THE KINETICS OF CRYSTALLISATION OF PARACETAMOL AND PHENACETIN FROM AQUEOUS ETHANOL

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The solubilities of paracetamol and phenacetin in water, in ethanol and in mixtures of the two have been determined. During the making of the measurements it became apparent that crystallisation from water favoured the production of flat ended prisms, whilst from ethanol the tendency was towards slightly larger pyramidal-ended prisms.

The solubility (S) of paracetamol as a function of temperature (T) for a particular solvent mixture could be expressed by a second order polynomial of the type:

$$S = a + bT + cT^2$$

For the range of conditions studied, namely temperatures between 20°C and 60°C, and ethanol strengths up to 30% w/w, the solubility varied from about 1% w/w to around 20% w/w. The values of the parameters a, b and c were functions of the ethanol concentration. Phenacetin is practically insoluble in water but dissolves more readily in ethanol. The effect of temperature on the solubility could be represented adequately by a straight line relationship, the slope of the line being a function of the strength of the ethanolic mixture used.

Solutions of paracetamol in these aqueous ethanolic mixtures have been crystallised in a laboratory fluid bed crystalliser of the type described by Mullin and Garside (1968) and used in earlier work at the School of Pharmacy (Glasby & Ridgway 1968, Ridgway & Aulton 1971), modified by the addition of a dissolving tank with a separate temperature control to allow more solute to be introduced into the circulating system during operation. This enables a run to be carried on for a longer period without serious depletion of the solute concentration by deposition.

Batches of seed crystals of known size and surface area were grown in the crystallizer for known periods of time at temperatures of 30°C, 40°C and 50°C. The product was withdrawn, rinsed and dried, and then sieved. Microscopic examination of the crystals established their length to diameter ratio so that, from their size distribution and their average length, the surface area on which deposition was occurring could be determined. Knowing the degree of supersaturation of the mother liquor, the value of the mass transfer coefficient could be found.

Plotting the logarithm of the mass transfer coefficient against the reciprocal of the absolute temperatures gave a series of straight lines whose slopes gave the activation energy for the crystallisation process. The width of the metastable region, the zone between the solubility line and the line of supersaturation beyond which spontaneous nucleation will take place, was also determined.

Mullin, J.W., & Garside, J. (1968). Trans. Instn. Chem. Engrs., 45, 283-295.
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