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DISSOLUTION PROPERTIES OF POLYETHYLENE GLYCOLS AND POLYETHYLENE GLYCOL–DRUG SYSTEMS

O.I. CORRIGAN, C.A. MURPHY and R.F. TIMONEY

Department of Pharmaceutics, School of Pharmacy, Trinity College, Dublin (Ireland)

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SUMMARY

The release of polyethylene glycol from discs prepared using polyethylene glycols o differing molecular weight was determined. The influence of polyethylene glycol weigh fraction on the release of hydroflumethiazide and bendrofluazide from drug–polyme solid dispersions was also investigated. While the dissolution of both drugs was consider ably enhanced, the dissolution of polyethylene glycol from the solid dispersions was in al cases lower than that of the pure polymer. Comparison of the relative movement of th solid–liquid boundary of each component indicated that both components were bein released simultaneously from the disc surface. In addition, the observed maximun enhancements in drug dissolution were orders of magnitude greater than the theoretica values expected, assuming the solution interaction model. It was concluded that molecu· lar dispersion is involved in the release mechanism.

INTRODUCTION

The dispersion of poorly water-soluble drugs in physiologically inert, water-soluble carriers has been shown to enhance drug dissolution in vitro (Chiou and Riegelman, 1969) and drug absorption in vivo (Chiou and Riegelman 1971b). Previously we have reported on the ability of both polyethylene glycol (PEG) (Corrigan and Timoney 1976) and polyvinylpyrrolidone (PVP) (Corrigan and Timoney 1975) to enhance the dissolution rate of hydroflumethiazide from constant surface area discs prepared by mixing, coprecipitation and, in the case of PEG, by melting both components. The major difference in the drug release patterns obtained between these two polymers occurred at intermediate weight fractions where X-ray diffraction analysis indicated that the higher dissolution from PVP coprecipitate systems was probably due to the formation of an amorphous form of drug. The change in hydroflumethiazide dissolution rate with PEG weight fraction was in

qualitative agreement with the theory of Higuchi et al. (1965) for the dissolution from discs of two components which interact to form soluble complexes. At high PEG weight fractions, the disparity between the dissolution rates of systems prepared by the melt and solvent methods indicated that the formation of solid solutions may be an important contributing mechanism controlling drug release. Such a mechanism was proposed by Chiou and Riegelman (1971a), to explain the release of sulphathiazole from sulphathiazole–PVP systems at high polymer weight fractions, from a comparison of the dissolution profiles of both components.

In order the clarify the mechanism of release from PEG–drug systems, data on the dissolution properties of pure PEG and of PEG from PEG–drug systems is required.

MATERIALS AND METHODS

Dissolution rate determinations

The procedure used for dissolution rate determinations was similar to the beaker method (Levy and Hayes, 1960) modified for intrinsic dissolution rate determinations (Levy and Procknal, 1964). Dissolution rates were determined in deionized water at 37°C and a stirrer rotation speed of 59 rpm. Discs were prepared and mounted as previously described (Corrigan and Timoney 1975). However, in the case of PEG 1000, because of its softness, this method proved unsuccessful. Discs of PEG 1000 were therefore prepared by pouring melted PEG 1000 into precast paraffin moulds 1.3 cm in diameter.

Assay procedures

Polyethylene glycols (4000, 6000 and 20,000 supplied by Brome and Schimmer Ltd. and 1000 supplied by BDH Chemical Ltd.) were assayed by either method I or II below. Method II was used to estimate PEG release from the low PEG weight fraction systems.

Method I. A modification of the assay method of Evans and Dennis (1973) for ethylene glycols was employed initially as follows. Suitably diluted 5 ml aliquots of PEG in the concentration range 0–60 mg/litre were measured into 10 ml volumetric flasks. To each flask was added 0.5 ml of 4 N sulphuric acid solution followed by 1.0 ml of 0.126 M potassium permanganate solution. The contents were well mixed and placed on a steam bath for exactly 5 min. On removal from the steam bath 1.0 ml of 0.07 M sodium arsenite solution and 1.0 ml of 2% w/v 3-methylbenzothiazol-2-one hydrazone hydrochloride (MBTH reagent) solution were added and the flasks returned to the steam bath for a further 6 min. Samples were then removed and cooled to room temperature by allowing them to stand in cold water for 2 min. One ml of iron-chloride-sulphamic acid solution was then added and the final volume adjusted to 10 ml. After 40 min the optical density of each solution was read at 630 nm in a 1 cm cell with water as reference. The net optical density was obtained by subtracting the reagent blank value from the individual readings. Linear plots of absorbance versus concentration were obtained with each polymer, the slope tending to increase slightly with increase in molecular weight. Because of variability in the slopes obtained with different batches of standards, controls were included with each batch of unknowns. Neither hydroflumemethiazide nor bendrofluazide, at the concentrations encountered during dissolution runs, interfered with the assay results.

Method II. Recently Childs (1975) introduced a method for the determination of polyethylene glycol in gamma globulin solutions, a modification of which was found to be simpler than the above. To 1.0 ml of PEG solution was added 3.0 ml distilled water. To this mixture 1.0 ml of 5% $BaCl_2$ solution and 0.5 ml of 0.1 N iodine solution were added and mixed. The resulting solution was allowed to stand for 15 min before reading the absorbance at 535 nm.

Linear plots of absorbance versus concentration in the range 0–10 mg/litre were obtained. The thiazides did not interfere with the procedure.

Thiazides. Hydroflumethiazide and bendrofluazide were assayed from the ultra violet absorbance at 273 nm. At this wavelength PEG did not show any absorption of light and both drugs obeyed Beers Law.

Solubility determinations

The effect of PEG concentration on the apparent drug solubility in water at 37°C was determined by a method similar to that of Shefter and Higuchi (1963).

Diffusion coefficients

The diffusion coefficients of PEG 4000, hydroflumethiazide and bendrofluazide were determined using a modification of the apparatus and method of Goldberg and Higuchi (1968). The hydrodynamics were controlled using two single speed (250 rpm) synchronous motors (TYPM10 Internationale Lab. GMBH 7801 Dottingen). Millipore (microweb) filters were used as the diffusion membrane. The membrane was mounted between the ground glass ends of the modified 250 ml conical flasks using soft paraffin and the flasks clamped together using a rectangular clamp fastened by nuts and bolts. Cells made in this manner were calibrated using potassium chloride and gave cell constants of the order of 125 cm.

Preparation of PEG–drug systems

Systems containing PEG 4000 to drug ratios of 20 : 1 and 10 : 1 were prepared by the melt method while 3 : 10 and 1 : 10 systems were prepared by the solvent method as previously described (Corrigan and Timoney, 1976).

RESULTS AND DISCUSSION

The dissolution profiles obtained for polyethylene glycols, of nominal molecular weights 1000, 4000, 6000 and 20,000 from constant surface area discs are illustrated in Fig. 1. It is evident that dissolution rate is inversely related to molecular weight and the dissolution profiles have a positive curvature. The linear least squares lines of best fit obtained are given in Table 1. The negative intercepts confirm the positive curvature of the lines and indicate an increase in curvature with increasing molecular weight. Nogami et al. (1970) have investigated the dissolution of pure PVP in a water–acetone mixed solvent system and observed an initial curvature in the profiles obtained. They suggested that this effect may be related to polymer swelling. It is of interest that in studies on the swelling of polymers during dissolution Heyd et al. (1969) reported that disc swelling increased with increasing molecular weight. The results are also consistent with the

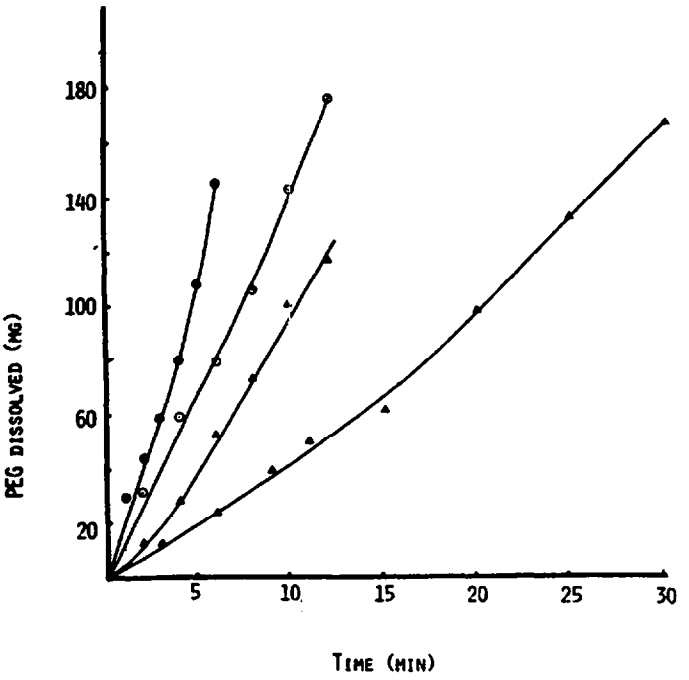


Fig. 1. Effect of molecular weight on the release profile of PEG in water at 37°C at a stirring speed of 59 rpm. Key: ●, PEG 1000; ○, PEG 4000; ▲, PEG 6000 and △, PEG 20,000.

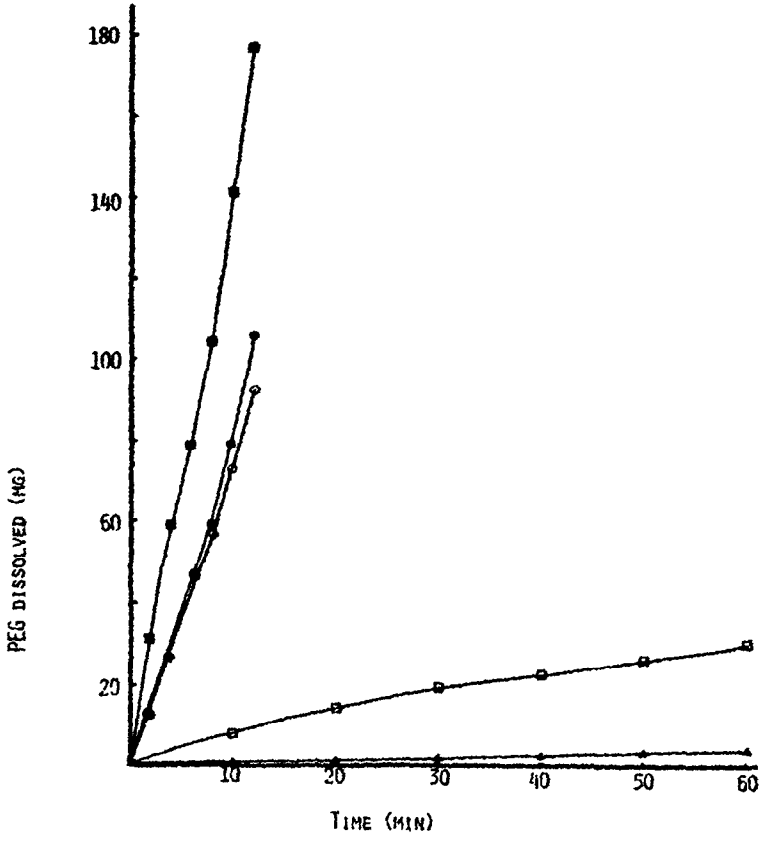
previously reported dissolution data for hydroflumethiazide from PEG melt systems (Corrigan and Timoney, 1976), i.e. dissolution of drug increased with decreasing polymer molecular weight. The influence of the presence of hydroflumethiazide in the disc on the dissolution of PEG 4000 is illustrated in Fig. 2. Also included is the profile for pure PEG 4000. It is evident that in all systems the polymer release rate is lower than that of pure polymer, the rate declining as the weight fraction of PEG decreased. The release rate of PEG from the 10 : 1 system is about half that of pure PEG. A similar trend was evident when bendrofluazide was the dispersed drug, the decrease being of a lower magnitude at high PEG weight fractions, but of greater magnitude at the lower weight fractions (Fig. 3).

TABLE 1

DISSOLUTION OF PURE PEGs: LINEAR LEAST-SQUARES PARAMETERS

PEG	Intercept	Slope	Standard error of slope	Correlation coefficient	Dissolution rate [a] mg/cm²/h
1000	−2.18	22.53	1.04	0.9655	1018.2
4000	−2.32	14.37	0.73	0.9588	649.2
6000	−11.62	10.76	0.32	0.9849	486.2
20,000	−14.01	5.75	0.17	0.9800	259.7

[a] Estimated from slope



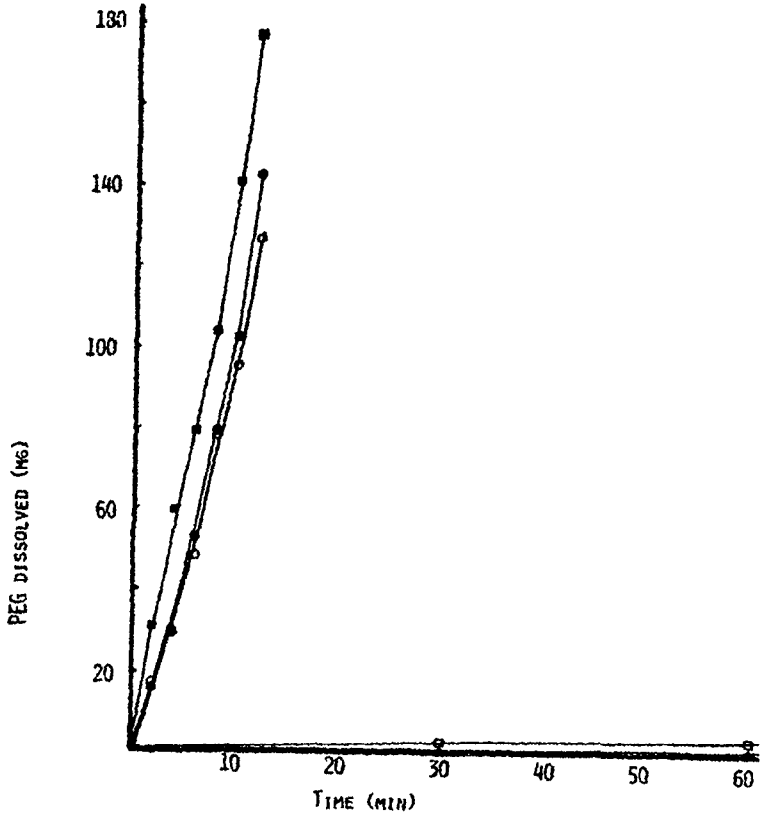


Fig. 2. Release profiles of PEG 4000 from PEG–hydroflumethiazide systems in water at 37°C and a stirring speed of 59 rpm. Key: ■, pure PEG; ●, 20 : 1; ○, 10 : 1; □, 3 : 10; △, 1 : 10 PEG–hydroflumethiazide ratios.

Fig. 3. Release profiles of PEG 4000 from PEG–bendrofluazide systems in water at 37°C and a stirring speed of 59 rpm. Key: ■, pure PEG; ●, 20 : 1; ○, 10 : 1; □, 3 : 10; △, 1 : 10 PEG–bendrofluazide ratios.

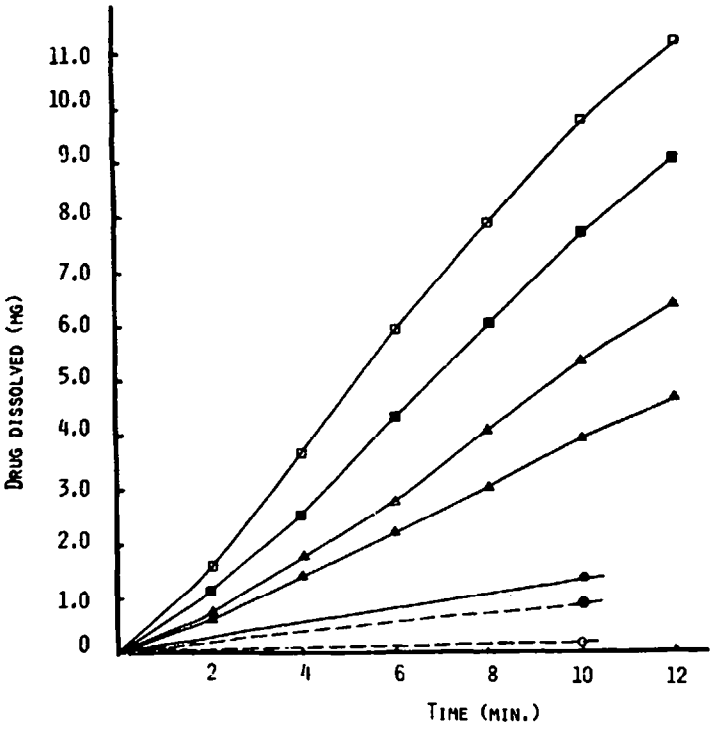


Fig. 4. Drug release profiles from drug–PEG systems in water at 37°C. Key: □, 10 : 1; △, 20 : 1 PEG–bendrofluazide ratios; ○, pure bendrofluazide; ■, 10 : 1; ▲, 20 : 1; ●, 3 : 10 PEG–hydroflumethiazide ratios and –●–, pure hydroflumethiazide.

The drug dissolution from representative hydroflumethiazide–PEG, bendrofluazide–PEG discs, together with those of the pure drugs are shown in Fig. 4. Drug release was highest from the 10 : 1 system for both drugs, in the case of bendrofluazide the rate was 180 times that of pure drug. The hydroflumethiazide release was increased 13-fold, which is in agreement with the enhancements of 15–17-fold previously reported in acid media (Corrigan and Timoney, 1976). It is noteworthy that, in spite of the large differences in the relative enhancement of drug dissolution, the absolute rates are of the same order of magnitude. The positive curvature in the dissolution profiles, noted with pure PEGs is also evident in the drug profiles at the high PEG weight fractions.

It is evident that, at high polymer weight fractions, as the drug dissolution rate increased from zero to its maximum the polymer dissolution rate decreased. This result is consistent with the concept that at high PEG weight fractions a pure PEG surface layer is controlling dissolution. The identity of the controlling layer, at a particular weight fraction can be determined by comparing the relative movement of the solid liquid boundary of each component Q_aA_b/Q_bA_a, where Q_a and Q_b are the component dissolution rates and A_a and A_b are the amounts per unit volume of the two components a and b respectively.

The ratios obtained are summarized in Table 2. The four ratios are approximately one.

TABLE 2

DISSOLUTION DATA FROM HIGH PEG WEIGHT FRACTION SYSTEMS

System	Dissolution rate (mg/cm^2/h)		$\frac{Q_a/A_a}{Q_b/A_b}$
	PEG	Drug	
PEG : hydroflumethiazide (10 : 1)	335.79	36.29	0.95
PEG : hydroflumethiazide (20 : 1)	390.96	18.40	1.06
PEG : bendrofluazide (10 : 1)	479.08	43.85	1.09
PEG : bendrofluazide (20 : 1)	544.60	26.06	1.04

This suggests that both components are being released simultaneously from the disc surface and supports the contention that molecular or colloid dispersion is involved in the release from PEG systems at high polymer weight fractions (Chiou and Riegelman, 1971a).

The apparent solubility of both drugs increased with PEG concentration and molecular weight, indicating the formation of soluble complexes. This effect, in the case of PEG 4000, could be expressed by the following linear relationships:

$$C^s_h = 0.48 + 9.58 \times 10^{-3}\ Cp \qquad r^2 = 0.9837 \tag{1}$$

and

$$C^s_b = 0.032 + 1.69 \times 10^{-3}\ Cp \qquad r^2 = 0.9886 \tag{2}$$

where C^s_h and C^s_b represent the apparent solubilities of hydroflumethiazide and bendrofluazide (mg ml^{-1}), respectively, and Cp the concentration of polyethylene glycol. These results are not consistent with the diffusion control model for the dissolution from binary systems interacting to form soluble complexes (Higuchi et al., 1965), which predicts at the critical mixture ratio, an increase in rate of magnitude equal to $D_{ab}K \cdot C^o_a \cdot C^o_b/h$, where D_{ab} is the diffusion coefficient of the complex formed in solution, K is the equilibrium constant for the complex, h is the diffusion layer thickness and C^o_a and C^o_b are the solubilities of the individual components.

Assuming that the enhancement in drug dissolution was solely due to drug transported as PEG complex, i.e. a PEG carrier effect, the enhancement in dissolution rate should be given by

$$G_{max} = \frac{D_d C^s_d}{h} + \frac{D^* C^*}{h} \tag{3}$$

where D_d and C^s_d are the drug diffusion coefficient and solubility, respectively, and D* and C* the corresponding values for drug transported as complex. For the critical mixture case when both the drug and polymer boundary layers co-exist at the disc surface in contact with an aqueous layer saturated with both components, an estimate of C* for each

drug can be obtained using Eqns. 1 and 2. The solubility of PEG 4000 was estimated gravimetrically at 706 mg ml^{-1}. The diffusion coefficients of hydroflumethiazide, bendrofluazide and PEG 4000 at 37°C were estimated as 10.3×10^{-6}, 9.52×10^{-6} and 3.1×10^{-6} cm^2 sec^{-1}, respectively. From these values and assuming $D^* \approx D_{PEG}$ theoretical relative maximum enhancements in dissolution rate for hydroflumethiazide and bendrofluazide of the order of 4 and 9 respectively were calculated using Eqn. 3. Similar relative enhancements were also predicted from Eqn. 4 (Higuchi et al., 1965):

$$G_{max} = \frac{D_a C^0{}_a + D_{ab} C^0{}_a \cdot C^0{}_b K}{h} \quad (4)$$

where K the equilibrium constant was estimated from solubility data, assuming a 1 : 1 stoichiometry between drug and polymer functional unit, as described by Higuchi and Connors (1965). Since the experimentally determined relative rates were 13 and 180 for hydroflumethiazide and bendrofluazide, respectively, we conclude that the formation of soluble complexes in solution is insufficient to explain the observed findings. In addition, the fact that the release rates of both drugs, which differ 12-fold in absolute aqueous solubility, are of a similar order of magnitude lends support to the involvement of molecular dispersion in the release mechanism from polyethylene glycol–drug systems.

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