Thus glasses containing from 1 to 30% w/w primidone (m.p. 295° approximately) were prepared by fusing the drug with citric acid (m.p. 153°) followed by rapidly cooling.

The glasses were metastable and devitrified over a period of time. Thus, before determination of the phase diagram of the system, devitrification was aided by storing the glasses in an oven at 60° for up to 3 days. The phase diagram was constructed by determining the onset and completion of melting of the various dispersions by hot stage microscopy and differential scanning calorimetry.

X-ray powder diffraction was also used to assess the nature of the solid dispersions present. For example, it was found that the 30% w/w glass was amorphous in nature, and this suggested that in the glass state primidone was molecularly dispersed. Devitrified samples containing 5 to 15% w/w primidone exhibited diffraction lines typical of the drug, suggesting that a eutectic mixture had crystallized out. This correlated with the phase diagram obtained from the melting point data. The primidone recrystallized from the glass as the Form II polymorph whereas the starting material (commercial material) was the Form I polymorph (Daley, 1973). X-ray diffraction data of devitrified samples containing from 1 to 3% w/w of the drug were inconclusive, but melting point data suggested that at these low concentrations the drug was present in molecular dispersion.

The influence of citric acid on the solubility of primidone was assessed by equilibrating commercially available drug, and the two prepared polymorphic forms, with distilled water and citric acid solutions of varying concentrations overnight at 37°. A 0·5 g ml^{-1} citric acid solution increased the solubility of the commercially available drug from 56·4 mg per 100 ml to 172·2 mg per 100 ml.

REFERENCES

CHIOU, W. L. & RIEGELMAN, S. (1969). *J. pharm. Sci.*, **85**, 1505–9.
CHIOU, W. L. & RIEGELMAN, S. (1971). *Ibid.*, **60**, 1281–1302.
DALEY, R. D. (1973). In *Analytical Profiles of Drug Substances*, **2**, Editor: Florey, K. p. 409–437, New York: Academic Press.
SEKIGUCHI, K. & OBI, N. (1961). *Chem. Pharm. Bull.*, **9**, 866–872.

Some effects of polyvinylpyrrolidone on the solubility and dissolution rate of allopurinol

J. H. COLLETT* AND G. KESTEVEN†

**Department of Pharmacy, The University of Manchester, Manchester M13 9PL, U.K. †The Wellcome Foundation Ltd., Crewe, U.K.*

There is considerable interest in the use of water soluble polymers in the modification of drug solubility and dissolution rate. Various theories have been put forward to account for the observed modifications in individual systems. However, theoretical dissolution rates calculated for other systems using these theories are often not consistent with experimentally determined ones. This is a preliminary report of work aimed at determining the mechanism controlling the dissolution of allopurinol from polymer/drug mixtures.

Solubilities of allopurinol in P.V.P. of different molecular weight (K15, 10,000, K30, 40,000, K90, 100,000, Plasdone 30,000, G.A.F. Ltd.) were measured at 15, 25, 35 and 40°. In all cases solubilities increased with temperature and concentration of polymer. Thermodynamic parameters were calculated using standard equations. Differential heats of solution ΔH ranged from 25·2 to 33·6 K Joules mol^{-1}, the value decreasing with increasing polymer concentration, suggesting possible complex formation between drug and polymer. Free energies of partitioning ΔFp were negative and small 0·3 to 1·8 K Joules mol^{-1} and increased with polymer concentration at any one temperature, indicative of a more favourable environment for the drug. In contrast a decrease in value was noted at constant P.V.P. concentration with increase in temperature, probably due to a decreasing affinity of polymer for solvent with temperature increase. These thermodynamic parameters are all consistent with binding between polymer and drug. The binding is a composite one involving the polymer and drug in a hydrated form and will be considered in terms of ordering of water molecules around the solute (Frank & Evans, 1945).

Assuming that drug and polymer exist as a complex in solution then it is possible that drug dissolution rate will be affected. For example, if a diffusion layer is operating, dissolution rate would be governed by the solubility of the complex and the diffusion coefficients of all species. Dissolution rates of the following non-disintegrating discs were measured

(a) allopurinol into 0·1 M HCl and into P.V.P. solutions up to 20% w/v.

(b) allopurinol/P.V.P. physical mixtures into 0·1 M HCl and into P.V.P. solutions.

Dissolution rates of allopurinol into P.V.P. solution decreased with increasing P.V.P. concentration. The presence of P.V.P. in the disc did not influence dissolution rate even when present up to 40% w/w of the disc. These findings indicate that the controlling factor in dissolution is viscosity of the dissolution medium rather than a change in diffusion coefficient of the drug due to complexation in the diffusion layer. Estimates of diffusion coefficients are required before these findings can be regarded as conclusive.

The authors wish to thank Dr. C. McDonald for helpful discussions.

REFERENCE

FRANK, H. S. & EVANS, M. W. (1945). *J. Chem. Phys.*, **13**, 507–532.

The dissolution kinetics of sulphathiazole form I

J. E. CARLESS AND D. JORDAN

Department of Pharmacy, Chelsea College (University of London), Manresa Road, London SW3 3LX, U.K.

Work on the growth of sulphathiazole Form I under temperature cycling conditions has already been reported (Carless & Foster, 1966) and this present study was designed to investigate, in detail, the dissolution kinetics involved. Sulphathiazole Form I was prepared by recrystallization from 95% ethanol in water and characterized by differential scanning calorimetry, infrared and melting point behaviour.

Sulphathiazole discs were made at a compressional pressure of 238 kNm^{-2} and the dissolution profile determined in distilled water at 25° to 45° using a rotating disc apparatus. The theoretical rate constant K_t for the diffusion process was calculated from the Levich equation

$$K_t = 0{\cdot}620\, D^{\frac{2}{3}} \nu^{-\frac{1}{6}} \omega^{\frac{1}{2}}.$$

where ν is the kinematic viscosity and ω the angular rotation of the disc. This was compared with the experimental rate constant calculated from the Noyes-Whitney equation which assumes that diffusion control operates. Agreement between the two rate constant values at temperatures above 30° indicated that diffusion control was operating but at lower temperatures, the dissolution was controlled by the interfacial reaction. Energies of activation derived from Arrhenius plots were consistent with diffusion control and interfacial control operating at the higher and lower temperatures respectively.

Dyestuffs reduce the rate of dissolution of sulphathiazole (Piccolo & Tawashi, 1970). In this study, the presence of malachite green reduced the rate of dissolution, this being explained by the interfacial reaction control operating over the temperature range 25–45°. This was consistent with adsorbed dye interfering with the detachment of sulphathiazole molecules from the crystal surface.

Extensive grinding of the original sulphathiazole crystals resulted in the dissolution being changed from interfacial controlled to diffusion controlled. This is not unexpected since grinding will increase crystal defects and dislocations and so would be expected to enhance interfacial reaction.