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The dissolution of nortriptyline HCl from polyethylene glycol solid dispersions

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Summary

The dissolution characteristics of nortriptyline hydrochloride dispersions in a range of different molecular weight polyethylene glycol carriers have been investigated. The release rate was found to be higher from dispersions in PEG 3400 than from the drug alone, while a logarithmic decrease was seen with increasing carrier molecular weight. Studies indicated that there was little difference in release rate from flash- and slow-cooled dispersions. A linear relationship was found between drug dissolution rate and concentration in PEG 20000 up to 25% w/w drug. The release rate was shown to increase with rotation speed, although the results obtained were not consistent with the relationship proposed by Levich (Levich, V.G., *Physicochemical Hydrodynamics*, Prentice Hall, NJ, 1962, pp. 60–72). A hypothesis has been presented for the involvement of solubilisation of the drug at the solid-liquid interface as a mechanism for the observed dissolution behaviour.

Introduction

The dissolution rates of poorly soluble drugs may be enhanced by incorporation into water-soluble polymers such as polyethylene glycols (PEGs) (Chiou and Riegelman, 1971). This manufacturing process usually involves heating a physical mixture of the drug and carrier to the fluid state, followed by cooling to room temperature. The mechanisms involved in the observed increases are as yet poorly understood, although several explanations have been proposed. These include particle size reduction, decreased aggregation and agglomeration, improved particle wetting and increased drug solubility.

One of the principal difficulties in studying drug release from solid dispersions has been the separation of the roles of solid-state phenomena from those of solution phenomena in the dissolution process. It is intended that the present study will examine the mechanisms involved in the dissolution of a relatively simple binary system, whereby the drug is believed to exist largely as

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discrete particles within the dispersion due to the use of a low-temperature fusion technique (Craig and Newton, 1991a). The systems under study are therefore considered to be similar to physical mixtures of the drug and carrier. In this respect, it is useful to examine the relationship between the dissolution rate of physical mixtures and their corresponding dispersions.

When powder mixtures and ground dispersions are compared by addition of the loose powder to a dissolution bath, the dissolution rate is usually considerably higher from the dispersion systems (e.g., Ravis and Chen, 1981; Venketaram and Rogers, 1984). However, the powder mixture may also show an increase in dissolution rate compared to the drug alone. A study by Maulding (1978) showed that a physical mixture of micronised hydrocortisone with urethan resulted in a considerable increase in dissolution rate compared to that of the drug alone. Moreover, the dissolution rate of the drug in a solution in which urethan had previously been dissolved was not significantly enhanced. Similarly, physical mixtures of phenacetin with PEG 6000 and urea yielded higher release rates than that of the drug alone (Daabis and Mortada, 1980), while Jackowicz (1987) showed an increase in prednisolone release from powder mixtures with mannitol. This increase was similar to that seen for the corresponding disperse systems, although when sorbitol was used as the carrier the dispersion yielded a much higher dissolution rate than the physical mixture.

Increases in dissolution rates compared to the drug alone have also been reported for systems whereby physical mixtures of the drug and carrier have been tabletted to form a constant surface area disc (e.g., Badawi and El-Sayed, 1980). A study by Ford and Rubinstein (1978) compared compressed discs of physical mixtures containing indomethacin and PEG 6000, discs of dispersions prepared by the melt method and direct compression discs of indomethacin alone. The melt discs gave considerably higher dissolution rates than did the physical mixtures, which in turn gave higher rates than the indomethacin alone. Corrigan and Timoney (1976) showed little difference in release rate from constant surface area discs of dispersions and physical mixtures of hydroflumethiazide and PEG 4000 up to high carrier concentrations.

A similar set of observations have been made for low-temperature fusions. For example, Chemtob et al. (1987) compared powdered physical mixtures of niclosamide and PEG 6000 with fused systems prepared at 368 K and at a temperature corresponding to complete drug dissolution in the carrier. While the higher temperature fusions yielded faster drug release rates than did the other two samples, no clear rank order was seen between the rate from the low-temperature fusions and physical mixtures containing various drug concentrations. All three systems gave higher dissolution rates than the drug alone.

The above results imply that two processes are involved in the dissolution of the solid dispersions. Firstly, there is probably a mechanism common to the physical mixtures and both the low- and high-temperature fusions, causing all three to yield increased dissolution rates compared to the drugs alone. A possible explanation for this phenomenon is that the presence of the carrier reduces aggregation and agglomeration of the drug particles, thereby increasing the area available for dissolution. However, it is also interesting to note that the heats of solution of both physical mixtures and solid dispersions of nortriptyline HCl in PEGs have been reported to be lower than predicted by the values of the individual components (Craig and Newton, 1991a). The authors suggested the involvement of an interaction between the two components during dissolution. The second process involves the differences in dissolution behaviour between the low- and high-temperature fusions. This must be a function of differences in the solid-state structure of the dispersions.

The present investigation involves the study of 10% w/w dispersions of the relatively water-soluble drug nortriptyline HCl in four PEGs of different molecular weights. This differs from most previous studies, which usually involve the use of water-insoluble drugs as model systems. The dispersions were both slow and flash cooled from 373 K, as previously described (Craig and Newton, 1991a). This temperature is sufficiently high

to melt the PEGs but too low to melt the drug. The effects of drug concentration and rotation speed on the release of nortriptyline HCl from PEG 20000 dispersions have also been investigated.

Materials and Methods

Samples of PEGs 3400 (CSD, Cheshire), 6000 (CSD, Cheshire), 10000 (BDH, Poole), 20000 (BDH, Poole) and nortriptyline HCl (Eli Lilly, Basingstoke) were characterised as previously described (Craig and Newton, 1991a,b). All calculations involving the use of the PEG molecular weight were performed using the measured, as opposed to nominal number average molecular weight values. Dispersions were prepared using a low-temperature fusion method (Craig and Newton, 1991a), involving slow cooling at 5 °C/h or flash cooling from 373 K to room temperature in stainless-steel nipples (exposed area 2.01 cm^2). However, the integrity of the solid surface was considered unsatisfactory at concentrations above 25% w/w drug for slow-cooled samples and 10% w/w drug for flash-cooled samples, hence while the method has the advantage of producing fusions of constant surface area, the range of dispersions that may satisfactorily be prepared is limited.

Dissolution studies were conducted using a glass flat-bottomed vessel containing 1 l of deaerated double distilled water, maintained at 298 K in a water bath. The nipples were screwed onto the shaft of the apparatus which was rotated at 100 rpm unless otherwise stated. 10-ml samples were withdrawn using a syringe at specific time intervals. The samples were passed through a 0.45 μm filter prior to UV assay. 10 ml of fresh double distilled water equilibrated at 298 K were placed in the bath after sample withdrawal to maintain a constant volume. Samples were taken up to 25 min and all runs were performed in triplicate, the individual results being within 5% of the mean value in all cases. Although the area exposed to the dissolution fluid remained constant throughout the experiment, the intrinsic release rates measured are those of the dispersions and not the drug alone. Therefore, the measured dissolution rates per unit surface area are referred to as the apparent intrinsic dissolution rates.

Compacts of nortriptyline HCl were prepared by compressing 0.5-g samples of powder in a 1 cm diameter die at an equivalent force of 3 ton using a Specac Press (Specac Ltd, London). Preliminary studies indicated that this pressure resulted in the lowest dissolution rate, hence reducing errors due to water penetration into the tablets at higher porosities. The compacts were attached to the nipples using beeswax such that the tablet surface was flush with the open end of the nipple. This allowed comparisons to be made between the dissolution of the drug from the compacts and dispersions.

Results

Effects of PEG molecular weight and thermal history

A number of studies have been conducted comparing dispersions prepared using a range of molecular weight PEG samples. In many cases, the dissolution rate has been shown to decrease with increasing polymer chain length (e.g., Corrigan and Timoney, 1976; Ford et al., 1986). However, several dispersions have shown an increase in drug dissolution rate as the molecular weight of the PEG is increased, while other authors have found a maximum or minimum in dissolution rate at an intermediate molecular weight (Ford, 1986). Moreover, other studies have shown no discernible differences in dissolution behaviour as the PEG molecular weight is changed (e.g., Sumnu, 1986). It may therefore be concluded that the effects of PEG molecular weight on dissolution behaviour are complex and, as yet, unpredictable.

The dissolution profiles of the 10% dispersions are shown for the slow-cooled samples in Fig. 1, all the curves being linear over the time period studied. The profiles for the flash-cooled dispersions were also linear. The dissolution rate decreased logarithmically with increasing molecular weight, as indicated in Fig. 2. The apparent in-

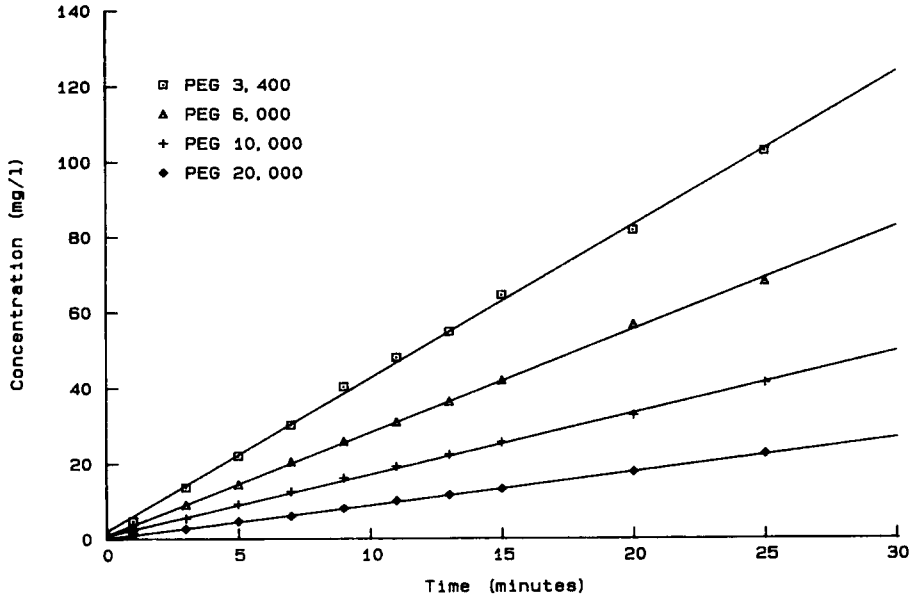

Fig. 1. Dissolution of nortriptyline HCl from slow-cooled solid dispersions in a range of molecular weight PEG carriers.

trinsic dissolution rates of the dispersions are listed in Table 1. Analysis by paired t-test indicated that there was no significant difference in release rate from slow- and flash-cooled samples at a 5% confidence level. This is in contrast to studies by Collett et al. (1976) which showed significant differences in the dissolution rates of dispersions containing salicylic acid in urea, de-

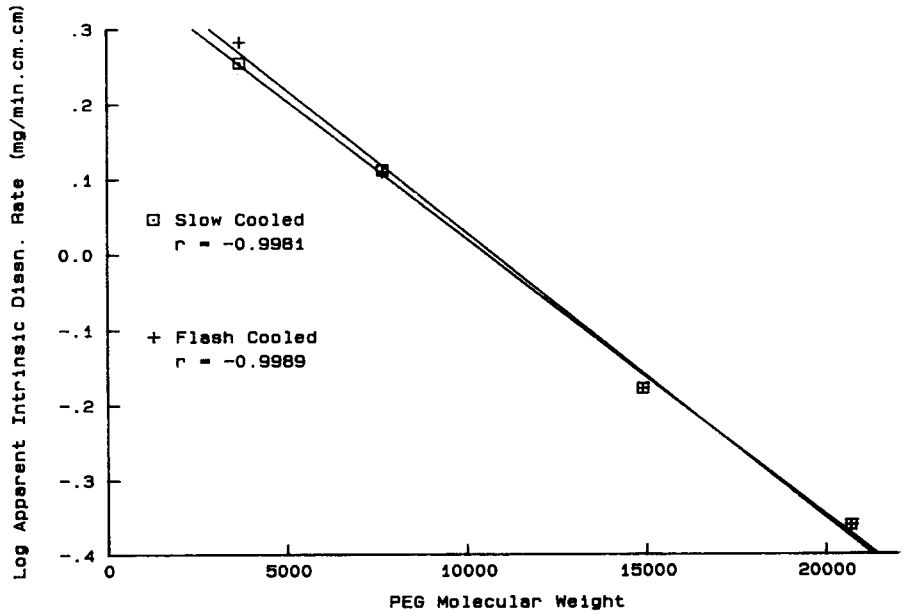

Fig. 2. Relationship between the dissolution rate of nortriptyline HCl solid dispersions and molecular weight of PEG carriers.

TABLE 1

Apparent intrinsic dissolution rates of 10% w/w nortriptyline HCl dispersions in polyethylene glycols of different molecular weights

Polyethylene glycol molecular weight	Apparent intrinsic dissolution rates (mg/min per cm^2)	
	Slow cooled	Flash cooled
3400	1.916	1.799
6000	1.285	1.294
10000	0.769	0.665
20000	0.416	0.436

pending on the cooling conditions used. Furthermore, studies by Chatham (1985) indicated a greater difference in the dissolution rate of trimethoprim from slow- and flash-cooled PEG 4000 samples, this difference also being seen for the polymers themselves. However, comparison of the heats of fusion (and hence degree of crystallinity) of the PEGs used in the two studies indicates that the difference between the slow- and flash-cooled PEG 4000 used by Chatham (1985) was considerably greater than those corresponding to the PEGs used in the present study (Craig and Newton, 1991b). The differences in sensitivities of dissolution rate may therefore be ascribed to variations in the degree of crystallinity of the PEGs. The crystal form of the PEGs did not appear to influence the dissolution rate, as previous studies (Craig and Newton, 1991a) have indicated that the slow- and flash-cooled dispersions used in the present study contained different polymorphs of PEG.

The intrinsic dissolution rate of nortriptyline HCl was found to be 1.656 mg/min per cm^2. Although this rate is higher than most of the values shown in Table 1, the quantity of drug present in the solid dissolving surface of the dispersion is considerably less than in the compact. On this basis, the dispersions in PEG 3400 clearly represent an increase in dissolution rate, while the other molecular weight samples may also correspond to an increase when the smaller proportion of drug in the exposed surface is taken into account.

Effects of drug concentration

The dissolution curves of the various drug concentrations in PEG 20000 were found to be linear, the corresponding apparent intrinsic dissolution rates for the slow-cooled samples being shown in Fig. 3. The differences between the flash- and slow-cooled samples were again negligible. The relationship between drug concentration and release rate was also linear, implying that the increase in dissolution rate was a simple function of the higher drug content and did not reflect any mechanistic change. A number of other studies using constant surface area discs have shown a similar linear increase in dissolution rate with drug concentration at high carrier contents (e.g., Ford and Rubinstein, 1978; Chatham, 1985; Dubois and Ford, 1985). It may be observed that the concentration up to which linearity was observed is higher in the present case than in the majority of systems described by Dubois and Ford (1985).

Effects of rotation speed

The dissolution rates of slow- and flash-cooled PEG 20000 dispersions containing 10% w/w drug were measured at different rotation speeds. The curves were again linear, the apparent intrinsic dissolution rates being shown in Fig. 4. For both heat-treated samples, the dissolution rate showed

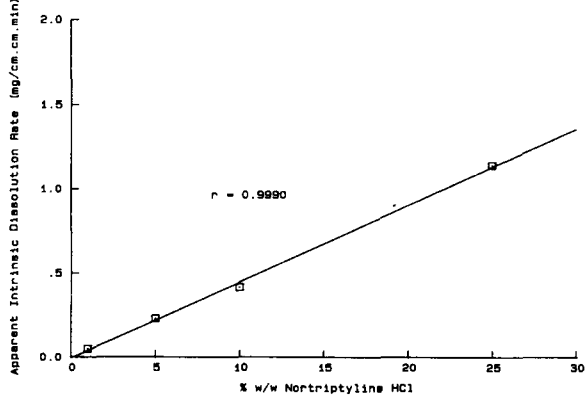

Fig. 3. Apparent intrinsic dissolution rates of nortriptyline HCl from slow-cooled solid dispersions in PEG 20000.

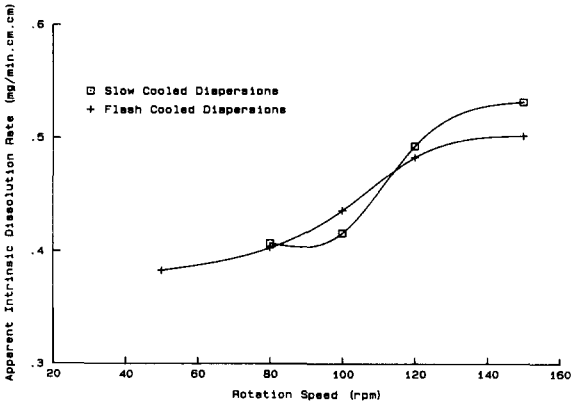

Fig. 4. Effect of rotation speed on the dissolution rate of nortriptyline HCl from slow- and flash-cooled dispersions in PEG 20000.

a sigmoidal increase with rotation speed. Hamlin et al. (1962) suggested an empirical relationship

$$k = a\omega^b \tag{1}$$

where a and b are constants, ω represents the rotation speed and k is the rate constant, derived from the Noyes-Whitney equation

$$\frac{dm}{dt} = k(C_s - C) \tag{2}$$

where dm/dt is the dissolution rate, C denotes the bulk concentration and C_s is the solubility of the drug. A more detailed equation was proposed by Levich (1962), namely

$$k = \frac{D}{h} = 0.62 \cdot D^{2/3} \cdot \upsilon^{-1/6} \cdot \omega^{1/2} \tag{3}$$

where D is the diffusion coefficient, h represents the diffusion layer thickness and υ is the kinematic viscosity. For a constant surface area disc dissolving under sink conditions, a linear relationship is predicted between the dissolution rate and the square root of the rotation speed. Chatham (1985) and Najib and Suleiman (1989) found such a relationship for the dissolution of PEG 4000 itself and for diflunisal in PEG 4000, respectively, from which the authors were able to calculate the diffusion layer thickness and diffusion coefficient. The results shown in Fig. 4 indicate that no such relationship exists in this case.

Discussion

The study has indicated that the rate of drug dissolution from the solid dispersions is affected by the release rate of the polyethylene glycol itself, as shown by the relationship between dissolution rate and PEG molecular weight. This in turn means that one of the controlling steps to drug release is the recession of the PEG solid-liquid interface. Such carrier-controlled dissolution has been described previously by Corrigan (1985) and Dubois and Ford (1985), although the mechanisms by which this takes place are not yet understood. It is therefore of interest to consider possible mechanisms by which carrier-controlled dissolution occurs.

Consideration of the dissolution process indicates that either the drug is being released as discrete particles due to the dissolution of the solid PEG in which it is embedded, or else the drug is dissolving as soon as the particles are exposed to the aqueous media. Previous studies (Corrigan et al., 1979) have indicated that the intrinsic dissolution rate of the PEGs is considerably higher than that found here for the drug. Therefore, if the drug is being released as discrete particles, one would expect an accumulation of solid drug in the medium, as the release rate of the particles will be high compared to the dissolution rate of the drug. This being the case, one would not expect to see linear dissolution profiles for such systems, as the area of drug available for dissolution would be continually increasing due to the accumulation of slowly dissolving, 'free' particles in the dissolution medium. Furthermore, it is unlikely that there would be a clear relationship between dissolution rate and carrier molecular weight, as the rate-limiting step to dissolution would effectively be the release of the drug from the individual particles.

The second possibility is that the drug within the dispersion is dissolving as soon as the particles are exposed to the dissolution medium. However, as the dissolution rate of the drug is less

than that of the polyethylene glycols, the release rate of the drug must be being augmented by the presence of the polymer (at least in the case of the PEG 3400 dispersions). It has been previously reported that while drug solubility may not be greatly affected by the presence of low concentrations of polyethylene glycols, at higher PEG levels the solubility is considerably enhanced (e.g., Chatham, 1985). It is reasonable to assume that high concentrations of polymer may be present at the solid-liquid interface, hence the solubility of the drug may be considerably higher there than in the bulk aqueous phase (Hargreaves, 1982). This explanation is also consistent with the Noyes-Whitney equation (Eqn 2), as the solubility term (C_s) in fact refers to the concentration of the drug in the diffusion layer rather than the aqueous solubility per se. The two values are usually taken as equivalent due to the diffusion layer being considered to contain a saturated solution of the dissolving substance. According to the above hypothesis, the C_s term would therefore be considerably higher in the presence of polyethylene glycol, leading to a greater dissolution rate. It is also possible that the PEG may be improving the wetting properties of the drug, hence aiding dissolution.

If dissolution is indeed carrier controlled, then the release rates of the drug from the 10% dispersions should be approx. 10% the dissolution rate of the carriers themselves, as has been previously reported for trimethoprim (Chatham, 1985), bendrofluazide and hydroflumethiazide (Corrigan et al., 1979) in PEG 4000. The theoretical drug dissolution rates may therefore be estimated using the values for PEG 6000 and PEG 20000 given by Corrigan et al. (1979) as 0.810 and 0.433 mg/cm^2 per min, respectively. Examination of Table 1 shows these values to be in reasonable agreement with those obtained experimentally, considering that the batches of PEG and the manufacturing conditions used were different. Furthermore, Dubois and Ford (1985) showed the dissolution rates of a range of drugs in PEG 6000 to be similar in the region where the drug dissolution rate increases linearly with concentration. Using the data given by Dubois and Ford (1985), the average release rate for a 10% dispersion (obtained from the dissolution rate/concentration slopes) may be recalculated to take account of the surface area of the dispersions. This gives an apparent intrinsic dissolution rate of 1.401 mg/min per cm^2, which is again in reasonable agreement with the values given for PEG 6000 systems in Table 1. These observations therefore support the hypothesis that the dissolution rate of the drug is in this case controlled by that of the carrier.

Conclusions

The study has demonstrated the use of the low-temperature fusion method as a means of enhancing drug dissolution rate and as a tool for examining the mechanisms responsible for the increase. The release rate was found to decrease logarithmically with PEG chain length, indicating carrier-controlled dissolution and also highlighting the importance of accurately characterising the molecular weight of the polymer. The thermal history of the dispersions did not appear to have a significant effect on the dissolution rate, possibly due to similarities in the degree of crystallinity of the slow- and flash-cooled PEG samples used. Used in conjunction with the studies by Chatham (1985) these results indicate that the degree of crystallinity is of greater importance in determining drug release rate than is the crystal form of the PEGs. An argument has been presented for the involvement of an interaction between the drug and the carrier at the solid-liquid interface, leading to carrier-controlled dissolution.

It is advantageous to establish the mechanism of dissolution in as many cases as possible, as such an approach will undoubtedly lead to the development of more effective systems and facilitate the manufacture of commercial dosage forms. For example, if the dissolution rate of a given system is carrier controlled, then it is more important to define the characteristics of the carrier (such as molecular weight or degree of crystallinity) than it is to establish those of the drug such as the particle size. However, it should be emphasised that carrier-controlled dissolution is

by no means a general phenomenon, as exemplified by studies such as that by Sjokvist and Nystrom (1988), whereby the dissolution rate of griseofulvin from dispersions in PEG 3000 was shown to be highly dependent on the particle characteristics of the drug, rather than the dissolution characteristics of the carrier. It would therefore be desirable to establish which factors determine whether the dissolution rate of a system will be controlled by the carrier or by the properties of the drug itself.

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