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Characterisation of polyethylene glycol solid dispersions using differential scanning calorimetry and solution calorimetry

D.Q.M. Craig and J.M. Newton

The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX (U.K.)

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Summary

Solid dispersions of nortriptyline HCl in a range of molecular weight PEG samples were manufactured using a low temperature fusion method, whereby the drug remained intact within the dispersion. The phase diagrams obtained using differential scanning calorimetry were monotectic in nature, suggesting that these diagrams represent systems whereby little or no interaction is present between the solid components. Electron micrographs also showed the drug particles to remain largely intact following the fusion process. Studies using solution calorimetry indicated that the heats of solution of the binary systems were lower than theoretically predicted, indicating an interaction between the two components during the dissolution process.

Introduction

The dissolution rates of poorly soluble drugs may be enhanced via incorporation into water soluble polymers, these dosage forms being known as solid dispersions (Chiou and Riegelman, 1971). Polyethylene glycols (PEGs) have been used extensively as carriers for these dispersions due to their favourable solution properties, low toxicity, low melting point and comparatively low cost. PEG solid dispersions are usually manufactured using the fusion method, whereby a physical mixture of the drug and carrier is heated to the fluid state and subsequently cooled to room temperature. The physical states in which the drug and polymer exist within these dispersions are not yet fully understood, although a number of solid-state systems have been reported, including eutectics, solid solutions and glass structures.

The importance of the preparation method on the structure and properties of solid dispersions has previously been outlined (e.g. Chatham, 1985). In the present study, the effect of changing the preparation conditions and the use of a range of molecular weight PEG samples will be described. A low temperature fusion method has been employed in order to study the behaviour of dispersions in which the structure of the drug particles remains largely unchanged during the manufacturing process. This has been performed for two reasons.

Firstly, while some studies have been reported on low temperature fusions (e.g. Hargreaves, 1982; Chatham, 1985), the majority of work has been based on systems whereby complete dissolu-

Correspondence: D.Q.M. Craig, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, U.K.

tion of the drug in the molten carrier has been achieved. However, the temperature required to melt both components may result in drug degradation. Furthermore, if the fluid is to be filled into hard gelatin capsules (Walker et al., 1980), the maximum filling temperature that may be used is approx. 70°C, above which degradation of the capsule shell occurs (Cole, 1989). The low temperature method may therefore offer advantages in terms of drug stability and ease of manufacture. Secondly, if the drug particles remain largely intact within the carrier, the solid state of the resulting dispersions should be largely predictable. If so, this may lead to a greater understanding of the properties and behaviour of solid dispersions in general, as solid state changes to the drug may be excluded as an explanation for any observed phenomena. In particular, differential scanning calorimetry (DSC) and solution calorimetry will be used in order to characterise the solid state and solution properties of the dispersions.

Materials and Methods

Materials

PEGs 3400 (CSD, Cheshire), 6000 (CSD, Cheshire), 10 000 (BDH, Poole) and 20 000 (BDH, Poole) were used, these batches having been previously characterised (Craig and Newton, 1991a,b). The model drug was nortriptyline hydrochloride (Eli Lilly, Basingstoke), a tricyclic antidepressant (molecular weight 299.8) formerly used in the treatment of endogenous depression and nocturnal enuresis in children. While the drug now has limited clinical application, preliminary studies showed the drug to possess suitable physical and chemical properties for the present investigation. These include a sufficiently high aqueous solubility for solution calorimetry work and a measurable melting peak for DSC studies. This melting point is given in the British Pharmacopoeia (1988) as approx. 491 K, although a melting range of 489–492 K has been reported (Peters and Hennion, 1964). No evidence has been reported for the presence of additional polymorphic forms. The material was passed through a 120 μm sieve and the undersize fraction used for subsequent experimental work. Samples were stored away from light in airtight containers.

Batches (25 g) of polyethylene glycol-nortriptyline HCl mixes were prepared by weighing the appropriate quantities of drug and PEG into 100 ml plastic centrifuge flasks. A glass stopper was added to the samples in order to improve mixing and the flask was placed on a roller mixer. The powder batches were blended for 10 min to produce a homogeneous mix and then transferred to a ball mill, whereupon the samples were ground for 30 min in order to break up any aggregates of drug formed during the mixing process.

The dispersions were prepared from the mix by placing 5 g of each mix in a stainless steel nipple and heating to 100°C in an LTE G150 digitally controlled oven (LTE, Oldham). Samples were then slowly cooled at 5°C/h or flash-cooled in liquid nitrogen, as previously described (Craig and Newton, 1991a). The dispersions were ground in a pestle and mortar, the 120–250 μm sample being used for subsequent studies. The resulting powders were assayed to determine the concentration of nortriptyline HCl as preliminary studies showed the quantity of drug in each size fraction to be variable. Studies using nortriptyline HCl alone indicated that the manufacturing protocol used did not result in drug degradation. All fusions were analysed on the day of manufacture.

Methodology

Differential scanning calorimetry (DSC) and solution calorimetry studies were carried out as previously described (Craig and Newton, 1991a,b). DSC studies were conducted on the drug alone and on slow cooled dispersions of nortriptyline HCl in the four molecular weight PEGs over a range of concentrations. Physical mixes and flash cooled dispersions were analyzed at a weight fraction of 10% nortriptyline HCl, while a wider range of physical mixes were analysed for PEG 20 000 systems. All calculations were performed using the measured, as opposed to nominal drug concentrations in the dispersions and mixes.

Examination using scanning electron microscopy was performed using a Joel JSM35 Mi-

croscope (Jeol Ltd., Japan). Samples of PEG 10000, nortriptyline HCl and 10% w/w slow cooled drug dispersions in PEG 10,000 were studied. Solution calorimetry studies were carried out at 298 K on the drug alone and on flash cooled, slow cooled or physically mixed samples, containing a nominal drug level of 10% w/w. The sample size used was 45–50 mg unless otherwise stated, using 50 ml of dissolution fluid. All studies were repeated at least twice, with good reproducibility being found between measurements.

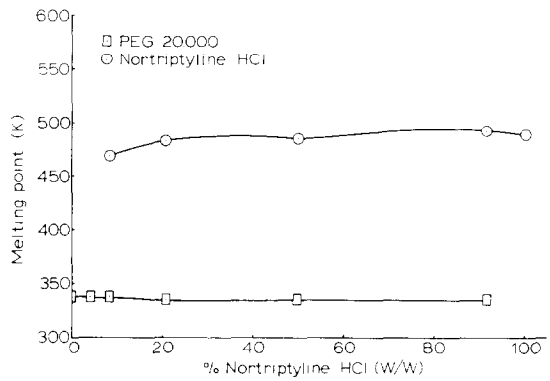

Fig. 1. The melting points of slow cooled solid dispersions containing PEG 3400 and nortriptyline HCl.

Results and Discussion

Differential scanning calorimetry studies

The phase diagram of the slow cooled drug dispersions in PEG 20000 is given in Fig. 1. All other phase diagrams for the slow cooled dispersions showed similar profiles. The diagram indicates that the melting point of the polymer remained approximately constant, with a very small decrease being seen as the proportion of drug increased. A decrease in drug melting point and a broadening of the endotherm was seen as the nortriptyline HCl content was lowered, with no peak being clearly visible for concentrations below 10% w/w.

The molar heats of fusion remained approximately constant over the concentration range studied, with a small decrease as the proportion of either component was lowered. Table 1 shows the melting points (where detectable) and heat of fusion values for the slow and flash cooled 10% w/w samples and the corresponding physical mixes. The heats of fusion for the drug have not been included as extensive peak broadening precluded accurate measurement. It can be seen that the preparation method and molecular weight of the PEG sample may have a significant effect on the resulting endotherms, as discussed in a previ-

TABLE 1

Melting points and molar heats of fusion for 10% w/w physical mixes, flash cooled and slow cooled dispersions of nortriptyline HCl in polyethylene glycols

Polyethylene glycol mol. wt.	Treatment	Melting point (PEG) (K)	Heat of fusion (kJ/mol)	Melting point (Drug) (K)
PEG 3400	Physical mixture	331.2	712.8	475.7
	Flash-cooled	323.4, 331.3	681.4	465.8
	Slow-cooled	330.8	678.2	468.3
PEG 6000	Physical mixture	335.5	1579.0	478.9
	Flash-cooled	326.2, 332.8	1345.1	–
	Slow-cooled	335.6	1475.2	476.0
PEG 10000	Physical mixture	336.0	2911.5	470.8
	Flash-cooled	334.5	2670.2	470.5
	Slow-cooled	335.6	3031.7	469.0
PEG 20000	Physical mixture	336.2	4169.3	474.9
	Flash-cooled	334.2	3462.3	–
	Slow-cooled	336.2	4234.4	468.2

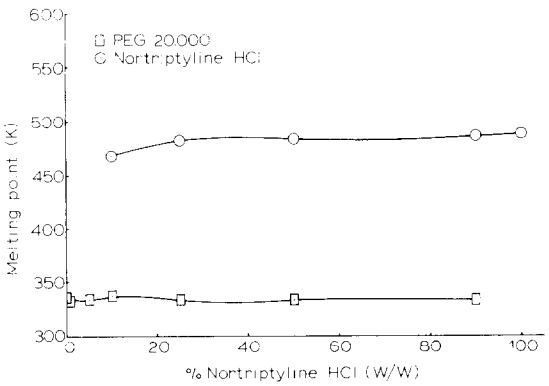

Fig. 2. The melting points of physical mixes containing PEG 20000 and nortriptyline HCl.

ous report (Craig and Newton, 1991a). Furthermore, the flash-cooled PEG 6000 dispersions showed two melting endotherms for the PEG while the drug endotherm could not be clearly distinguished from the baseline. It has been suggested (Craig, 1990) that such a combination of responses may lead to difficulties in interpreting phase diagrams, as in certain systems the endotherms for the two PEG crystal forms may be confused for separate drug and PEG melting peaks. The phase diagram corresponding to physical mixes of the drug and PEG 20000 is given in Fig. 2. The melting point of the drug again decreased at low concentrations, with only a small change being seen in the melting point of PEG 20000.

The phase diagrams obtained from the melting point data of the dispersions and mixes showed no evidence for the presence of eutectics or solid solutions. The diagrams were similar, however, to those reported as monotectic systems (e.g. Najib and Suleiman, 1989; Craig, 1990), as the melting points of the PEGs remained essentially constant while a more sizeable change was seen for the nortriptyline HCl, especially at low drug levels. Monotectic systems are binary mixtures whereby the melts are miscible but there is negligible interaction in the solid state (Vasil'ev, 1964). This may also be considered in terms of bond energies, whereby the energy between the drug and polymer in the liquid state (U_{DP}) is effectively the same as that between drug molecules (U_{DD}). If $U_{DP} > U_{DD}$, then a eutectic system will be formed, while if $U_{DD} > U_{DP}$, then a region of liquid-liquid immiscibility will be seen. However, two further considerations must be taken into account. Firstly, the decrease in drug melting point was not as marked as has been reported for other monotectic systems (e.g. Chatham, 1985; Najib and Suleiman, 1989). However, in the present case it was not possible to identify a specific drug melting point at the lowest concentrations as the endotherms could not be clearly distinguished from the baseline. These broad endotherms nevertheless corresponded to temperatures well below the melting point of the drug alone. Secondly, it is unlikely that U_{DD} and U_{DP} will be truly identical, hence strictly speaking a monotectic will seldom be present, in the same way that a pure eutectic with no solid solubility may not occur. However, the distinction between monotectic and eutectic systems is useful because it allows description of dispersions whereby the extensive particle size reduction implicit in eutectic formation is not present. Instead, the term monotectic implies that the drug remains essentially intact or recrystallises back into discrete particles after melting.

Electron microscopy studies

Electron micrographs for PEG 10000, nortriptyline HCl and slow-cooled 10% w/w drug dispersions in PEG 10000 are shown in Fig. 3a, b and c respectively. The drug particles appeared to remain essentially intact after fusion but were partially covered by the recrystallised PEG. No evidence of eutectic formation was seen. These results are in qualitative agreement with the conclusions drawn from the DSC studies.

Solution calorimetry studies

The heat of solution of nortriptyline HCl was measured as 27.66 ± 0.32 kJ/mol (equivalent to 92.26 kJ/kg) using a sample size of approx. 50 mg. The values for the 10% solid dispersions and physical mixes are shown in Table 2. Erb (1984) has suggested that the total heat of solution (ΔH_{ST}) for a non-interacting binary system will

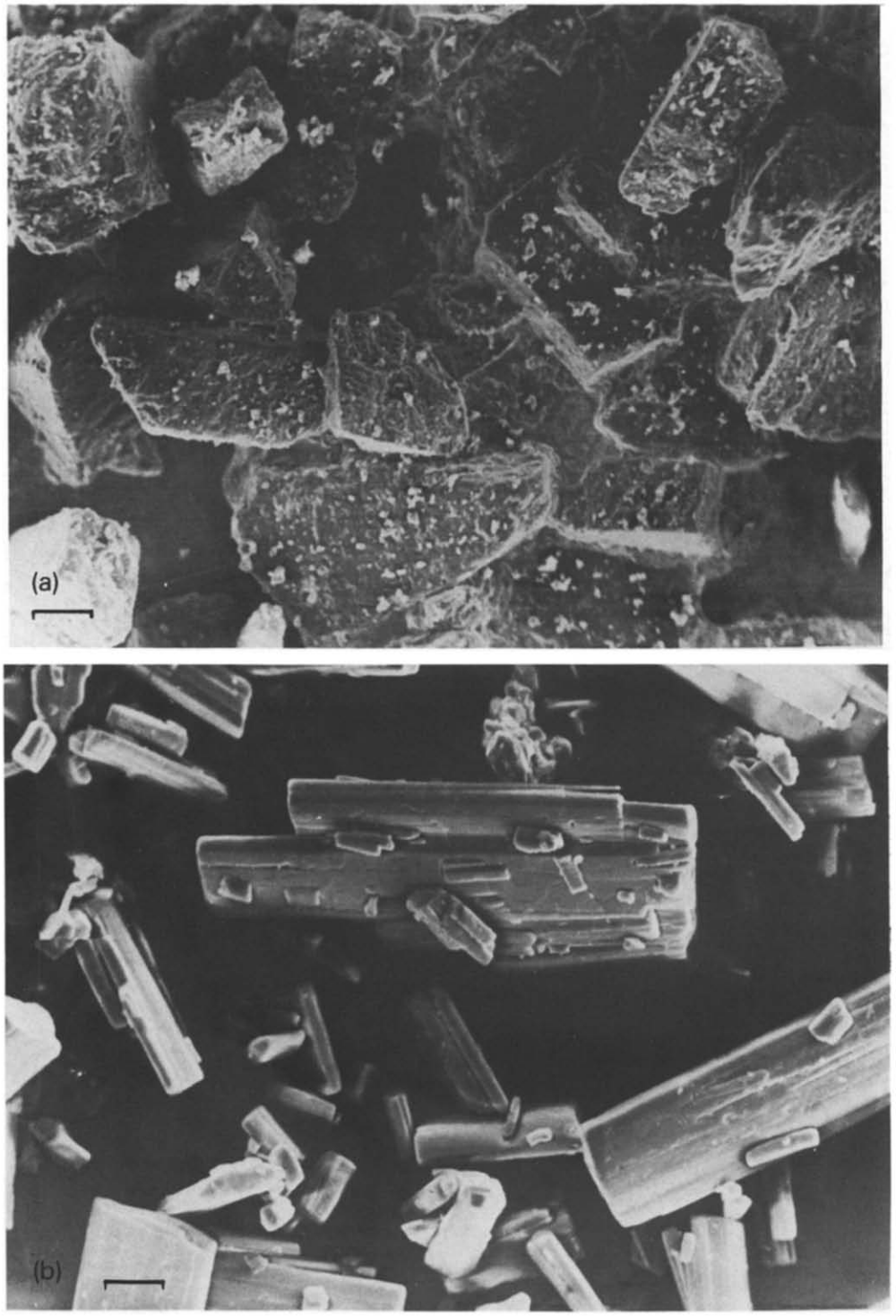

Fig. 3. Electron micrographs of (a) PEG 10000, (b) nortriptyline HCl, (c) slow cooled 10% w/w nortriptyline HCl in PEG 10000. Bar in (a) 133 μm, in (b) 20 μm, in (c) 26 μm.

TABLE 2

Heats of solution at 298 K for 10% nortriptyline HCl in polyethylene glycols subjected to various preparation conditions (theoretical values in parentheses)

Nominal molecular weight	Heats of solution (kJ/kg)		
	Powder mixes	Slow-cooled	Flash-cooled
3400	12.53	11.88	8.69
	(17.31)	(15.35)	(9.39)
6000	18.32	10.72	8.03
	(20.11)	(16.18)	(11.08)
10000	13.53	17.31	3.48
	(13.04)	(17.75)	(4.83)
20000	9.84	16.09	0.54
	(11.23)	(19.20)	(2.39)

be equal to the sum of the heats of the individual components. This may be given by

$$\Delta H_{ST} = X_A \cdot \Delta H_{SA} + X_B \cdot \Delta H_{SB} \quad (1)$$

where X and ΔH_S are the weight fractions and specific heats of fusion for two non-interacting substances, A and B. Using Eqn 1, it is possible to calculate theoretical values for ΔH_S of the dispersions, using the data for the pure polyethylene glycols given in a previous report (Craig and Newton, 1991b) and the value for nortriptyline HCl given above. These theoretical values are shown in Table 2 with each experimental result.

While there was reasonable agreement between the theoretical and experimental values, in the majority of cases the theoretical values were higher (i.e. more endothermic) than those found experimentally. The observed discrepancies may be a reflection of a solid state interaction between the drug and PEG as a result of the fusion process, although this is considered unlikely as the manufacturing protocol was designed specifically to prevent any such interaction. Furthermore, the observation that ΔH_S for the physical mixes were also less than the theoretical values is

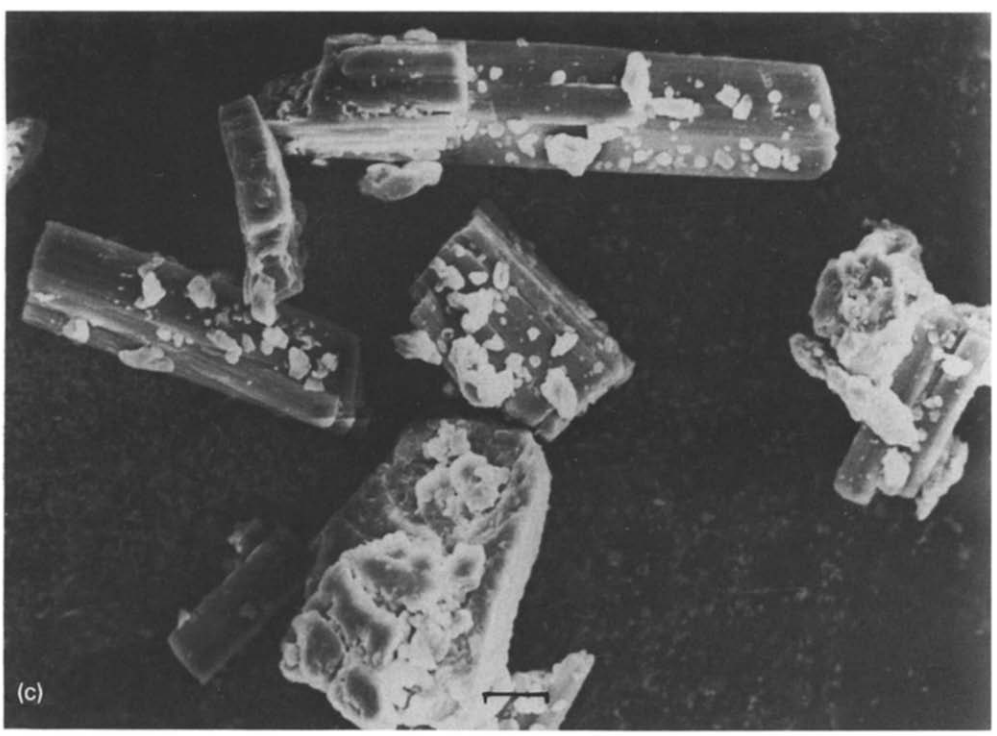

Fig. 3 (c).

not consistent with this hypothesis. An alternative explanation is that there could be an interaction between the two components during the dissolution process. This possibility was investigated by measuring the heat of solution of the PEGs 3400 and 20000 in an aqueous solution of 0.01% w/v nortriptyline HCl. The values were found to be 34.21 kJ/mol and 89.42 kJ/mol respectively. Comparison with the results given in a previous study (Craig and Newton, 1991b) indicated that there was little difference between the values of ΔH_S in the two solvents. 5 mg samples of nortriptyline HCl were then dissolved in a 0.1% solution of PEG 3400 and PEG 20000. The heats of solution were found to be 29.16 kJ/mol and 29.15 kJ/mol respectively. While these values are higher than those found for the 50 mg sample of nortriptyline HCl in water, studies using 5 mg of drug in water gave a heat of solution of 29.13 kJ/mol which is in good agreement with the above measurements. However, the non-linearity between the heat of solution and the drug sample size does not explain the discrepancy between the theoretical and experimental results obtained for the dispersions. On the contrary, if the value of ΔH_S corresponding to 5 mg of drug is used in Eqn 1, the discrepancy becomes larger. The results therefore indicate that an interaction may be occurring between the PEG and drug, but only when both components are dissolving simultaneously.

Conclusions

The study has investigated the use of a low temperature fusion technique in the preparation of solid dispersions, both as a method of manufacturing these systems and also as a means of producing dispersions in which the solid state of both components is largely predictable. As the temperature of fusion was considerably below the melting point of the nortriptyline HCl, the drug was expected to remain essentially intact throughout the manufacturing process. This hypothesis has been supported by the electron microscopy and DSC studies, the latter producing monotectic phase diagrams for both the dispersions and corresponding physical mixes. The study has also highlighted the observation that changes in the melting points of the components may occur in the absence of eutectic and solid solution formation.

The solution calorimetry studies indicated that less heat was absorbed during the dissolution of the binary systems than was expected from the ΔH_S values of the individual components. However, these changes were only apparent when both components were dissolving simultaneously. This observation may be of relevance to the interpretation of the increase in drug dissolution rate noted for many solid disperse systems.

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