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An investigation into the mechanisms of dissolution of alkyl *p*-aminobenzoates from polyethylene glycol solid dispersions

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Summary

The solubility, melting and dissolution behaviour of methyl, ethyl, propyl and butyl *p*-aminobenzoates (PABAs) have been studied, both alone and as dispersions in polyethylene glycol (PEG) 6000 prepared by the fusion method. The aqueous solubility was found to decrease logarithmically with molecular weight of the PABAs, while a linear increase was found between solubility and initial dissolution rate. The phase diagrams of physical mixtures of the PABAs and PEG 6000 were monotectic in nature, while evidence was found for eutectic formation when the samples were prepared as dispersions. A linear relationship was found between the initial dissolution rate of the dispersions and the aqueous solubility of the PABAs, with the 10% w/w dispersions showing the fastest dissolution rates and the 20% w/w and 50% w/w dispersions and pure PABAs yielding similar results. A model has been proposed whereby at low concentrations within the dispersion the drug is considered to be released into the medium as individual particles, with dissolution occurring over a large surface area, while at higher drug levels, the drug forms a continuous diffusion layer over the dissolving surface.

Introduction

The use of drug dispersions in water-soluble carriers as a means of enhancing the dissolution rates of poorly soluble drugs has been well documented and reviewed (e.g., Chiou and Riegelman, 1971; Ford, 1986). However, despite the large number of publications on the subject of such solid dispersions, few commercial products are available using this technology. This is primarily due to problems associated with the production of a viable solid dispersion dosage form, these including difficulties in large scale manufacture and changes in dissolution behaviour on storage. Furthermore, as the mechanisms by which release rate enhancement occur are not yet fully understood, it has proved difficult to predict the dissolution behaviour of solid dispersion systems and to find methods by which the physical stability may be improved.

The suggested mechanisms by which drugs dissolve from solid dispersions include decreased particle size, decreased agglomeration and aggre-

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gation of drug particles, increased drug solubility via complex formation or solubilisation and improved wetting (Chiou and Riegelman, 1971). However, few studies have specifically examined the question of which, if any, of these factors is in operation for a particular system. Sjökvist and Nyström (1988) demonstrated that the dissolution rate of drugs from dispersions in PEG 3000 was related to both the solubility and particle size of the drug. In particular, the readily soluble sodium salicylate gave very rapid release profiles compared to the poorly soluble griseofulvin. Furthermore, a linear relationship was found between the external surface area of the griseofulvin and the dissolution rate from dispersions containing 1–20% w/w drug prepared by the solvent method, indicating that the particle size of the drug was the most important factor controlling the release rate in this case. Corrigan (1985), however, reported that the dissolution rates of a number of systems appeared to be governed by the dissolution rate of the carrier, especially at low drug contents. Dubois and Ford (1985) suggested that carrier controlled dissolution occurs with most drugs at low drug contents, although the concentration to which this takes place may vary considerably. The authors also suggested that above this critical concentration, dissolution occurs from a continuous drug layer at the dispersion surface. The exact mechanism by which carrier controlled dissolution occurs is not yet fully understood. Several authors (e.g., Goldberg et al., 1966; Chiou and Niazi, 1971; Sjökvist et al., 1991) have suggested that a contributing factor to dissolution rate enhancement may be solubilisation of the drug by the carrier in the diffusion layer surrounding the particles. Craig and Newton (1992) have suggested that this mechanism may itself lead to carrier controlled dissolution. Furthermore, Sjökvist and Nyström (1988) have discussed the significance of the role of improved wetting in the dissolution of solid dispersions.

In the present investigation, the melting and dissolution behaviour of an homologous series of *p*-aminobenzoates (PABAs) with a range of aqueous solubilities have been examined, both alone and as particulate dispersions in polyethylene glycol (PEG) 6000. These substances have been previously characterised (e.g., Yalkowsky et al., 1972a) and their physico-chemical properties are therefore relatively well understood. The relationship between the properties of the drugs and the dissolution behaviour of the dispersions will be examined in order to clarify the mechanism by which drugs are released from solid dispersions.

Experimental

Materials

Samples of methyl, ethyl, propyl and butyl *p*-aminobenzoates (PABAs) (APIN Chemicals Ltd, U.K.) were used as model drug substances. Samples of PEG 6000 (CSD, Cheshire) were ground in an end-runner mill (Pascall Ltd, London) and sieved to obtain the $< 250\ \mu m$ fraction.

Methods

Sample preparation

Samples (3 g) of PABA or physical mixtures of PABA and PEG 6000 were weighed into stainless-steel nipples, as described by Craig and Newton (1991). The nipples were capped and placed in an LTE G150 programmable oven (LTE Ltd, Oldham). The pure PABAs were heated from 30°C at 3°C/min to 115, 95, 75 and 60°C for the methyl, ethyl, propyl and butyl analogues, respectively. These temperatures were just above the melting points of the four compounds, thus allowing complete melting of the samples without causing decomposition. The maximum temperature was held for 1 h and the samples cooled at 10°C/min to 30°C, resulting in the compounds crystallising within the nipples to produce a flat surface flush with the end of the nipple. The samples were then stored in a refrigerator for 24 h and at room temperature for a further 24 h to ensure complete crystallisation. There was no evidence of decomposition caused by the cycling process.

The dispersions were prepared in an identical manner, except that the maximum temperature used was 100°C in all cases except the 50% w/w and 80% w/w methyl PABA samples, for which a

temperature of 110°C was used. These temperatures were found to be sufficient to result in complete melting of both components but did not result in degradation of the PABAs. For the melting temperature measurements, the solid dispersions were pulverised in a mortar and sieved to obtain the < 250 μm fraction.

Characterisation of raw materials, physical mixtures and solid dispersions

Solubility measurements Solubility measurements were performed using the method described by Molyneaux (1984), whereby samples of drug were placed in a Sovirel tube containing the solvent, into which was placed a further Sovirel tube capped with a sintered glass filter. The samples were left to equilibrate in a water bath at 25°C for at least 48 h, during which time the dissolved PABA diffused into the inner chamber, leaving the residual solute particles in the outer chamber. The filtrate was analysed spectrophotometrically at 283 nm, with three measurements being made from each assembly. All studies were repeated twice.

Melting temperature measurements An Olympus BH-2 microscope (Olympus Ltd, Japan) was used, fitted with a Mettler FP5/FP5Z hot stage (Mettler, Switzerland). The initial and final melting temperatures of the samples were recorded, with the stated results being the mean of three determinations.

Apparent particle density measurements The densities of the PABAs were measured using an Air Comparison Pycnometer (Beckman 930, U.S.A.). Air was used as the penetrating medium in all samples. The results presented are the mean values of three determinations.

Dissolution studies Dissolution measurements were performed using the method outlined by Craig and Newton (1992). Studies were performed by attaching the nipples to a stainless steel shaft and immersing the assembly in 1 l of deaerated double-distilled water at 25°C. The nipples were rotated at 100 rpm and 10-ml samples were withdrawn and filtered at specified time intervals, the liquid being replaced by further samples of double distilled water. All studies were repeated at least twice.

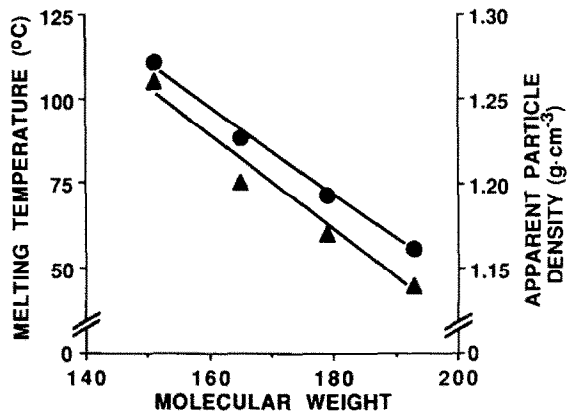

Fig. 1. Variation of apparent particle density (▲) and melting temperature (●) with molecular weight of PABAs.

Results and Discussion

Characterisation of raw materials

The melting temperatures of the PABAs were found to show a linear decrease with molecular weight, as previously reported by Yalkowsky et al. (1972a). It was noted that the densities also showed a linear decrease. The two sets of data are plotted in Fig. 1. The results may be a reflection of the strength of bonding within the crystal, with methyl PABA having a stronger lattice structure than the longer chain analogues.

The aqueous solubilities of the PABAs decreased with increasing chain length, with values of 8.71, 5.12, 1.95 and 0.671 mmol l^{-1} for the methyl, ethyl, propyl and butyl analogues, respectively. A log-linear relationship was found between solubility and PABA molecular weight (Fig. 2), as has been previously reported in a study performed at 37°C (Yalkowsky et al., 1972a). The slopes of the two curves are very similar (0.0268 and 0.0273 for 25 and 37°C, respectively). This implies that the temperature dependence of the solubilities of the various PABAs does not differ greatly between analogues, although further investigations are required before this may be confirmed. The results found in the present study are in reasonable agreement with those measured at 25°C given by Paruta (1984).

In all four cases, the dissolution profiles were linear, thus validating the constant surface area

disc method used. A linear relationship was also observed between dissolution rate and the solubilities of the PABAs (Fig. 3). This may initially appear to be an unexpected result when considering the Noyes-Whitney equation under sink conditions

$$dm/dt = DA/h \cdot (C_s) \quad (1)$$

where dm/dt is the dissolution rate, D denotes the diffusion coefficient, A is the area of the dissolving surface, h represents the diffusion layer thickness and C_s is the concentration in the diffusion layer, taken as being equal to the aqueous solubility. As A is identical for all samples, the linear relationship between dm/dt and C_s indicates that D/h is constant for the four analogues. However, D is related to the molecular volume of the dissolving species, as shown by the Stokes-Einstein equation

$$D = \frac{kT}{6\pi\eta r} \quad (2)$$

where k is Boltzmann's constant, T denotes the temperature, η is the viscosity of the medium and r represents the radius of the diffusing molecule. As the diffusion coefficient will be related to the molecular volume, and hence weight, the value of D will not remain constant for all four samples.

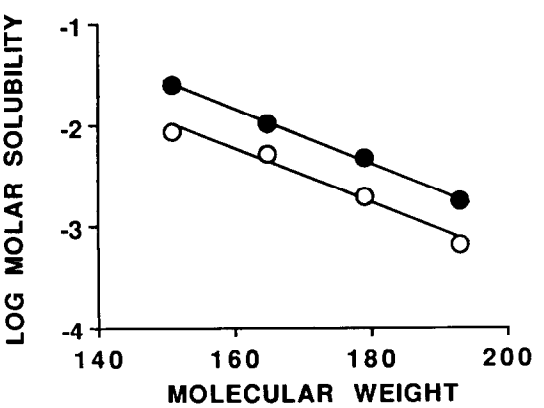

Fig. 2. Log molar solubility dependence of molecular weight at 25°C (○) and 37°C (●). The data shown for 37°C are taken from Yalkowsky et al. (1972a).

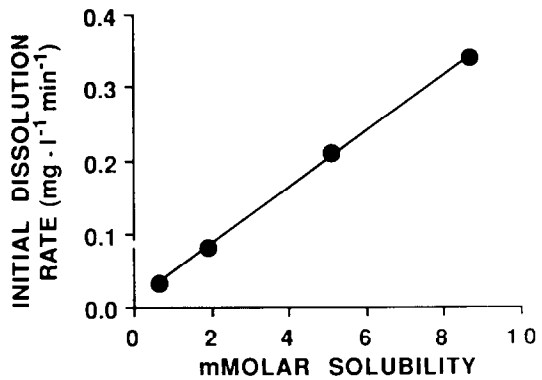

Fig. 3. Relationship between initial dissolution rate and molar solubility of PABAs.

This may, however, be largely explained by considering the factors determining the diffusion coefficient. From Eqn 2, the ratio of diffusion coefficients between the method and butyl PABAs is given by

$$\frac{D(\text{methyl})}{D(\text{butyl})} = \frac{r(\text{butyl})}{r(\text{methyl})} \quad (3)$$

as all other terms in Eqn 2 will remain constant. The radius may be estimated from the molar volumes (V) given by Yalkowsky et al. (1972a), assuming the molecules to be spherical, hence

$$\frac{D(\text{methyl})}{D(\text{butyl})} = \frac{\sqrt[3]{V(\text{butyl})}}{\sqrt[3]{V(\text{methyl})}} = \frac{\sqrt[3]{176.6}}{\sqrt[3]{128.0}} = 1.113 \quad (4)$$

Inspection of Fig. 3 indicates that differences in D of this magnitude are unlikely to result in a substantial change in slope at either end of the curve, providing h does not vary greatly between the PABAs. The diffusion layer thickness may be estimated by

$$h = [\eta/\rho(\text{rps})]^{1/2} \quad (5)$$

where η and ρ are the viscosity and density of the medium and rps is the rotation speed (Nel-

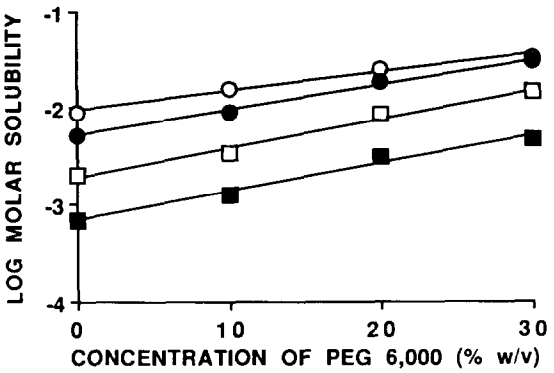

Fig. 4. Relationship between log molar solubility and solvent composition: (○) methyl PABA; (●) ethyl PABA; (□) propyl PABA; (■) butyl PABA.

son, 1957). As none of these parameters will change on altering the PABA used, the assumption that h remains constant is reasonable. It may therefore be concluded that the data may be explained by the Noyes-Whitney equation.

The solubilities of PABAs in solutions of increasing concentrations of PEG 6000 are shown in Fig. 4. It was not possible to investigate the solubility of more concentrated solutions due to the high viscosities of solutions containing greater quantities of PEG 6000. In all cases, a log-linear relationship was found. This is in agreement with the empirical relationship for drug solubility in cosolvent systems proposed by Yalkowsky et al. (1972b)

$$\log S = \log S_w + \sigma f \tag{6}$$

where S is the solubility in the solvent under investigation, S_w denotes the solubility in water, σ is a constant and f the proportion of PEG present in the solvent.

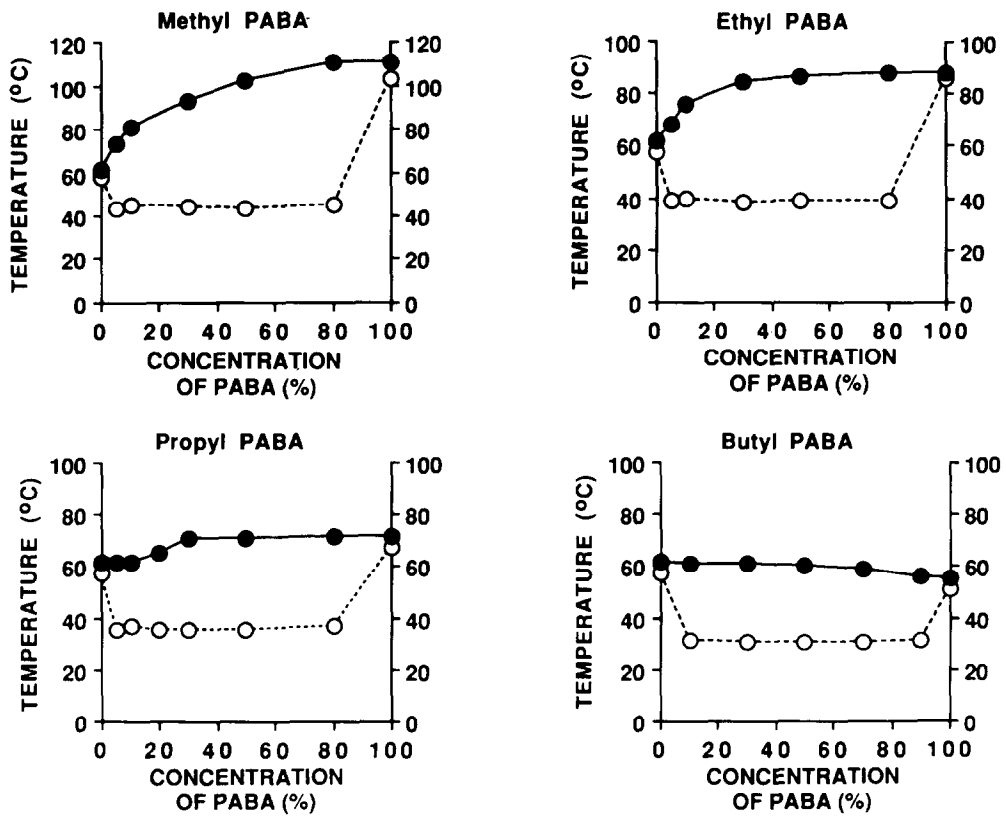

Fig. 5. Phase diagrams for physical mixtures of PABAs and PEG 6000: (○) initial melting temperature; (●) final melting temperature.

Characterisation of PABA / PEG 6000 physical mixtures

The phase diagrams of physical mixtures of the substances have been determined (Fig. 5). Little evidence for eutectic formation was apparent. It is interesting to note that the PEG commenced melting at considerably lower temperatures in the presence of the PABAs. Further studies are required in order to explain this phenomenon.

Characterisation of PABA / PEG 6000 solid dispersions

The phase diagrams for the solid dispersions are shown in Fig. 6. There was evidence for eutectic formation in all four cases, both from the melting behaviour and from observations using optical microscopy.

The dissolution curves of the solid dispersions were initially linear but then showed some curvature, as shown for the methyl PABA profiles given in Fig. 7. The initial dissolution rates have therefore been calculated and will be used for subsequent discussions. The rate was highest from the 10% w/w dispersions in all cases, with smaller changes being seen for the 20 and 50% w/w dispersions compared to the pure PABAs. The dissolution data for the PABA systems are shown in Fig. 8. A linear relationship was found between drug dissolution rate from the dispersions and solubility of the pure materials (Fig. 9), with correlation coefficients of 0.981, 0.984 and 0.952 for the 10, 20 and 50% w/w dispersions, respectively. This linear relationship was also seen for the pure materials themselves (Fig. 3).

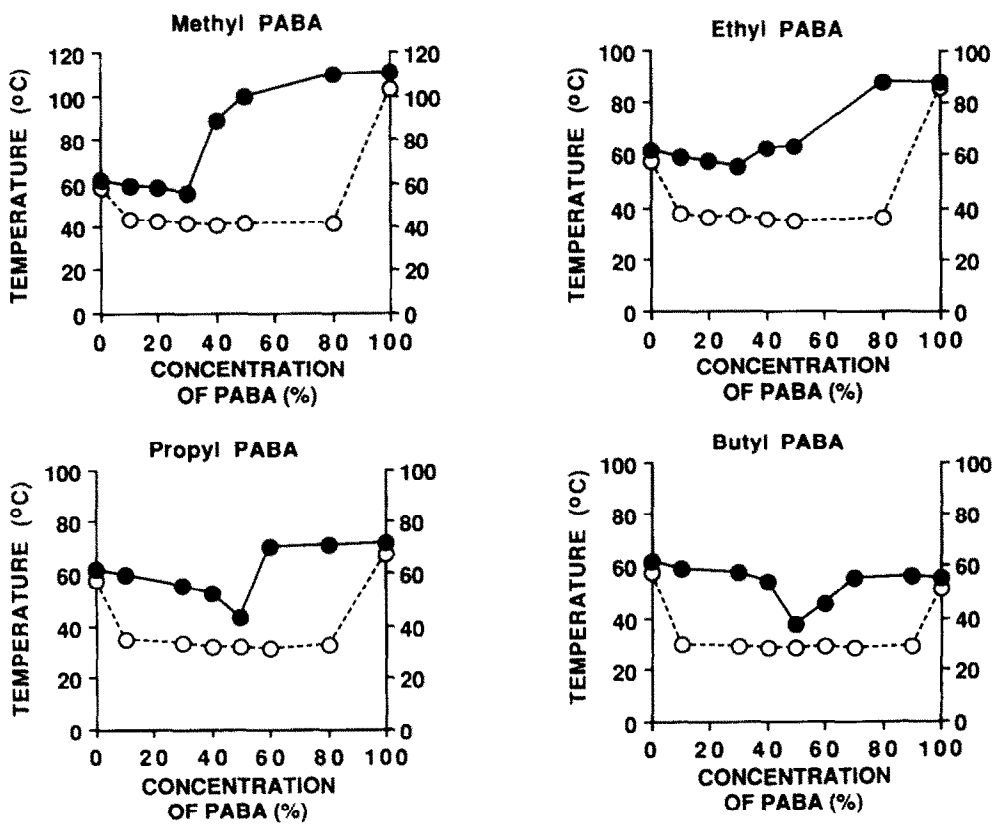

Fig. 6. Phase diagrams for solid dispersions of PABAs and PEG 6000: (○) initial melting temperature; (●) final melting temperature.

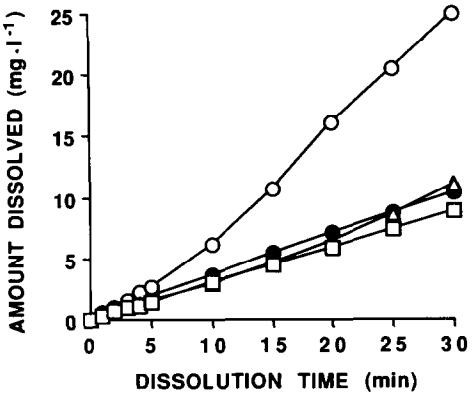

Fig. 7. Dissolution rate profiles for raw material and solid dispersions of methyl PABA. (●) Raw material; (○) 10% w/w solid dispersions; (△) 20% w/w solid dispersions; (□) 50% w/w solid dispersions.

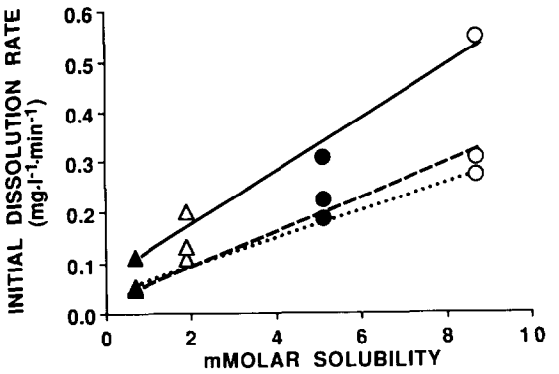

Fig. 9. Initial intrinsic dissolution rate of PABA dispersions vs aqueous PABA solubility. (○) Methyl PABA; (●) ethyl PABA; (△) propyl PABA; (▲) butyl PABA. Concentrations: (———) 10%; (– – – – –) 20%; (· · · · ·) 50% w/w drug.

Mechanisms of dissolution

The difference in release rates of the PABAs from the dispersions indicates that dissolution is not solely controlled by that of the PEG 6000, as were this the case, then the dissolution rates of all four PABAs from the various dispersions at any particular drug concentration would be largely similar. Carrier controlled dissolution has been previously reported in a number of studies (e.g., Corrigan et al., 1979; Dubois and Ford, 1985; Craig and Newton, 1992) in which evidence was presented for the dissolution rate being independent of the nature of the drugs used in these particular studies up to certain concentrations. However, both the present study and that of Sjökvist and Nyström (1988) demonstrate that different mechanisms predominate in the dissolution of various solid disperse systems.

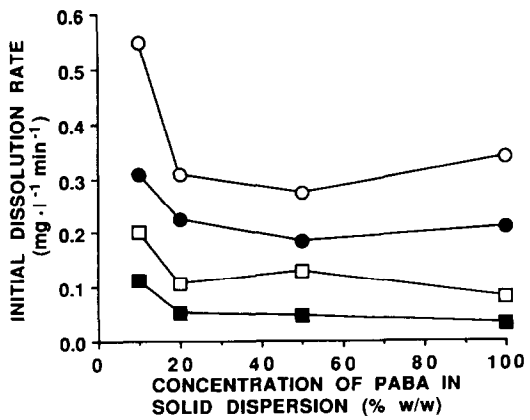

Fig. 8. Relationship between initial intrinsic dissolution rate and concentration of PABA in solid dispersions. (○) Methyl PABA; (●) ethyl PABA; (□) propyl PABA; (■) butyl PABA.

If the dissolution of the PABAs is diffusion rate limited, then it is reasonable to assume that the dissolution rate from the solid dispersion is similarly diffusion controlled, as it would be highly coincidental for a second, unrelated mechanism to also show a linear relationship with aqueous solubility of the pure material. If the mechanism of dissolution is similar or identical for the pure materials and the solid dispersions, then the question arises as to why the dispersions show increased dissolution rates compared to the pure materials (Fig. 8), at least at lower drug contents. It should also be noted that the 10% w/w dispersions give a higher absolute dissolution rate than the pure materials, despite the smaller proportion of drug present in the solid surface. In this respect, re-examination of the Noyes-Whitney equation is helpful (Eqn 1).

Assuming sink conditions, there are four parameters which could differ between the PABA raw materials and the solid dispersions. Firstly, the diffusion coefficient could differ between the two systems. Consideration of Eqn 2 indicates that the only parameter liable to change is the

viscosity, which is likely to increase in the presence of PEG, thus decreasing the diffusion coefficient and hence dissolution rate.

Secondly, the diffusion layer thickness could be reduced. However, examination of Eqn 4 indicates that this is also unlikely, as again the increase in viscosity caused by the presence of PEG in the diffusion layer is likely to result in a thicker layer, hence a slower rate.

Thirdly, the value of C_s could be increasing. It has been argued previously that the solubility in the diffusion layer may be of relevance to a number of systems (e.g., Goldberg et al., 1966; Chiou and Niazi, 1971; Collett and Flood, 1976; Sjökvist et al., 1991; Craig and Newton, 1992). However, if the drug solubility in the diffusion layer is sufficient to render the dissolution of PEGs to be the rate limiting step, then the system would be carrier controlled and no difference would be seen between the different PABAs. Alternatively, if the dissolution of the PEG interface was faster than the dissolution of the drug particles, then those particles would be released largely intact into the bulk medium and would not be exposed to the high concentrations of PEG necessary for this mechanism to operate.

Finally, the area available for dissolution could be increased. This could occur if the particles were being released into the medium as the PEG dissolved, as discussed above. The positive deviation of the dissolution curves from linearity seen in Fig. 7 may then be interpreted in terms of the accumulation of drug particles in the medium, as predicted by Craig and Newton (1992). While this mechanism is in accordance with the data obtained, there are further points that should be considered. Solubilisation of the PABAs may take place to some extent prior to release of the particles from the matrix, hence the mechanism may be more complex than a simple increase in surface area. Furthermore, the linear relationship between apparent initial intrinsic dissolution rate from the dispersions and PABA aqueous solubility requires the DA/h term in Eqn 1 to remain similar for all four molecular weights, as this term is essentially the slope of the graphs given in Fig. 9. This will be the case if the sizes of the released particles are similar for each corresponding PABA dispersion, from which it follows that the number of particles released in unit time will be the same.

It is also noted that the 10% w/w dispersions dissolved faster than the 50% w/w systems, despite a smaller particle size for the latter due to eutectic formation. Higuchi (1967) predicted that when two non-interacting systems dissolve together, one species may form a layer across the surface of the solid at high concentrations of that component, from which diffusion and dissolution take place. Corrigan (1985) and Dubois and Ford (1985) have suggested that such a mechanism may be of relevance to solid dispersions at high drug concentrations. The relatively constant values of the dissolution rates at high drug concentrations reported here would support this hypothesis. It is therefore suggested that for the present systems there is a critical drug content between 10 and 20% w/w, below which particles are released intact into the medium but above which the continuous diffusion layer forms on the surface of the dispersion.

Conclusions

This study has investigated the dissolution and melting behaviour of a range of PABA dispersions in PEG 6000. The results have established that linear relationships exist between melting temperature, log molar solubility and the molecular weight of the PABAs. A linear relationship was also found between initial dissolution rate and aqueous solubility of the pure substances for both the PABAs alone and the PABA dispersions in PEG 6000. For solid dispersions containing the PABAs, dissolution was most rapid from the systems containing 10% w/w drug, while the 20% w/w, 50% w/w and pure drugs gave similar initial dissolution rates. These findings suggest that at relatively low drug concentrations (10% w/w), the drug is released into the medium as individual particles, hence providing a large surface area for dissolution. At higher concentrations, the results are consistent with the concept that the drug forms a continuous layer across the dissolving surface, hence producing a rate con-

trolling barrier which is independent of drug loading.

The data presented here indicate that in addition to the mechanisms of carrier controlled dissolution and continuous drug layer formation suggested by Dubois and Ford (1985), there is a third mechanism which involves the release of intact particles, from which dissolution occurs over a large surface area. The importance of this mechanism has frequently been suggested (e.g., Chiou and Riegelman, 1971) but few studies have provided evidence for its involvement, one exception being the investigation of griseofulvin dispersions in PEG 3000 by Sjökvist and Nyström (1988). The factors which determine the predominance of the different mechanisms are still not understood, although these considerations are of direct practical relevance, as a knowledge of the mechanisms involved for a particular product will enable the formulator to control the dissolution behaviour and physical stability of the system.

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References

Chiou, W.L. and Niazi, S., Phase diagram and dissolution rate studies on sulphathiazole-urea solid dispersions. *J. Pharm. Sci.*, 60 (1971) 1333–1338.

Chiou, W.L. and Riegelman, S., Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.*, 60 (1971) 1281–1302.

Collett, J.H. and Flood, B.L., Some effects of urea on drug dissolution. *J. Pharm. Pharmacol.*, 28 (1976) 206–209.

Corrigan, O.I., Mechanisms of dissolution of fast release solid dispersions. *Drug Dev. Ind. Pharm.*, 11 (1985) 697–724.

Corrigan, O.I., Murphy, C.A. and Timoney, R.F., Dissolution properties of polyethylene glycols and polyethylene glycol-drug systems. *Int. J. Pharm.*, 4 (1979) 67–74.

Craig, D.Q.M. and Newton, J.M., Characterisation of polyethylene glycols using differential scanning calorimetry. *Int. J. Pharm.*, 74 (1991) 33–41.

Craig, D.Q.M. and Newton, J.M., The dissolution of nortriptyline HCl from polyethylene glycol solid dispersions. *Int. J. Pharm.*, 78 (1992) 175–182.

Dubois, J.-L. and Ford, J.L., Similarities in the release rates of different drugs from polyethylene glycol 6000 dispersions. *J. Pharm. Pharmacol.*, 37 (1985) 494–495.

Ford, J.L., The current status of solid dispersions. *Pharm. Acta Helv.*, 61 (1986) 69–88.

Goldberg, A.H., Gibaldi, M. and Kanig, J.L., Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II. Experimental evaluation of a eutectic mixture: urea-acetaminophen system. *J. Pharm. Sci.*, 55 (1966) 482–487.

Higuchi, W.I., Diffusional models useful in biopharmaceutics. *J. Pharm. Sci.*, 56 (1967) 315–324.

Molyneaux, P., A versatile and compact piston-filter device for small-scale filtration and related applications. *Lab. Pract.*, 33 (1984) 86–88.

Nelson, E., Solution rate of theophylline salts and effects from oral administration. *J. Am. Pharm. Assoc., Sci. Ed.*, 46 (1957) 607–614.

Paruta, A.N., Thermodynamics of aqueous solutions of alkyl *p*-aminobenzoate. *Drug Dev. Ind. Pharm.*, 10 (1984) 453–465.

Sjökvist, E. and Nyström, C., Physicochemical aspects of drug release. VI. Drug dissolution rate from solid particulate dispersions and the importance of carrier and drug particle properties. *Int. J. Pharm.*, 47 (1988) 51–66.

Sjökvist, E., Nyström, C. and Aldén, M., Physicochemical aspects of drug release XIII. The effect of sodium dodecyl sulphate additions on the structure and dissolution of a drug in solid dispersions. *Int. J. Pharm.*, 69 (1991) 53–62.

Yalkowsky, S.H., Flynn, G.L. and Slunick, T.G., Importance of chain length on physicochemical and crystalline properties of organic homologs. *J. Pharm. Sci.*, 61 (1972a) 852–857.

Yalkowsky, S.H., Flynn, G.L. and Amidon, G.L., Solubility of nonelectrolytes in polar solvents. *J. Pharm. Sci.*, 61 (1972b) 983–984.