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Phase equilibria and stability characteristics of chlorpropamide-urea solid dispersions

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Physical mixtures and melts of various compositions of chlorpropamide and urea have been prepared. The phase diagrams and the effects of ageing of the systems have been measured by differential scanning calorimetry. The eutectic composition was found to contain 89% w/w chlorpropamide. Greater concentrations of chlorpropamide produced solid solutions of urea in chlorpropamide, whereas solid solution formation did not occur at compositions less than 89%. Melts in the range 50–100% chlorpropamide, which included the eutectic, existed as glass solids. The effect of ageing produced generally an increase in the liquidus peak temperature which was considered to be due to a gradual increase in crystal size.

Sekiguchi & Obi (1961) first proposed the use of solid dispersions to increase the bioavailability of poorly water soluble drugs. They showed that a eutectic of the water-soluble but physiologically inert carrier urea and the poorly soluble drug sulphathiazole increased the absorption rate of the drug by effectively increasing the available surface area for dissolution.

Goldberg, Gibaldi & others (1965, 1966a,b,c) examined this increased dissolution rate and produced phase diagrams for paracetamol-urea, griseofulvin-succinic acid and chloramphenicol-urea. They concluded that the increased dissolution rate was attributable to the formation of a solid solution. Subsequently Chiou & Niazi (1973) and Chiou (1971) found little evidence for the formation of solid solutions in the griseofulvin and chloramphenicol systems and these authors felt that the increased dissolution was probably a surface area phenomenon. Wells, Rubinstein & Walters (1975) produced results indicating that chlorpropamide-urea fused mixtures could be formulated to produce a fast release form of the drug. We have examined more fully the chlorpropamide-urea system to ascertain whether a solid solution or glass solid exists and to observe ageing effects of the melts produced.

MATERIALS AND METHODS

Materials

Urea (Analar) and chlorpropamide B.P. (Pfizer Ltd) were used as received.

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Sample preparation

Method A—The physical mix. Both chlorpropamide and urea were weighed accurately in various proportions and mixed thoroughly by trituration in a glass mortar. Samples between 2 to 5 mg were used for thermal analysis by differential scanning calorimetry (D.S.C.).

Method B—The melt. The materials were blended as in method A. 500 mg samples were heated in a glass tube in an oil bath at 135–140° for 5 min. The samples were allowed to cool to, and were stored at, 20° in a desiccator over anhydrous copper sulphate. Samples (2–5 mg) were withdrawn after 1 h, 2 weeks and 4 weeks and used for D.S.C.

Method C—The prematurely aged melt. The samples were prepared as in method B. After fusion the melts were stored at 60° for 96 h before samples (2–5 mg) were withdrawn and used for D.S.C.

Differential scanning calorimetry

A Perkin-Elmer Model DSC–1B was used. Aluminium sample pans and pan lids provided for the DSC–1B were used for all samples, the lids being crimped into position. All samples were run from 320–420°K at a scanning rate of 4° min^{-1}. Nitrogen was used as a carrier gas at a flow rate of 20 ml min^{-1}. Peak temperatures were taken as the melting point, after calibration with an indium standard.

RESULTS AND DISCUSSION

Typical thermograms for physical mixes are shown in Fig. 1. The thermograms have endothermic peaks

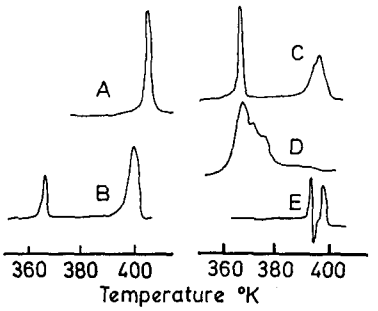

FIG. 1. D.S.C. thermograms of (A) urea, (B) 20% chlorpropamide 80% urea, (C) 50% chlorpropamide 50% urea, (D) 90% chlorpropamide 10% urea and (E) chlorpropamide.

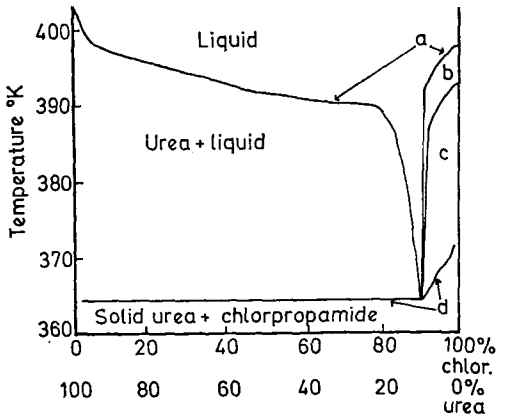

FIG. 2. Phase diagram of the chlorpropamide-urea system constructed from D.S.C. data from physical mixes. a—Liquidus lines, b—chlorpropamide form I and liquid, c—chlorpropamide forms I and II and liquid, d—solidus lines.

corresponding to the melting of the eutectic component and then the excess component. The endothermic peak areas due to urea became smaller with increasing chlorpropamide content and simultaneously the peak area due to the eutectic became larger. At the eutectic composition only one peak at 364°K was found and with increasing chlorpropamide concentration two further peaks became apparent. Studies revealed that two polymorphs of chlorpropamide existed in the original sample having melting points of 392·5 and 397°K. The thermogram of chlorpropamide indicated that after form II had melted, it crystallized to form I which then subsequently melted. Vigorous grinding of the drug also produced this conversion to form I. This conversion is similar to that experienced by Shenouda (1970) for sulphathiazole. Simmons, Ranz & Gyanchandani (1973) investigated polymorphs of chlorpropamide but did not find such an easy conversion between forms. Chlorpropamide recrystallized from the melt showed only a single endotherm corresponding to form I.

Peak temperatures were used to produce the phase diagram (Fig. 2) which shows the eutectic composition to contain 89% chlorpropamide. There is little evidence of a solid solution of chlorpropamide in urea as indicated by the solidus line continuing from 1 to 89% chlorpropamide at the eutectic temperature. However, at concentrations of drug greater than the eutectic composition the solidus line deviates towards the drug's melting point which is indicative of solid-solution formation.

Chiou & Niazi (1971) investigated the presence of solid solutions in a sulphathiazole-urea system. They found that using physical mixtures could lead to the mistaken assumption that binary systems could be regarded as simple eutectics with negligible solid solution formation because of a thaw temperature at the eutectic temperature. More intimately mixed solid melts showed a thawing temperature higher than the eutectic temperature which is indicative of solid solution formation. Since the phase diagram showed an increase of thaw temperatures on the excess chlorpropamide side of the eutectic, even with a physical mix, then it may be assumed that a solid solution of chlorpropamide in urea exists at high chlorpropamide compositions.

Chlorpropamide itself was found to undercool from the melt and form a glass solid, a metastable state that showed no typical melting endotherms. This supercooling ability continued even in the presence of urea and melts containing as much as 60% urea showed an ability to supercool. An indication of this was given by the time melts took to show visual signs of crystallization under storage at room temperature (20°). Melts containing 90 and 100% chlorpropamide existed as a transparent glass after one month's storage, whereas melts containing 70 and 80% drug became opaque within two weeks. Crystallization occurred within 2 h for 60% melts and with further decreasing chlorpropamide content crystallization occurred more rapidly. Despite this obvious crystallization having taken place, melts containing more than 50% chlorpropamide remained viscous for several weeks indicating that the melts were not entirely crystalline. Only melts containing 30% chlorpropamide, or less, crystallized rapidly to a hard pulverisible mass. The amorphous nature of these supercooled melts is similar to that found for sulphathiazole-urea (Chiou & Niazi, 1971) where

it was shown that melts containing more than 75% of the sulphonamide were able to supercool.

D.S.C. studies on aged premelted samples showed changes in the thermograms. Aged samples from either method B or method C showed no peaks corresponding to the solidus line for any composition. Peaks corresponding to the liquidus line were found for mixtures corresponding to 0–40% chlorpropamide and 94–100% chlorpropamide, and the peak temperatures from 1 h old melts were generally 2–3° lower than those obtained from physical mixes. However, with ageing at room temperature the peak temperatures of the melts gradually increased and after 4 weeks were approximately 1–2° higher than the 1 h old melts. With melts containing more drug than the eutectic only one endotherm was observed indicating that only one chlorpropamide polymorph had crystallized in the melt. Sekiguchi, Ueda & Nakamori (1963) produced phase diagrams of several systems and found also that the physical mixes produced melting points several degrees higher than the corresponding melts. The reason for this seems to be that the interface of both components in the simple mix is much less than that of a fused mixture and the presence of air trapped between particles prevents heat transmission in a physical mix. With premelted mixes the gradual increase of temperature at the extremities of the phase diagram is probably due to increased crystal size as the ageing process continues and again the presence of trapped air due to contraction of the melt on cooling. Ellerstein (1966) investigated the annealing times of polystyrene at different storage times and found that D.S.C. thermograms showed an increase in peak temperature as the ageing process continued, and this would appear to be an analagous effect.

Melts prepared by method B exhibited no peaks in the range 50–92% chlorpropamide. However, small endothermic inflections on the thermograms were found, between 325–348°K. These inflections were probably due to a glass transformation in the melt; the melt changing from a glass solid to a supercooled liquid. For these transitions, the thermograms were similar for any one particular melt composition and duplicate results could be obtained from the same melt. However, different melts of the same composition were not reproducible to temperature position, though the general shape remained unaltered. This lack of endothermic melting peaks was found by Guillory, Hwang & Lach (1969) for menandione-deoxycholic acid systems which also formed a glass solid. However, Chiou & Niazi (1971) found that, due to their intimate nature, melts tended to be better for producing phase diagrams than physical mixes, in regions where solid solutions might exist. For materials that show this ability to supercool to a glass solid it is perhaps advisable to study data from both a physical mix and a melt before drawing conclusions about phase diagrams.

The fact that no eutectic endotherm was observed with the premelted system between 40–92% chlorpropamide indicated that the eutectic composition itself existed as a glass. Hence the eutectic composition once melted would probably form the most stable glass. The addition of urea as well as promoting crystallization, also increases the hardness of the melt. Similarly the addition of chlorpropamide tends to promote crystallization, although it itself is able to supercool to a glass.

The free flowing granulate of a solid solution of chlorpropamide-urea reported by Wells & others (1975) contained 28·6% chlorpropamide (Wells, personal communication). It would seem, therefore, that a solid solution of chlorpropamide-urea was not used by these workers but rather a system of eutectic and excess urea.

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