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The kinetics of dissolution of diflunisal and diflunisal-polyethylene glycol solid dispersion

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Summary

This work attempts to provide an additional insight into the mechanism of dissolution rate enhancement of diflunisal caused by its dispersion in polyethylene glycol (PEG). This required the determination of the macroscopic dissociation constant and hence observed pK_a, dissolution kinetics, diffusion coefficient and hydrodynamic layer thickness of diflunisal and how these parameters were influenced when the drug is dispersed in PEG. The work also included determination of the variation of the diffusion coefficient of diflunisal with pH and of the relationship between the pH of the diffusion layer (pHo) and the pH of the dissolution medium (pH bulk) in buffered and unbuffered saturated solutions of diflunisal. Dispersing diflunisal in PEG reduces its dissociation constant, an effect which was attributed to the non-polar character of PEG. The dissolution of diflunisal was diffusion controlled and the dissolution kinetics was found to adhere to the Noyes-Whitney and the Levich equations. The diffusion coefficient of diflunisal was found to increase in the presence of PEG concentrations of more than 75% in the dispersion. The diffusion layer thickness was also found to increase at these concentrations. The diffusion coefficient increased with decrease in pH, suggesting that the diffusion of the nondissociated species is greater than that of the dissociated ones. The work also emphasizes the importance of the pH of the diffusion layer and de-emphasizes the importance of bulk pH in studying dissolution and solubility of drugs especially in unbuffered systems.

Introduction

Dispersing water-insoluble drugs in a hydrophilic polymer such as polyethylene glycol (PEG) is one of the most commonly used techniques to enhance the rate of dissolution and hence biological availability of such drugs (Chiou and Riegelman, 1971a). This approach has been used for this purpose for several drugs. These include griseofulvin (Chiou and Riegelman, 1971b; Kaur et al., 1980a and b), chloramphenicol (Goldberg et al., 1965 and 1966), hydroflumethiazide (Corrigan and Timoney, 1976), ibuprofen (Najib and Sheikh Salem, 1987), indomethacin (Ford and Elliott, 1985), and diflunisal (Najib and Suleiman, 1989).

It has been previously reported that the dispersion of diflunisal in PEG resulted in an increase in its dissolution rate (Najib and Suleiman, 1989). The effect was attributed to eutectic formation. The purpose of this work is to study how dispersing diflunisal in PEG would affect its macroscopic dissociation constant and hence its observed pK_a, diffusion coefficient and hydrody-

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namic layer thickness as these parameters greatly influence the dissolution rate of drug particles. This would possibly enable a better understanding of the possible mechanism of enhancement of dissolution caused by the dispersion process. The work also included investigation of the variations in flux rate with pH for both free and dispersed diflunisal, changes in the diffusion coefficient of diflunisal with pH and the relationship between bulk pH and the diffusion layer pH in buffered and unbuffered systems.

Background

The factors which influence the rate of dissolution of drugs are described by the Noyes-Whitney equation (Noyes and Whitney, 1897) which states that for a diffusion-controlled dissolution process

$$J = KA(C_s - C) \quad (1)$$

where J is the dissolution rate per unit surface area of the dissolving solid (A), K is the dissolution rate constant, C_s is the saturation solubility of the drug and C its concentration in the dissolution medium at a particular time. The constant K according to the diffusion layer theory (Serajuddin and Jarowski, 1985a and b) is given by

$$K = \frac{D}{h} \quad (2)$$

where D is the coefficient of diffusion of the drug through the diffusion layer and h is the thickness of such a layer. Therefore, under sink conditions i.e. $C_s \gg C$ Eqn. 1 becomes

$$J = \frac{DAC_s}{h} \quad (3)$$

Therefore 'for diffusion-controlled dissolution processes J is directly proportional to D and inversely related to h.

Levich (1962) developed equations which can be used to calculate both D and h, which have the following forms:

$$J = 0.62 D^{2/3} \nu^{-1/6} \omega^{1/2} C_s \quad (4)$$

$$h = 1.612 D^{2/3} \nu^{1/6} \omega^{-1/2} \quad (5)$$

Where ν is the kinematic visosity of the dissolution medium and ω is the angular speed of rotation. According to Eqn. 4, a plot of J vs. $\omega^{1/2}$ would be linear with a slope equivalent to:

$$\text{Slope} = 0.62 D^{2/3} \nu^{-1/6} C_s \quad (6)$$

Therefore, D can be calculated. The value of D can be used in Eqn. 5 to evaluate h at any given stirring rate. Eqn. 5 predicts that for a diffusion-controlled dissolution process, h would decrease with increase in ω.

In this work Eqns. 1–6 are used to determine the mechanism of dissolution of dispersed and free diflunisal and to calculate the diffusion coefficient of diflunisal and the hydrodynamic layer thickness for both free and dispersed diflunisal particles.

Materials and Methods

Materials

Diflunisal and polyethylene glycol 4000 were obtained from Sigma (U.S.A.). Disodium phosphate was obtained from BDH (U.K.). Anhydrous citric acid was obtained from Aldrich (U.S.A.). The water used was double distilled with a surface tension of 71–72 $mN \cdot m^{-1}$ at 25 °C.

Methods

Determination of the equilibrium solubility. Excess solid of diflunisal free or dispersed in PEG was shaken in screw-capped vials for 24 h with 20 ml of McIlvain buffer of the required pH and adjusted to an ionic strength of 0.5 with KCl at 37 °C. The pH of the saturated solutions was measured prior to the sampling procedure. The samples were then filtered through 0.3 μm filter unit (Millipore, London, U.K.) and diluted with the appropriate buffers. Absorbance values were measured on a 240 Shimadzu spectrophotometer (Shimadzu, Kyoto) at a wavelength of 315 nm against the appropriate blank. Samples were run in triplicates and the average values were taken. In all cases the standard deviation was less than 4%.

Determination of dissolution rate. The dissolution rates of free and dispersed diflunisal were

determined in triplicates at 37 °C and the required stirring rate using a USP dissolution apparatus. The dissolution medium consisted of 500 ml McIlvain buffer at the required pH and of ionic strength 0.5 adjusted with KCl. The discs in their moulds were attached centrally on the surface of the top part of the USP dissolution basket apparatus leaving a lower surface of 1.53 cm^2 available for dissolution. The pH of the dissolution medium was monitored throughout the experiment and was found to remain constant. 5-ml samples were withdrawn at the designated time intervals and immediately replaced with a similar volume of fresh dissolution medium. The samples were transferred to a syringe and rapidly filtered through a 0.3 μm membrane filter unit (Millipore). The samples were then spectrophotometrically assayed for drug content. In all cases the standard deviation was less than 4%.

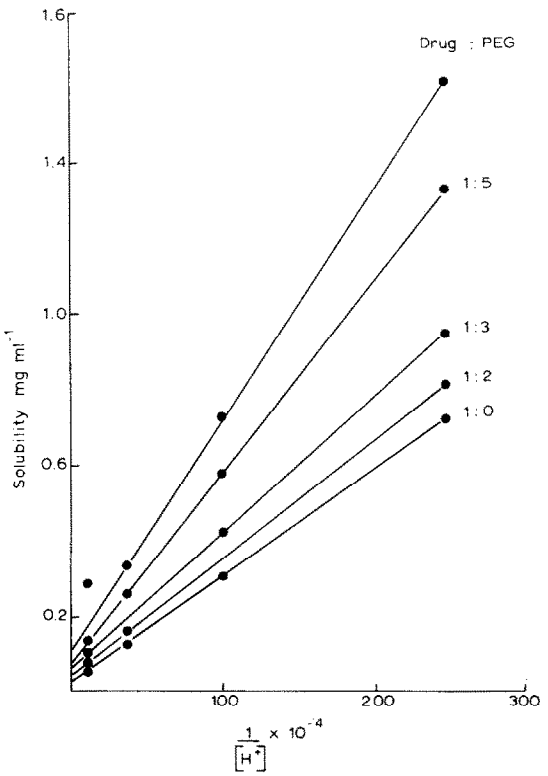

Fig. 1. Equilibrium solubility of free and dispersed diflunisal (S) as a function of the reciprocal hydrogen ion concentration $1/[H^+]$.

Determination of the pH of the diffusion layer (pHo). The pH of the diffusion layer is considered to be equivalent to that of a saturated solution of diflunisal (Serajuddin and Jarowski, 1985a and b). Therefore, to determine the pHo values for different values of the bulk pH, an excess of the drug was placed in each of a series of screw-capped vials containing 20 ml of distilled water adjusted to the required pH with 0.1 N NaOH or 0.1 N HCl or 20 ml of McIlvain buffer of the required pH. The ionic strength was adjusted to 0.5 with KCl. The vials were shaken for 24 h and the pH was then recorded. This pH value is equivalent to pHo.

Viscosity determinations. Viscosities of all solutions were determined at 37 °C using an Ostwald Viscometer with water as a reference.

Results and Discussion

Fig. 1 shows the equilibrium solubility of diflunisal and diflunisal dispersed in different proportions of PEG plotted vs. the reciprocal of the hydrogen ion concentration. In all cases the plots obtained were linear, suggesting that the solubility data of either the dispersed or nondispersed diflunisal can be described by the following equation (Stella et al., 1984):

$$S = S_0 + \frac{K_a[S_0]}{[H^+]}$$

where S represents the total solubility of diflunisal, S_0 the intrinsic solubility of the undissociated species, and K_a the macroscopic dissociation constant. Therefore, according to Eqn. 1 the intercept obtained from Fig. 1 is equivalent to the intrinsic solubility of the undissociated diflunisal $[S_0]$ and the slope is equivalent to $[S_0]K_a$. Dividing the slope by the intercept gives the value of K_a. The K_a value was used to calculate the pK_a of diflunisal.

Table 1 lists the values of the macroscopic dissociation constant (K_a) and the corresponding pK_a values for diflunisal dispersed in different amounts of PEG. Table 1 indicates that increasing

TABLE 1

Values of the macroscopic dissociation constant and the corresponding pK_a values for free and dispersed diflunisal

Dispersion composition (drug : PEG)	$K_a(\times 10^5)$	pK_a
1 : 0	1.236	4.91
1 : 1	0.837	5.07
1 : 3	0.710	5.15
1 : 5	0.637	5.19
1 : 7	0.620	5.21

the amount of PEG incorporated results in a decrease in the dissociation constant. The decrease in K_a results in an increase in S_0, i.e. the solubility of the nonionized species. This might be attributed to the reduction in polarity of the dissolution medium and the hydrodynamic layer resulting from the presence of PEG which is a nonionic polymer. The decrease in K_a is reflected in a slight increase in pK_a of the drug.

Fig. 2 shows the amount of diflunisal released from constant surface area discs as a function of time at pH 7.0, and at a stirring rate of 100 rpm. The plots obtained were linear suggesting the adherence of the dissolution process to the Noyes-Whitney equation. This indicates that dissolution of free and dispersed diflunisal is diffusion controlled. Thus, although dispersing diflunisal in PEG increases its dissolution rate, the kinetics of the dissolution process remain unaltered. The same

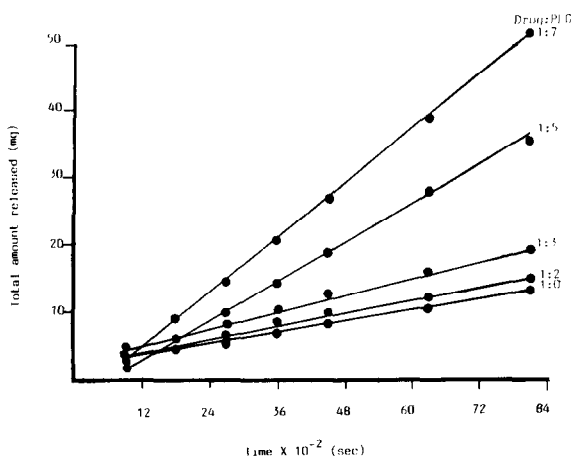

Fig. 2. The amount of diflunisal released from a disc of constant area as a function of time.

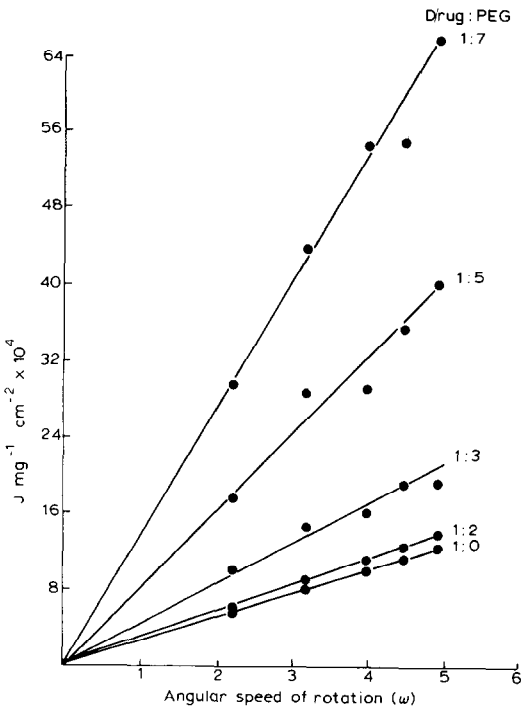

Fig. 3. Flux J of diflunisal dispersed in various concentrations of PEG as a function of the angular speed of rotation (ω).

behaviour was noted with all stirring rates and pH values studied.

Fig. 3 shows the dissolution rate of diflunisal per unit area (J) plotted as a function of the square root of the angular speed of rotation. The linearity of the plots is indicative of the adherence of the dissolution data to the Levich equation (Eqn. 4). This, therefore, suggests that a true diffusion mechanism operates in the dissolution of diflunisal whether free or dispersed in different amounts of PEG.

The slopes of the Levich plot were used to calculate the diffusion coefficient (D) of dispersed and free diflunisal according to Eqn. 6. The values of D obtained were plotted as a function of PEG incorporated in the solid dispersion as shown in Fig. 4. It is evident from the figure that D remains almost unaltered as the percentage of PEG in the dispersion is increased up to 80%. However, when the percentage of PEG exceeds 80% an increase in the diffusion coefficient is noted. This could be

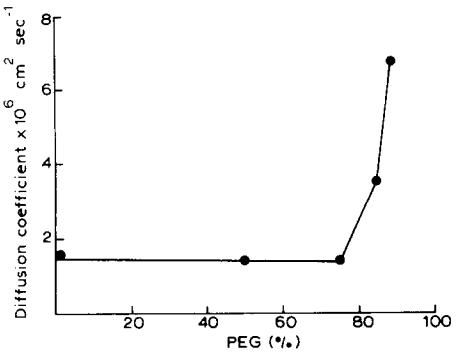

Fig. 4. Relationship between the diffusion coefficient of diflunisal and the amount of PEG present in the dispersion.

due to the high concentration of PEG in the hydrodynamic layer and the bulk present at these concentrations. This would result in increasing the non-polar character of this layer and therefore increasing the proportion of the undissociated molecules. As the diffusivity of the nonionized species is greater than that of the ionized forms (Collett el al., 1972), an increase in the diffusion coefficient is noted at these concentrations of PEG.

The hydrodynamic layer thickness was calculated using Eqn. 5 (Levich, 1962). This equation indicates that for diffusion-controlled processes h would decrease as the rotation speed is increased. The values of h as calculated using Eqn. 5 for diflunisal and diflunisal dispersed in PEG were plotted as a function of the rotation speed. The plot obtained is shown in Fig. 5. In Fig. 5 it is clearly observed that for any one particular system h decreased as rpm increased. This dependency of h on the speed of rotation further suggests that the dissolution of dispersed and free diflunisal is diffusion controlled. Fig. 5 also indicates that in the case of dispersions of drug : PEG (1 : 1 and 1 : 3), the values of h obtained at any particular stirring rate are similar to those of the drug. For dispersions of compositions 1 : 5 and 1 : 7 the values of h obtained are higher than those of the free drug at all stirring rates. This is to be expected, since both D and ν in Eqn. 5 are increased at these PEG concentrations and hence h will increase.

The effect of pH on the rate of dissolution was studied by determining the variation in relative dissolution rate (J_r) as a function of pH. J_r is

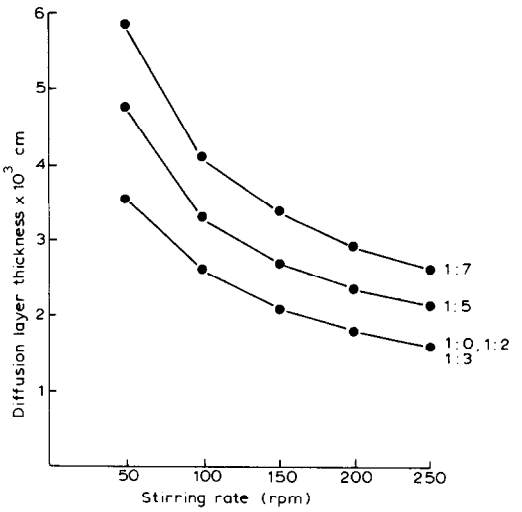

Fig. 5. Relationship between the hydrodynamic layer thickness (h) and the speed of rotation (rpm).

defined as the ratio of the dissolution rate at a particular pH (J) to that at the pH where ionization of the drug is negligible (J_0) and the only undissociated species is diffusant, i.e. pH 2.2 for diflunisal (McNamara and Amidon, 1986).

The values of J_r plotted as a function of pH for diflunisal and diflunisal dispersed in PEG (1 : 7) are shown in Fig. 6. It is evident from the figure that the value of J_r remains almost constant up to pH 4, indicating that the amount of drug present in solution is very small at these pH values. J_r then increases with rising pH due to the greater

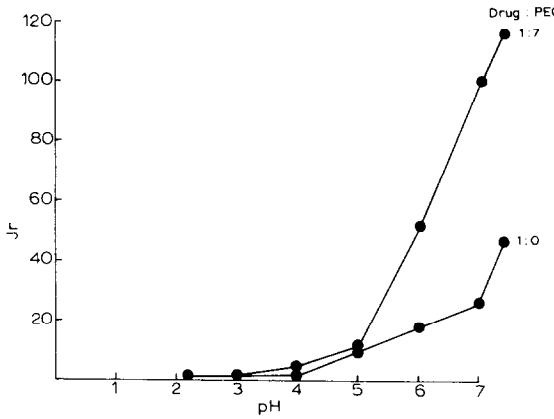

Fig. 6. Relationship between the relative flux rate (J_r) and pH for free and dispersed diflunisal.

degree of ionization of the drug. This would be expected, since diflunisal is a weakly acidic drug. Other drug : polymer ratios show the same behaviour and their profiles fall within the range between the drug and drug : PEG 1 : 7.

Table 2 lists the values of the diffusion coefficient of diflunisal determined as a function of pH using Eqn. 4. Table 2 clearly shows that increasing the pH results in a decrease in the diffusion coefficient. Since increasing pH is associated with increase in the degree of dissociation of diflunisal, the results indicate that the diffusivity of the dissociated diflunisal is less than that of the undissociated form. Similar results were reported by Collet et al. (1972).

Fig. 7 shows the relationship between the pH of the diffusion layer (pHo) and the pH of the bulk (pH bulk) in unbuffered and buffered saturated solutions of diflunisal. For unbuffered solution the pHo and pH bulk are identical under strongly acidic conditions, i.e. below pH 3. This is due to the suppression of ionization of diflunisal under strongly acidic conditions. Therefore, it does not contribute to pH of the diffusion layer. At pH greater than 3, diflunisal begins to dissociate, and to form a saturated solution of diflunisal in the diffusion layer exerting a self-buffering action in this layer (Mooney et al., 1981a) causing its pH to attain that of a saturated solution of diflunisal, which is about 3.3. Therefore, for any pH bulk value studied above this pH, the pHo value is 3.3. Similar results were reported by Mooney et al. (1981a and b) and Serajuddin and Jarowski (1985a and b).

In buffered system pHo and pH bulk are identical for all pHs. This is due to the buffering

TABLE 2

Variation of the diffusion coefficient of diflunisal with pH

pH	D ($cm^2 \cdot s^{-1}$)
7.4	1.281×10^{-6}
7.0	1.64×10^{-6}
6.0	2.54×10^{-6}
5.0	5.274×10^{-6}
4.0	5.8×10^{-6}
3.0	7.25×10^{-5}
2.2	22.14×10^{-5}

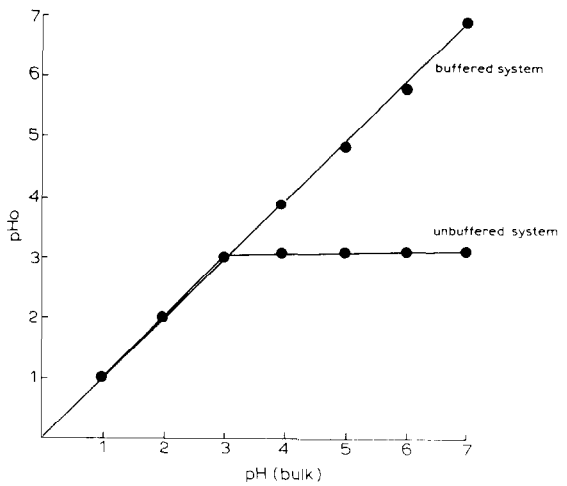

Fig. 7. Relationship between the pH of the diffusion layer (pHo) and the bulk pH (pH bulk) in buffered and unbuffered systems.

action exerted by the buffer components which are present in the diffusion layer. The presence of such components resists the change in pH caused by the dissociation of diflunisal and therefore maintains the pH value of the diffusion layer similar to that of the bulk.

The results indicate that in unbuffered systems it is important to consider the pH of a saturated solution of diflunisal, i.e. pHo and not only the initial pH bulk values in studying the dissolution and solubility of drugs. In buffered systems where the buffer capacity is high the pH of the bulk remains unchanged in the presence of solid diflunisal, thus emphasizing the importance of using buffers of an acceptable capacity in conducting release experiments.

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