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Research paper

A calorimetric investigation into the interaction between paracetamol and polyethlene glycol 4000 in physical mixes and solid dispersions

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Abstract

The solubility, heat of solution and dissolution rate of paracetamol and polyethyelene glycol 4000 (PEG 4000) systems have been studied in order to clarify the nature of the interaction between the two components during dissolution of solid dispersions. The logarithmic solubility of paracetamol demonstrated a non-linear increase with concentration of PEG 4000, while linear relationships between heat of solution in water and concentration were seen for both individual components. However, the heat of solution of paracetamol was found to decrease with increasing concentrations of PEG 4000. Similarly, the heats of solution in water of physical mixes and solid dispersions prepared using two manufacturing protocols were found to be lower than the theoretical values calculated from those corresponding to the individual components. Drug release studies showed a marked increase in paracetamol dissolution rate when prepared as a solid dispersion, with behaviour consistent with carrier controlled dissolution observed at low drug contents which was ascribed to enhanced dissolution of the drug into the diffusion layer of the PEG 4000. The implications of the understanding of this mechanism for the choice of carrier and manufacturing protocol for solid dispersion products is discussed.

Keywords: Dissolution; Calorimetry; Polyethyelene glycol; Solid dispersion; Solubility

1. Introduction

Solid dispersions of drugs in water soluble carriers such as polyethylene glycol (PEG) have been extensively studied as a means of improving the dissolution characteristics of poorly soluble materials [1–3]. The approach involves the preparation of a solid matrix of the two components, usually by melting physical mixes followed by cooling to room temperature. This preparation method has been shown to lead to often substantial increases in the dissolution rates of poorly soluble drugs. However, despite the relative simplicity of these systems, it has proved difficult to reliably characterise their solid state properties, particularly in terms of ascertaining the physical state of the drug within the dispersion [4,5]. Similarly, the mechanisms responsible for the observed increases in dissolution rate are not yet clear. A number of workers have associated the dissolution rate of the drug with that of the carrier (so called carrier controlled dissolution) whereby the rate limiting step to drug release appears to be the dissolution of the carrier itself [6,7], despite it having a higher solubility than the drug. Sjökvist Saers and Craig [8] have suggested that there are essentially three mechanisms involved in drug release, the predominance of each depending on the drug loading and solubility characteristics. Firstly, the carrier may form a concentrated diffusion layer into which the drug dissolves prior to release into the aqueous medium. This mechanism may lead to carrier controlled dissolution as the rate limiting step to drug release is the dissipation of the carrier diffusion layer. It is well established that materials such as polyethylene glycol may increase the solubility of a range of drugs, particularly at high concentrations, hence while the PEG concentration in the bulk medium is unlikely to be sufficiently high to lead to a substantial change in solubility, the concentration in the environment of the dissolving surface may be considerable. The second mechanism, which may be relevant to drugs which have extremely low solubilities, is that the drug particles are released largely intact into the dissolution medium, from which dissolution from a large surface area may take place. This has been suggested for alkyl *p*-aminobenzoates [8] and griseofulvin [9]. Finally, at high drug loadings a drug-rich diffusion layer forms on the

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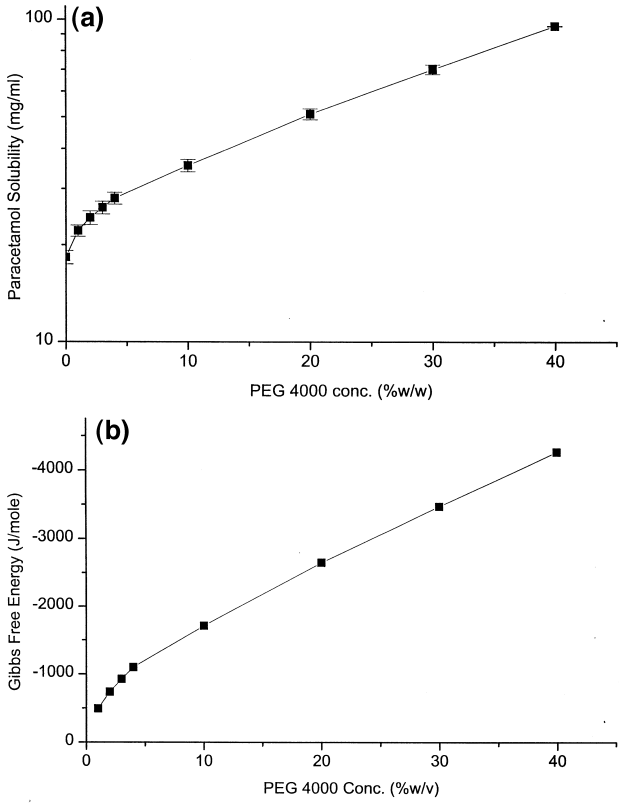

Fig. 1. (a) Solubility and (b) Gibbs free energy of transfer (ΔG_T) for paracetamol in aqueous PEG 4000 solutions at 37°C.

dissolving surface leading to lower dissolution rates relative to drug content compared to lower loadings.

The understanding of the mechanisms involved in the dissolution process is further complicated by the observation that physical mixes of the drug and carrier may also exhibit increases in dissolution rate compared to the drug alone. For example, Daabis and Mortada [10] reported higher phenacetin dissolution rates when mixed with PEG 6000 compared to the drug alone, while Jackowicz [11] reported faster dissolution of prednisolone when mixed with mannitol. Clearly, therefore, knowledge of the interaction between the drug and carrier during the dissolution process may be an essential feature of understanding the mechanism of release from solid dispersions. In this investigation, the use of solution calorimetry as a means of measuring the heat changes associated with the dissolution of physical mixes and solid dispersions is described. This method essentially involves the measurement of the temperature change on mixing a solid with a solvent housed in an adiabatic vessel and has been used as a means of characterising differences in crystal forms of drugs and polymers [12,13], the hydration of non-ionic surfactants [14], the interaction of hydroxypropyl methylcellulose with water [15] and for the detection of interactions between polyethylene glycol and a model drug, nortriptyline HCl [16]. The aim of the present investigation is to use the above approach in conjunction with solubility and dissolution rate studies in order to clarify the role of interactions between the carrier (polyethylene glycol 4000) and a model drug (paracetamol) during the dissolution process.

2. Materials and methods

2.1. Materials

PEG 4000 (Hoechst Ltd., Hounslow, England) was received as white flakes which were ground and sieved, with the <250 μm fraction used throughout the study. Paracetamol powder (Sterling Organics Ltd., Dudley) was sieved into two size fractions (<50, 300–350 μm). Physical mixes were prepared as described in a previous study [5]. Solid dispersions were prepared by weighing 3g quantities of physical mixes into stainless steel cylinders (also used for the dissolution studies) and heating in a programmable oven at 2°C/min to 70 or 100°C for 10 or 60 min as stated in the text, followed by cooling at 2°C/min to room temperature. Samples were then stored for 24 h over phosphorous pentoxide. For solution calorimetry studies, samples were ground, mixed and passed through a 500 μm sieve.

2.2. Solubility studies

Drug samples were placed in SVL22 solubility tubes, as described by Molyneux [17], and agitated for 24 h at 37°C, preliminary studies having indicated that this time period was sufficient to produce saturation. The samples were then filtered and assayed spectrophotometrically at 245 nm. All studies were repeated three times.

2.3. Solution calorimetry

A Tronac model 450 Adiabatic calorimetry (Tronac Inc., Utah) was used throughout the study. The apparatus consists of a silvered Dewar flask containing 50 ml of dissolution medium suspended in a constant temperature bath which was held at 37°C. Samples were filled into 1 ml glass ampoules (Thermometric AB, Järfälla, Sweden) which were sealed and held on a rotating platform. The platform was rotated at 600 rev./min and the system allowed to equilibrate for 1 h, after which electrical calibration was performed by means of a thermistor which imparted a known heating signal to the contents of the dewar. The ampoule was then shattered automatically by means of a plunger and the temperature change noted. The system was checked using potassium chloride and tris(hydroxymethyl)aminomethane, both of which have known heats of solution; a good correlation was found with the published values. Measurements of the heats of solution PEG 4000 and paracetamol in water and, in the latter case, aqueous PEG 4000 solutions were obtained using sample quantities as stated in the text. 50 mg of physical mixes and solid dispersions were also examined, using compositions and

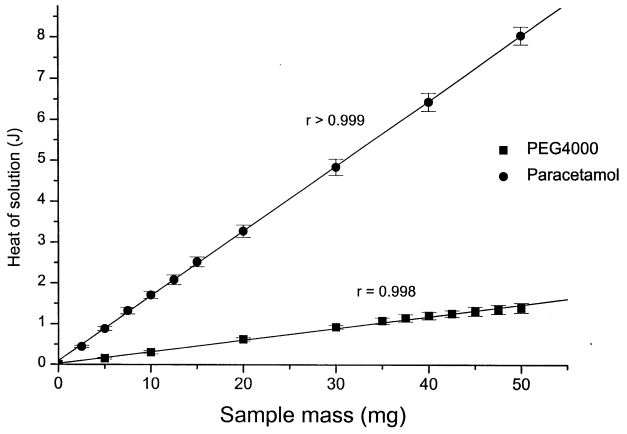

Fig. 2. Heats of solution for paracetamol and PEG 4000 in water at 37°C.

preparation conditions as stated. All experiments were repeated three times.

2.4. Dissolution studies

An adaptation of the method described by Craig and Newton [18] was used throughout the study. Dissolution studies were conducted in a 1 l flat-bottomed glass dissolution vessels maintained at 37°C in a waterbath. The stainless steel cylinders containing the dispersions were screwed onto a steel shaft attached to a motor and suspended in the dissolution vessel and rotated at 100 rev./min. Samples were then removed and measured spectrophotometrically; all experiments were repeated three times.

3. Results and discussion

3.1. Solubility studies

Fig. 1a shows the relationship between the solubility of paracetamol and PEG 4000 concentration. The solubility of the drug clearly increases in the presence of the polymer, with an approximately five-fold rise noted for the highest concentration of PEG 4000 under study compared to water. However, the relationship with polymer concentration appears to be complex. At concentrations >10% w/v, the system appears to follow the empirical relationship suggested for cosolvent systems [19]

$$\ln S = \ln S_w + f\sigma \quad (1)$$

where S is the solubility in the cosolvent system, S_W is the solubility in water, f is the volume fraction of cosolvent and σ is a constant representing the cosolvent solubilising power. The value of σ was calculated as +0.0139, which is in accordance with the suggestion by Gould et al. [20] that semi-polar drugs are expected to yield neutral or slightly positive values of σ in aqueous cosolvent systems. At lower concentrations, however, the solubility does not follow this relationship, with a greater concentration dependence seen below 10% w/v PEG 4000 than was noted for the higher concentrations. It should be noted that a more sophisticated approach to characterising drug solubility in PEG solutions has been suggested by Van den Mooter et al. [21] based on the mobile order and disorder (MOD) approach developed by Huyskens and coworkers [22–26] and further developed by the group of Ruelle for the study of drug solubility [27–33]; the MOD approach to study cosolvent systems is still in early stages and hence has not been utilized here, although it is undoubtedly a highly interesting concept. For the purposes of the present study, however, it is sufficient to calculate the free energy of solute transfer between the cosolvent system and water ΔG_T, which may be calculated via

$$\sigma G_T = -RT \ln S_c/S_w \quad (2)$$

where S_C and S_W are the solubilities in cosolvent and water, respectively. The calculated values are shown in Fig. 1b and indicate that, as expected from examination of the raw data, the negative free energy increases on increasing the concentration of PEG 4000, hence transfer of the drug into the polymer solutions is energetically favourable. These values are of the same order of magnitude as those reported for temazepam in water-PEG 6000 systems [21].

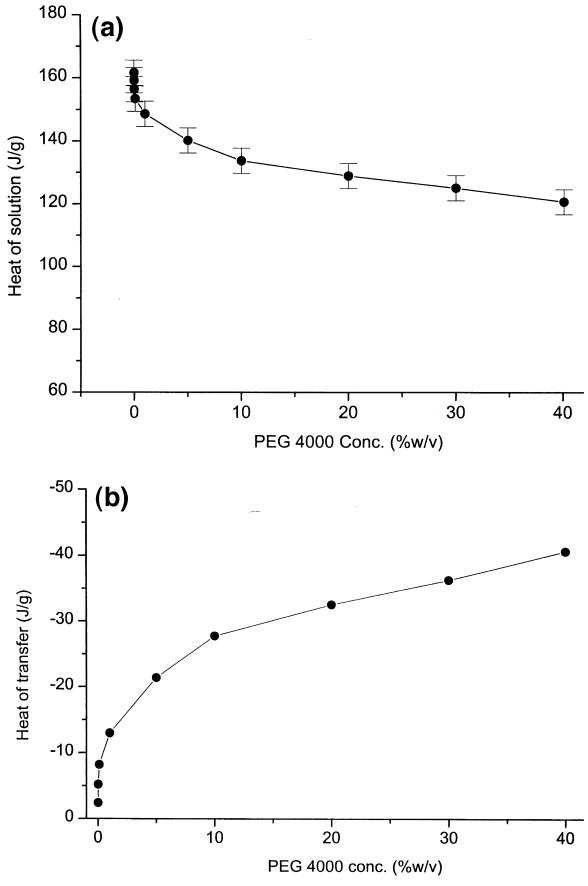

Fig. 3. (a) Heats of solution and (b) heat of transfer for 50 mg paracetamol in 50 ml aqueous PEG 4000 solutions at 37°C.

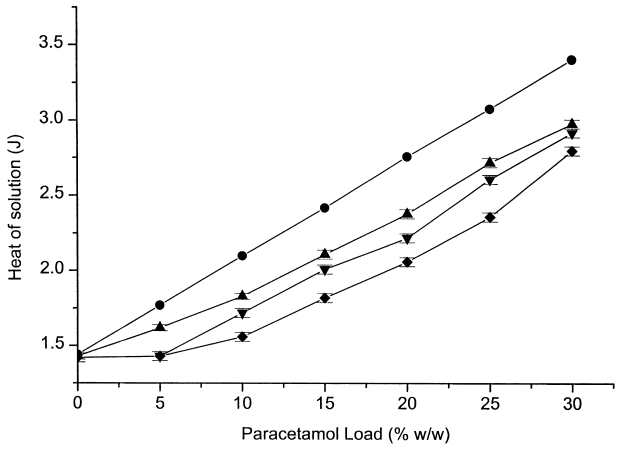

Fig. 4. Heats of solution of 50 mg paracetamol and PEG 4000 physical mixes and solid dispersions in 50 ml water at 37°C. (▲) Physical mixes; (▼) <50 μm, 70°C for 10 min; (◆) <50 μm, 100°C for 60 min; (●) theoretical values calculated from individual component responses (untreated PEG value used).

3.2. Heat of solution measurements

The heats of solution (ΔH_S) of PEG 4000 and paracetamol alone in water are shown in Fig. 2. In both cases, a linear relationship was noted over the concentration range under study. The heats of solution were found to be endothermic in both cases, yielding specific values of 160.0 and 28.9 J/g for paracetamol and PEG 4000, respectively. The enthalpy of paracetamol dissolution in various concentrations of PEG 4000 in water was then studied (Fig. 3a). A decrease in enthalpy of solution was noted with increasing PEG 4000 concentration, the decrease again showing greater concentration dependence at low PEG levels. Further insights into the interaction may be obtained by considering the differences between the heats of solution in water and aqueous PEG 4000 media. The enthalpy of transfer ΔH_T at the PEG concentration under study may be obtained simply from the difference between the heats of solution in water and cosolvent (ΔH_W and ΔH_C), hence

$$\Delta H_T = \Delta H_c - \Delta H_w \quad (3)$$

The calculated values are shown in Fig. 3b. From the solubility and heat of solution studies, it is clear that the presence of PEG 4000 renders the dissolution of paracetamol into aqueous systems more energetically favourable. The heat of solution may be considered to be composed of a solid-solid bond breakage component (ΔH_F^{310}) and an enthalpy associated with solute-solvent interactions (ΔH_M) [13]. As ΔH_F^{310} will be constant for each system under study, the value of ΔH_T reflects the additional interaction energy on mixing the paracetamol molecules with PEG solutions compared to water, with the exothermic values indicating that the process is enthalpically favoured. While caution is required in combining the free energy values from the solubility data with the heat of solution values due to the strong possibility of non-linear concentration effects, similar trends may be seen in both data sets. Both indicate that dissolution into solutions containing PEG 4000 is energetically favourable compared to dissolution into water; similarly, both indicate that the effect is non-linear, with greater concentration dependence seen at lower concentrations of PEG 4000. The mechanism responsible for this effect is not yet clear. Light scattering studies have indicated the existence of regions of microheterogeneity in PEG solutions [34] which may have a bearing on the cosolvency properties of these systems [21]. However, the near linearity of the relationship between ΔH_S and PEG 4000 sample weight shown in Fig. 2 does not support the involvement of such a structural change in this case. Alternatively, the non-linearity may reflect the equilibrium of complex formation between the paracetamol and PEG 4000. The data were found not to fit Hughes–Klotz or Scatchard plots, although given the high concentrations of PEG 4000 involved this is not surprising, as the interaction between the drug and polymer will almost certainly involve breakage of intermolecular polymeric hydrogen bonds which are not accounted for in the aforementioned models (and which render deconvolution of the enthalpy data with regard to the individual processes involved impracticable). Nevertheless, the data clearly indicate that there is an enthalpically favoured interaction between the paracetamol and PEG 4000 which it is reasonable to suggest is associated with the observed increase in solubility.

The heats of solution of physical mixes and solid dispersions were then measured as a function of paracetamol loading, maintaining a constant sample weight of 50 mg. Fig. 4 shows the data for physical mixes and ground dispersions prepared using a drug particle size of <50 μm, and either a fusion temperature of 70°C for 10 min or 100°C for 1 h. The figure also shows the theoretical response obtained by simply adding the individual values of the two components at each composition. Clearly, the measured heats of solution are lower in each case than those expected from the sum of the individual values, with the lower positive enthalpies indicating that the dissolution process is enthalpically favoured. There are probably two effects involved. The results for the solid dispersions may be a function of differences in the energy of solid state bond disruption (ΔH_F^T) indicated by the manufacturing process. A reduction in the heat of fusion of the dispersions compared to the physical mixes brought about by, for example, solid solution formation would be expected to result in a lower heat of solution. Lloyd et al. [5] have indicated that system prepared at higher temperatures using smaller initial drug particle sizes are more likely to form solid solutions, hence the data are compatible with the above hypothesis. The differences between the values for the physical mix and the theoretical data points obtained from the enthalpies of solution of the individual components may be a reflection of the interaction described above. The dissolution of the binary systems is likely to be a complex process, with the possibilities of

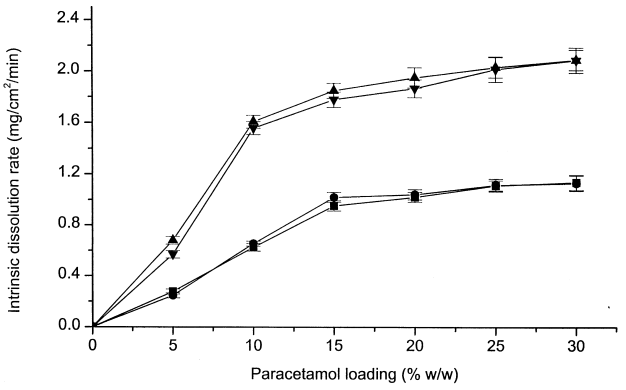

Fig. 5. Dissolution profiles for paracetamol solid dispersions in PEG 4000 at 37°C, not corrected for settling effects. (■) < 50 μm, 70°C for 10 min; (●) <50 μm, 100°C for 60 min; (▲) 300–350 μm, 70°C for 10 min; (▼) 300-350 μm, 100°C for 60 min.

interactions occurring both during dissolution of the particles and at equilibrium in aqueous solution. It is, however, reasonable to suggest that the observation of previous authors that physical mixes of drugs with carriers can result in faster dissolution rates [10,11] may be associated with the more favourable energetics of dissolution noted here.

3.3. Dissolution studies

The dissolution data for the samples prepared using various manufacturing protocols is shown in Fig. 5, with the data expressed in terms of the intrinsic dissolution rate (i.e. the area of the dissolving surface is accounted for). For purposes of comparison, paracetamol compacts were prepared using compression forces of either 3 or 5 tonnes for 30 s. The intrinsic dissolution rates were found to be 0.207 and 0.098 mg/cm^2·min, respectively. Clearly, therefore, preparation of the solid dispersions results in a marked increase in dissolution rate when one considers that the paracetamol compacts dissolved at a comparable rate to the 5% dispersions, despite the 'dry' paracetamol surface area being twenty-fold greater for the compacts. The profiles show a bimodal relationship with nominal drug loading; such profiles have been attributed to carrier controlled dissolution at low concentrations followed by the formation of a concentrated drug diffusion layer at higher loadings [e.g. 7]. It is interesting to note that the only manufacturing parameter which made a significant difference to the profiles was the particle size, with samples prepared from the 300–350 μm fraction showing faster apparent dissolution rates than those using smaller particle diameters. While the dispersions were ground and mixed prior to solution calorimetry studies, it is clearly of importance to ascertain whether the results are being influenced by the establishment of a drug concentration gradient within the stainless steel containers due to settling. UV assay of the underside of the dispersions indicated that the larger particle size system had undergone considerable settling during manufacture (Table 1). When this was accounted for the differences between the systems were considerably reduced; the 5% dispersions showed a proportionately greater dissolution rate, probably as a function of the establishment of a drug-rich diffusion layer for the more concentrated systems. However, the differences for the samples prepared using different particle sizes were extremely small. The settling effect is highlighted because it is not common practice to check whether the dissolving surface of dispersions contains the nominal drug level; the data shown above suggest that it may be advisable to do so.

The absence of a clear dependence of the dissolution rate on preparation method is encouraging from a manufacturing viewpoint and is also compatible with previous studies [18] which suggested that marked differences in cooling rate of the dispersions did not appear to alter the drug release rate. Furthermore, Sjökvist Saers and Craig [8] suggested that if carrier controlled dissolution was determined by the formation of a PEG-rich diffusion layer into which the drug dissolved, then the particle size of the drug should make no difference to the dissolution rate. As Lloyd et al. [5] have already indicated that the preparation methods used here do indeed have a profound effect on particle size, then these studies support the hypothesis that for systems exhibiting carrier controlled dissolution, drug morphology is irrelevant.

Table 1
Parameters associated with the dissolution of paracetamol solid dispersions in PEG 4000 (standard deviations in parenthesis)

Preparation method	Nominal drug load (%w/v)	Uncorrected intrinsic dissolution rate	(mg/cm^2·min)	Drug content upper region	(%w/w)	Drug content lower region	(%w/w)	Corrected intrinsic dissolution rate (mg/cm^2·min·%)
<50 μm, 100°C for 60 min	5	0.247	(0.006)	4.51	(0.1)	5.43	(0.12)	0.0455
300–350 μm, 100°C for 60 min	5	0.568	(0.014)	2.03	(0.1)	12.91	(0.20)	0.0440
<50 μm, 100°C for 60 min	30	1.205	(0.026)	27.87	(0.46)	33.67	(0.54)	0.0358
300–350 μm, 100°C for 60 min	30	2.094	(0.03)	9.43	(0.34)	63.46	(0.96)	0.0330

4. Conclusions

The study has examined the process whereby PEG causes an enhancement in the aqueous solubility of paracetamol, with a particular view to understanding the mechanism by which solid dispersions increase the dissolution rate of incorporated drugs. The data suggest that paracetamol undergoes an interaction with PEG 4000 in aqueous solution which may be associated with both the solubility and the energetics of dissolution of paracetamol into PEG solutions and indeed of solid dispersions and physical mixes. This is of relevance to solid dispersion technology as it has been suggested [8] that at low drug contents whereby carrier controlled dissolution is observed, drugs dissolve into the polymer-rich diffusion layer which then releases the drug into the bulk medium via dispersion of that diffusion layer. Consequently, an understanding of the interaction between the drug and the polymer in aqueous solution is of clear importance in the design and optimisation of solid dispersion dosage forms. For these systems, the manufacturing method had little effect on the dissolution rate (once artefacts due to settling were accounted for) which confirmed the suggestion of Sjökvist and Craig [8] that the particle size of the drug should have little effect on the dissolution rate for carrier controlled systems.

In practical terms, the study has provided a methodology for understanding the extent of interaction between the drug and polymer in solution which may then be used to predict whether carrier controlled dissolution is likely to take place. For example, as the hypothesis outlined by Sjökvist Saers and Craig [8] suggests a direct link between the ability of a polymer to solubilise a drug and its effectiveness as a carrier, it is then logical to suggest that this may be used as a means of screening and optimising carriers for a particular drug. Similarly, the study also suggests that if carrier controlled dissolution is achieved, then the manufacturing method may not necessarily be of importance in determining the release rate, in which case lower fusion temperatures and holding times may be used with no detrimental effects on release behaviour. Overall, therefore, it is suggested that successful exploitation of solid dispersion technology, which offers several advantages in relation to the preparation of poorly water soluble drugs, may be dependent on the development of our understanding of the mechanisms involved, from which the choice of both the formulation and manufacturing protocol may be made on a rational basis.

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