J. Pharm. Pharmac., 1976, **28**, 305–308 *Received August* 6, 1975

Some factors influencing dissolution from salicylic acid-urea solid dispersions

J. H. COLLETT†, B. L. FLOOD‡ AND F. R. SALE*

*Department of Pharmacy, *Department of Metallurgy, University of Manchester, Manchester, M13 9PL, U.K.*

Solid dispersion systems of salicylic acid-urea have been prepared using a fusion method. Two different methods of cooling the melt were employed, rapid cooling in liquid nitrogen and slow cooling in air. Differential scanning calorimetry and an X-ray diffraction technique were employed to investigate the nature of the fused mixture. Evidence was found of compound formation between the constituents. Dissolution rates of drug from non-disintegrating discs of solid dispersion systems were measured. Rapid cooling of the melt resulted in a much faster drug dissolution rate than from a corresponding mixture prepared by a slow cooling method. This phenomenon is explained by a difference in the sizes of drug particles produced under the different cooling conditions. Rapid cooling favoured the generation of many nucleation sites for the solid drug particles as the liquid was cooled, and hence many small particles were obtained. Conversely, slow cooling favoured the growth of the first few nuclei of solid drug particles, rather than the production of new nuclei, and hence large drug particles were obtained.

The preparation of a drug as a solid dispersion in a water-soluble carrier may result in a reduction of drug particle size, solid solution formation and drug solubilization (Chiou & Riegelman, 1971). These factors are believed to be responsible for the enhancement of drug dissolution from solid dispersions. However it is not known whether the relative contributions of each factor may be influenced by different interactions between drug and carrier resulting from the procedure for preparing dispersions. Furthermore, although it is often assumed that the active drug must be a minor component of a dispersion system, it is possible that interactions between drug and carrier may be affected by the proportion of each constituent with a subsequent effect on dissolution rate.

In this work solid dispersions have been prepared containing different proportions of salicylic acid and urea. A melting method followed by different cooling procedures was used. Dissolution rates from these dispersions have been measured. The purpose of the work is to relate the characteristics of the different dispersions, as measured by differential scanning calorimetry (D.S.C.) and X-ray diffraction, to dissolution rates.

MATERIALS AND METHODS

Materials

Drug-carrier physical mixtures were prepared containing different proportions of salicylic acid A.R. (BDH) and urea S.L.R. (Fisons).

Drug-carrier dispersion systems were obtained by heating physical mixtures of salicylic acid and different amounts of urea until the solids were molten. The fused mixtures melted at a temperature lower than the melting point of either component thus avoiding decomposition of urea (Gibaldi & Feldman, 1967). One half of each molten mixture was cooled rapidly by pouring into liquid nitrogen (−198°) and the remainder was allowed to cool gradually to ambient temperature. The cooled mixtures were ground to a fine powder.

Non-disintegrating discs were prepared by compression of the mixtures at a pressure of 300 kg m^{-2} in an Apex A14 hydraulic press.

Methods

Thermal analyses. A Perkin-Elmer differential scanning calorimeter (model 1B) equipped with a standard cell was calibrated with semi-conductor grade indium (m.p. 156·6°). A heating rate of 16° min^{-1} was employed for the calibration procedure and for all subsequent scans. A sample size of approximately 20 mg was adopted for all scans. Thermal analyses were performed on salicylic acid-urea dispersion systems containing the highest and lowest amounts of salicylic acid.

X-ray diffraction studies. Powder diffractograms were obtained using finely powdered samples of salicylic acid, urea or salicylic acid–urea dispersion systems. The powder was fixed onto a glass slide

† Correspondence.
‡ Present address: Geigy Pharmaceuticals, Macclesfield, Cheshire, U.K.

with collodion. X-ray diffraction spectra were obtained using a Siemens crystalloflex diffractometer and CuKα radiation.

Dissolution rate studies. A rotating disc type apparatus was used for dissolution rate studies. The apparatus and procedure have been described previously (Rees & Collett, 1974). Dissolution rates of drug were measured from non-disintegrating discs containing urea and salicylic acid within the range 5% urea–95% salicylic acid and 70% urea–30% salicylic acid. The non-disintegrating discs used were prepared from physical mixtures, rapidly cooled and slowly cooled dispersions of urea and salicylic acid. Dissolution media were maintained at 37° and pH 1·0.

RESULTS

Thermograms of the pure materials indium, urea and salicylic acid had sharply defined peaks representing fusion of the samples. Fig. 1 shows a typical thermogram obtained for a solid dispersion system and salicylic acid alone. A fusion peak with the thaw point at 144° and melting point at 151° were seen for slow cooled 5% urea–95% salicylic acid dispersion systems. Thaw and melting points of a rapid cooled system of the same composition occurred at 141 and 152°, respectively. Thermograms obtained for the 70% urea–30% salicylic acid systems showed less defined peaks. For dispersion systems prepared by rapid or slow cooling two regions representing endothermic transitions occurred roughly between 47–67° and 95–117°. The latter transition is regarded as the melting point transition. The thermogram of the slow cooled dispersion system for 70% urea–30% salicylic showed another endothermic region above 132° which continued up to a temperature of 187°. No return to the base-line had occurred at this temperature even though the temperature was much higher than the melting points of the two components in the dispersion system. This is probably because of decomposition of the urea to form ammonia and biuret.

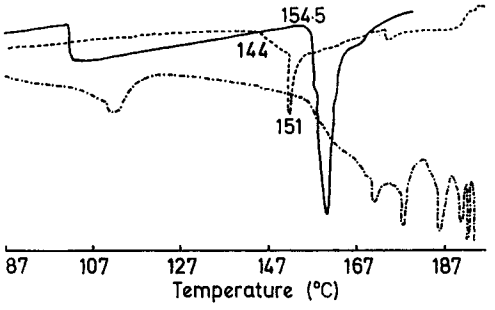

FIG. 1. D.S.C. thermograms of —— salicylic acid, - - - - 5% urea–95% salicylic acid, slow cooled. - · - · - 70% urea–30% salicylic acid.

X-ray diffractograms of urea and salicylic acid alone were obtained. The d-spacings and relative intensities represented by diffraction peaks were compared with reference tables (American Society for testing materials X-ray powder data file). Table 1 lists d-spacings and relative intensities for the dispersion systems and their individual components. The diffraction spectra were identical for dispersions prepared by slow or rapid cooling methods. In the case of 95% salicylic acid–5% urea fused mixtures mainly characteristic peaks of salicylic acid appeared with a few of the weaker peaks which could not be ascribed to either urea or salicylic acid. In contrast, characteristic peaks of urea appeared on the spec-

Table 1. *d-spacings of X-ray diffraction peaks of urea and salicylic acid and in salicylic acid–urea dispersion systems.*

Urea		70% urea–30% salicylic acid solid dispersion system		Salicylic acid		5% urea–95% salicylic acid solid dispersion system	
d-spacing	Relative intensity	d-spacing	Relative intensity	d-spacing	Relative intensity	d-spacing	Relative intensity
4·646	3	4·671*	12	7·900	98	—	—
3·986	82	—	—	5·096	100	5·185*	29
3·917	100	—	—	4·484	3	4·552*	16·3
3·648	3	3·678*	16	3·480	15	3·562*	50·9
2·212	7	2·206*	8	2·885	7	2·876*	5·22
				2·564	3	2·607*	4·74

* Characteristic peaks which have undergone shifts and alteration in relative intensity.

trum of 70% urea–30% salicylic acid systems along with a few weaker peaks which corresponded to those seen with the 95% salicylic acid dispersion. Thus, according to the X-ray diffraction data the component forming the smaller proportion of a binary dispersion system is not represented by its characteristic peaks on a diffractogram of the dispersion.

Plots of amount of salicylic acid dissolved from dispersion systems as a function of time were linear. Dissolution rate constants given in Table 2 were obtained from the slopes of these plots. The dissolution rate of drug varies according to the proportion of drug and urea in solid dispersion systems and to the method of preparation employed. For all three types of system used in this work the dissolution rate increases as the proportion of urea increases. The relation between dissolution rate and urea content is non-linear in each case. Drug dissolution rates from systems prepared by physical mixing and fusion–rapid cooling methods were similar, but dissolution was slower from systems prepared by the fusion–slow cooling method.

Table 2. *Dissolution rate constants* (mg ml^{-1} min^{-1} cm^{-2}) $\times 10^3$ *of salicylic acid urea systems containing different salicylic acid–urea proportions at* 37° *and pH* 1·0

Composition		Method of preparation		
Urea	Salicylic acid	Physical mixture	Fusion-rapid cooling	Fusion-slow cooling
0	100	1·57	1·57	1·57
5%	95%	2·11	1·90	1·68
10	90	2·13	1·87	1·59
30	70	3·26	3·17	2·49
50	50	5·62	5·20	3·72
70	30	14·56	12·53	7·51

DISCUSSION

Previous workers have presented solid dispersion systems to dissolution media in the form of powdered samples (Sekiguchi, Obi & Ueda, 1964; Chiou & Niazi, 1971). As dissolution of the drug proceeded the surface area of drug in contact with dissolution media decreased making for difficulties in the analysis of data. In the present work, examination of non-disintegrating discs after each experiment revealed that the surface of discs prepared from fused mixtures remained intact. However, discs prepared from physical mixtures tended to crumble presenting a changing surface area to the dissolution media. Drug dissolution rates, from discs prepared using fused mixtures, increased rapidly with concentration of urea in the disc greater than 10%. Dissolution was much more rapid from fused mixtures cooled rapidly than from mixtures cooled slowly; sevenfold and fourfold increases respectively were found relative to dissolution rate of salicylic acid alone. On the assumption that urea in the disc will increase the solubility of drug in the diffusion layer, then a two or three fold increase in drug dissolution rate may be expected when a large proportion of urea is present in the disc (Flood, 1975). Increases in dissolution rate for salicylic acid were much greater than expected particularly from mixtures cooled rapidly.

There are several possibilities to account for the large increase in dissolution rate from fused mixtures. An increased dissolution may be expected if the drug crystallizes in a metastable form on cooling. The metastable form would have a higher solubility and faster dissolution rate than the stable form. Other workers have reported polymorphic crystallization of sulphonamides and barbiturates (Haleblian & McCrone, 1969). There was no evidence of a polymorphic form from the X-ray diffraction data reported in this work.

It has been suggested that a solid solution of a poorly water-soluble drug in a soluble carrier would achieve more rapid dissolution than a eutectic mixture. The reason for the rapid dissolution is that the particle size of the drug in the solid solution is reduced to a molecular size. The differential scanning calorimetry studies reported in the previous section give no indication of solid solution formation. However the thermograms of fused mixtures exhibit an endothermic transition extending beyond the melting points of the two components, an indication that compound formation has occurred between salicylic acid and urea. If this is the case then the phase diagram of the salicylic acid-urea system is more complicated than a simple binary eutectic mixture. Fig. 2 shows a typical phase diagram for a system of two components which can form a stable compound. The points marked on the diagram represent the experimental data from this work. If the compound has a congruent melting point, i.e. it can exist as a solid compound in equilibrium with liquid of the same composition, then three solid-liquid equilibrium curves are seen on the phase diagram. The broken lines on the figure relate the experimental values of thaw and melting points to the composition of the solid dispersion systems. Further physical evidence is needed before the existence of this type of system can be regarded as definite. However, from the suggested phase diagram it may be seen that existence of compound-liquid equilibrium for the 70% urea mixtures at high

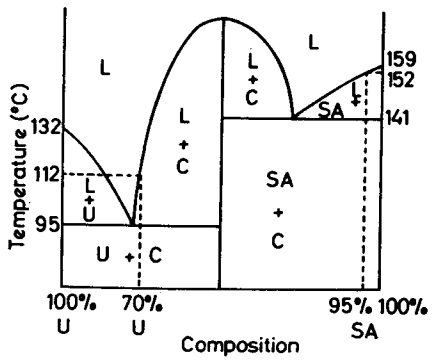

FIG. 2. Proposed phase diagram for salicylic acid–urea systems. L–liquid, C–compound, U–urea, SA–salicylic acid.

temperatures would account for the unusual nature of the thermograms. The 5% urea–95% salicylic acid fused mixture exists in the region of salicylic acid–liquid equilibrium at high temperatures accounting for the more definite peaks representing enthalpic transitions on the thermograms of this system.

X-ray diffraction data also support the theory of compound formation. When salicylic acid is the minor component of a salicylic acid–urea system, most of its characteristic peaks do not appear. Similarly, when urea is the minor component then only peaks characteristic of salicylic acid appear on an X-ray diffraction spectrum whilst the major peaks characteristic of urea do not appear. These observations suggest that a compound is formed between salicylic acid and urea. The increase in dissolution rate with increase in urea concentration in the fused mixture may be attributed to larger amounts of the salicylic acid–urea compound being formed.

The increased dissolution rate from a disc prepared from a rapidly cooled fused mixture over that seen with a slow cooled mixture is not due to a difference in composition of the fused mixture resulting from the method of preparation. Thermograms of rapid and slow cooled mixtures of the same composition were superimposable. Furthermore, X-ray diffraction spectra had identical d-spacing and relative intensity values. It may be concluded that increased dissolution rate from rapid cooled mixtures resulted from a smaller particle size of salicylic acid. Other workers (Chiou, 1971) have reported increased drug dissolution from fused mixtures and attributed it to a reduced particle size of drug. However, previous workers have not considered fully the effects of the rate of cooling.

According to the dissolution, D.S.C. and X-ray data in this work the interaction between salicylic acid and urea during the preparation of dispersions produces a compound with a greater solubility and dissolution rate than salicylic acid alone. The amount of compound prepared is related to the relative proportions of each component. The procedure used for cooling the molten salicylic acid urea influences the state of division of the salicylic acid in the dispersion. A rapid cooling method favours a small particle size. When considering the presentation of a drug as a dispersion system it is worthwhile considering an investigation of the influence of factors such as relative proportions of ingredients and procedures for preparation on drug dissolution rates.

REFERENCES

CHIOU, W. L. (1971). *J. pharm. Sci.*, **60**, 1406–1408.
CHIOU, W. L. & NIAZI, S. (1971). *Ibid.*, **60**, 1333–1338.
CHIOU, W. L. & RIEGELMAN, S. (1971). *Ibid.*, **60**, 1281–1302.
FLOOD, B. L. (1975). M.Sc. Thesis University of Manchester.
GIBALDI, M. & FELDMAN, S. (1967). *J. pharm. Sci.*, **56**, 370–375.
HALEBLIAN, J. & MCCRONE, W. (1969). *Ibid.*, **58**, 911–929.
REES, J. A. & COLLETT, J. H. (1974). *J. Pharm. Pharmac.*, **26**, 956–960.
SEKIGUCHI, K., OBI, N. & UEDA, Y. (1964). *Chem. Pharm. Bull.*, **12**, 134–144.