with phenazone in Fig. 3, but also happens to be the eutectic temperature for paracetamol with the complex and for the complex with phenazone in Fig. 5.

The great similarity between the behaviour of the physical mixtures and fused-cooled samples with respect to the phase changes and the phase diagrams, further emphasizes that the interaction in the 1 : 1 complex is weak, even in the solid state. The complex is also unstable in ethanol, being completely dissociated in this solvent, as indicated by the fact that the UV spectrum of the complex in this solvent is identical with the sum of spectra of paracetamol and phenazone (Dearden, 1972). Similarly, the complex between chloral hydrate and phenazone dissociates completely in aqueous solution (Ekeblad, 1965), whereas, in sharp contrast, p-quinone and phenazone interact to give marked spectral changes associated with the formation of a stable charge-transfer complex (Okano and Uekama, 1967).

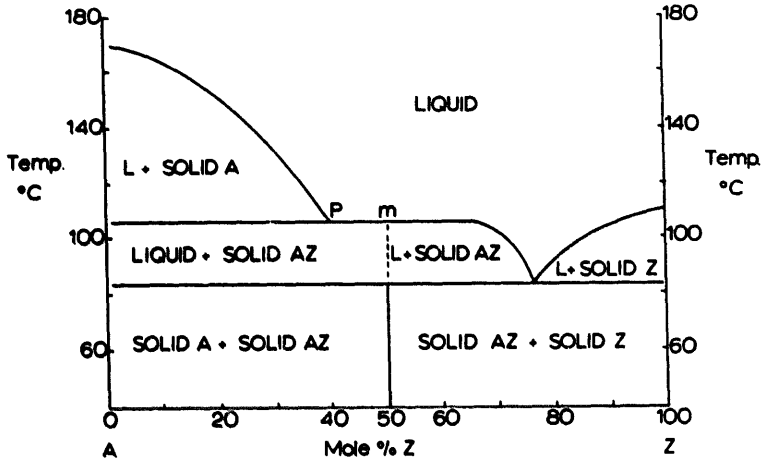

Fig. 5. Phase diagram obtained on heating fused-cooled mixtures of paracetamol (A) and phenazone (Z). AZ, 1 : 1 complex; L, liquid; p, peritectic point; m, congruent melting point of AZ.

The instability of the complex formed between paracetamol and phenazone in the solid state suggests that the thermodynamic activity of each drug in the complex is not much lower than that of each drug in the solid state. This relates to the fact that the complex dissociates in solution and may account for the fact that administration of the complex still affords similar analgesic and antipyretic properties to those produced by administration of the component drugs (Ridgway and Johnson, 1970). If a drug complex is very stable, therapeutic activity, as well as thermodynamic activity, is likely to be diminished.

In fact, phenazone and paracetamol potentiate each other's biological effects. Each inhibits the metabolism of the other in the rat and rabbit and penetration of the other through excised intestine (Niwa and Nakayama, 1968). Administration of the 1 : 1 paracetamol–phenazone complex appears to prolong the peak plasma level of free paracetamol (Heald and Evans, personal communication, 1974).

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