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Experimental evidence for the development of a microviscous layer near the surface of dissolving polyethylene glycol

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Abstract

The microenviromnent near the surface of dissolving polyethylene glycol 1450 (PEG 1450) samples was probed using microviscosity sensitive fluorescent probes. The microviscosity of 0.5 mm thick layers of solution was monitored by exciting the fluorescence of the soluble probe using a laser directed horizontally across the film at various distances above the solid. As the solid PEG dissolved slowly in an unstirred environment, fluorescence data revealed the development of a microviscosity gradient over the dissolving PEG. The microviscosity at each distance above the solid reached a plateau with respect to time which decreased with distance from the surface. Slow stirring homogenized the solution further from the surface, although a microviscous layer did develop close to the surface. These events are described in terms of a finite difference approximation to Fick's second law which takes into account the dependence of diffusivity on PEG concentration. © 1997 Elsevier Science B.V.

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1. Introduction

Solid dispersions of drugs in polyethylene glycol (PEG) are widely known to enhance drug dissolution rates. Since they were extensively studied by Chiou and Riegelman (1971), a variety of mechanisms underlying this enhancement have been proposed and examined. However, the pro-

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posed mechanisms do not yet allow accurate predictions of dissolution rate enhancement by the PEGs. For example, some investigators have reported that dissolution rates were enhanced more by the lower molecular weight PEGs, while others have reported that dissolution was enhanced to a greater extent by the higher molecular weight PEGs (Ford, 1984). Ford found that the dissolution rate of glutethimide was enhanced to the greatest extent by the lowest molecular weight PEG in his study, having a mean molecular weight of 1500. In contrast, the highest molecular weight PEG in his study, which had a mean molecular weight of 14 000, gave the most reproducible, but not the highest, dissolution rates for glutethimide.

Corrigan et al. (1979) reported that the dissolution rates of pure PEGs decreased as molecular weight increased, but did not suggest why this relationship existed. We reexamined their results in light of recently published work in which Craig and Newton (1991) studied the heats of fusion of various molecular weight PEGs. They reported that the molar heat of fusion of PEG increased with an increase in molecular weight. However, using their data we calculated the heat of fusion per gram, which is determined by dividing the molar heat of fusion by the weight average molecular weight of each PEG. This normalization of their data results in the heat of fusion being independent of molecular weight within a range of 178.3–187.8 J/g. In addition, the equilibrium solubilities of PEGs decrease only modestly with increasing molecular weight (Union Carbide, 1991). This suggests that the difference in the dissolution rates of the various molecular weight PEGs seen by Corrigan et al. is not explained by changes in the solid state properties. That is, the small decrease in solubility of PEG with molecular weight does not account for the corresponding large decrease in dissolution rates reported by Corrigan et al. In addition, the inconsistent dependency of dissolution enhancement on PEG molecular weight reported by Ford has led us to examine the microenviromnent near the surface of PEG 1450. We believe that release of drug from PEG is a function of the physical properties of PEG solutions, such as: viscosity, microviscosity and dielectric constant of the aqueous PEG-rich layer surrounding the surface of dissolving PEG solids, in addition to the well studied solid state interactions of various drugs with PEGS.

This paper focuses on the effect of microviscosity on the dissolution of PEG 1450. First, we present experimental evidence which demonstrates the existence of the microviscosity gradient close to the PEG surface. Next, we describe the phenomena leading to the development of a microviscosity gradient localized near the PEG surface as well as a mathematical model to predict the microviscosity gradient.

Observation of such localized gradients required investigation of the microenvironment near the surface; bulk measurements would have been insufficient. Others have explored polymer dissolution using laser interferometry (Krasicky et al., 1988; Nivaggioli et al., 1992). This method is limited in that it requires the use of very thin (≈ 1 μm) films. Since thicker films are generally used in pharmaceutical dosage forms, laser interferometry was inadequate for our model dissolution system. Therefore, we developed a technique to study the localized gradients using a laser to excite microviscosity-sensitive fluorescent probes at various positions above the dissolving PEG solid. The fluorescence intensities of the probes were previously shown to measure microviscosity (LaPorte et al., 1995).

2. Mathematical model

Generally, dissolution in a stagnant medium can be modelled using a variety of analytical solutions of Fick's second law. However, when the dissolving molecule changes the local viscosity, the analytical solutions to Fick's law are inapplicable. The effect of the dissolving molecule on its own ability to diffuse away from the solid surface must be determined. In this section, we describe the method used to characterize the development of a microviscous layer near the dissolving PEG surface.

Dissolution from a single face of a solid into a large, unstirred volume of solvent can be modelled by solution of Fick's second law,

$$\frac{\partial c}{\partial t} = D\frac{\partial c}{\partial x^2} \tag{1}$$

using the boundary conditions and $c = c_0$ at x = 0 for all t > 0, and $c = 0$ at $x > 0$ for $t = 0$, which, assuming a constant diffusion coefficient throughout the entire medium, yields the analytical solution

$$c = c_0 erfc\frac{x}{2\sqrt{Dt}} \tag{2}$$

at $x > 0$ for all $t > 0$.

However, when the diffusion coefficient is not constant, but rather a function of the concentration of the diffusing species, Fick's second law takes the form

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D(c)\frac{\partial c}{\partial x}\right) \tag{3}$$

where the diffusion coefficient, $D(c)$, is a defined function of concentration. Under most circumstances, this equation cannot be solved analytically. Instead Eq. (3) is solved numerically by finite differences, where the term on the left side of the equation is approximated by the first backward finite difference and the term inside the parentheses on the right side of the equation is approximated by the the first central finite difference to yield

$$\frac{c_{x,t} - c_{x,t-1}}{\Delta t} = \frac{\partial}{\partial x}\frac{D(c_{x,t-1})\cdot[c_{x+1/2,t-1} - c_{x-1/2,t-1}]}{\Delta x} \tag{4}$$

where $c_{x,t}$ is the concentration of the diffusant (PEG in this case) at any distance x from the surface of the solid (again, PEG in this case) and at any time t from the start of the dissolution process. Further, $D(c_{x,t-1})$ is the diffusion coefficient as a function of PEG concentration evaluated at the previous time point, Δt is the increment of time between each $c_{x,t-1}$ and $c_{x,t}$, and Δx is the increment of distance between each $c_{x-1,t}$ and $c_{x,t}$. The remaining partial differentiation is accomplished by again applying the second central finite difference to the right-hand side of the equation.

$$\begin{aligned}\frac{c_{x,t} - c_{x,t-1}}{\Delta t} = \{&D(c_{x-1/2,t-1})\cdot c_{x+1/2,t-1} \\ &- D(c_{x-1/2,t-1})\cdot c_{x,t-1}] \\ &- [D(c_{x+1/2,t-1}\cdot c_{x,t-1} \\ &- D(c_{x-1/2,t-1})\cdot c_{x-1,t-1}\}\ /\Delta x^2\end{aligned} \tag{5}$$

Terms are gathered to yield:

$$\begin{aligned}c_{x,t} = c_{x,t-1} &+ \{D(c_{x-1/2,t-1})\cdot[c_{x-1,t-1} - c_{x,t-1}] \\ &- D(c_{x+1/2,t-1})\cdot[c_{x,t-1} - c_{x+1,t-1}]\} \\ &\Delta t\ /\Delta x^2\end{aligned} \tag{6}$$

The first half of the second term corresponds to the flux into a volume element surrrounding position x, t and the second half of the second term corresponds to the flux out of that volume element. The problem with this equation is that it is difficult to evaluate the diffusion coefficients at half steps (i.e. $D(c_{x+1/2,t-1})$ and $D(c_{x-1/2,t-1})$). The diffusion coefficients at these points are calculated by the following equations:

$$D(c_{x+1/2,t-1}) = \frac{D(c_{x,t-1}) + D(c_{x+1,t-1})}{2} \tag{7a}$$

$$D(c_{x-1/2,t-1}) = \frac{D(c_{x,t-1}) + D(c_{x-1,t-1})}{2} \tag{7b}$$

The boundary conditions are set by assigning the value of 72% which is the solubility of PEG in water (Union Carbide, 1991) to all $c_{0,t}$ (i.e. concentration at the surface at any point in time) and zero to all $c_{x>0,0}$ (i.e. concentration in the bulk at zero time). Successive solution of each $c_{x,t}$ progessing from just above the surface to far distances along the x-dimension and progressing from short times to long along the t-dimension can be used to create a table of values of $c_{x,t}$. This matrix of concentration data makes a complete analysis of the dissolution process possible.

For convenience in mathematical modelling, we generally assume that the diffusion coefficient of small molecules in water is relatively constant over a broad range of concentrations. Implicit in this assumption are the further that the deviation of the molecule's concentration from its thermodynamic activity is negligible and

that the dissolved molecule has no effect on the viscosity of the surrounding medium. The second implicit assumption may be adequate for many small molecules, but is a poor assumption for others including glycerin, sucrose, and the lower molecular weight poly(ethylene glycol)s. In addition, the second assumption is clearly inadequate for higher molecular weight polymers. All of these molecules have the capacity to alter the mobility of themselves and surrounding molecules such as drugs as they dissolve or are released into the surrounding medium. For these viscous molecules, an analytical solution of Eq. (1) is impossible and numerical integration of the finite difference approximation in Eq. (6) becomes necessary.

3. Procedure for simulating PEG dissolution

To determine the effect of PEG 1450 on its diffusivity, it was necessary to determine the dependence of PEG viscosity on its concentration in water. An empirical relationship, Eq. (8), between PEG concentration (% w/v) and viscosity measured by cone-plate viscometry was determined from the data shown in Table 1.

$$\eta = 0.511e^{0.0731c} \tag{8}$$

The parameter η refers to the viscosity in centipoise (cps) and c is the concentration (%w/v). The diffusion coefficient of PEG at any concentration was calcuated by dividing the the infinite dilution diffusion coefficient of PEG 1450, 2.36×10^{-6} cm^2/s (Bandrup and Immergut, 1989), by the viscosity of the medium determined from Eq. (8) to yield,

Table 1
Viscosity of PEG 1450 solutions in water

PEG conc. (% w/v)	Viscosity (cps)
20	2.97 (0.02)
30	4.66 (0.03)
40	5.80 (0.06)
50	18.1 (0.1)
60	44.3 (0.3)
65	57.5 (0.3)

$$D = \frac{2.3 \times 10^{-6}}{0.511e^{0.0731c}} \tag{9}$$

For simulations of PEG 1450 dissolving in water, the values of $D(c_{x,\,t-1})$, $D(c_{x-1,\,t})$ and $D(c_{x+1,\,t-1})$ in Eq. (7a) and Eq. (7b) were determined from Eq. (9). The parameters Δx and Δt in Eq. (6) were set to 0.05 cm and 120 s, respectively. These values gave a stable solution and resulted in a solution to the finite difference approximation of Eq. (1) which agreed very well with the analytical solution found in Eq. (2).

4. Experimental

Polyethylene glycol 1450 (Carbowax Sentry, Union Carbide, Danbury, CT) was melted and poured on glass slides to form slabs using a cut-off cuvette as a mold. Solutions of the two probes, julolidine malononitrile (JMN) and *p*-*N*-dimethylaminocinnamylidine malonitrile (CMN), both from Molecular Probes, Eugene, OR, were prepared with concentrations of 2.0×10^{-5} M. The probe, JMN, was prepared in 20% v/v ethanol in water due to solubility considerations and CMN was prepared in 1% v/v ethanol in water. These solutions were used as the dissolution media. All experiments were performed at ambient conditions (ca. 25°C).

The dissolution medium was placed in a 1-cm cuvette. The solid PEG slab on its glass slide was fitted atop the filled cuvette, which was then inverted and placed on the adjustable stage (Fig. 1). The cuvette served as an dissolution vessel for use with the laser spectrometer. The cuvette was placed on a sample stage that was finely adjusted so the incident laser beam was parallel to the PEG slab. A micrometer which was attached to the sample stage allowed precise vertical positioning of the sample-filled cuvette relative to the incident laser beam. The laser (Coherent Innova 90-5) operating at 50 mW generated a beam of 488.6 nm. The beam was focused to a waist using a mirror, lens and two pinholes (Fig. 2). Thermal lensing within the dissolution medium spread the beam slightly yielding a horizontal resolution of less than 500 μm. A base height (0 mm) was established visually by adjusting the sample stage

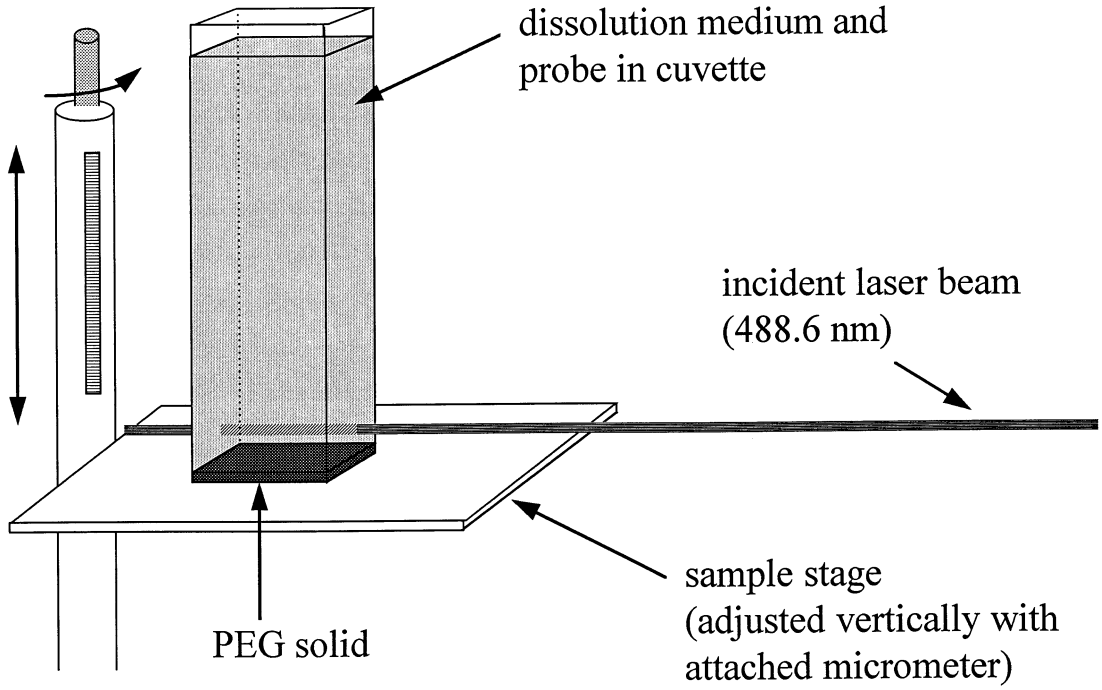

Fig. 1. Schematic of the cuvette used for dissolution studies. The sample stage is attached to a micrometer which is used to adjust the cuvette such that the relative position of the laser beam can be moved closer or further from the surface of the dissolving PEG solid slab. The fluorescent probe, either CMN or JMN is homogeneously dissolved in the dissolution medium.

such that the laser was just above the solid PEG and no light scattering was observed. Below the base height the laser deflected prominently due to contact with the PEG surface. The micrometer smoothly moved the PEG sample vertically with a resolution of 0.001 inches, which allowed the laser to pass through consecutive slices of the dissolution medium above the sample. Within each slice, the fluorescent probes were excited by the laser. The fluorescent quantum yield of each probe increased as the microviscosity of the enviromnent increased (LaPorte et al., 1995; Loutfy, 1981, 1982, 1986; Loutfy and Arnold, 1982). At a right angle to the excitation beam, a series of lenses were appropriately masked to permit the collection of the same solid angle of fluorescent emissions as the sample was moved relative to the incident beam. This constant solid angle of fluorescent emission was collected on a double monochromator (Spex 1403) coupled to a photomultiplier. Fluorescent intensities were integrated over the entire emission peak in order to account for shifts in the emission wavelength due to changes in micropolarity. The raw data of inte-

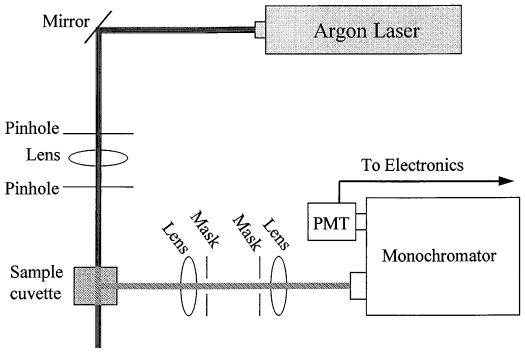

Fig. 2. Schematic of the laser spectrometer showing the pinholes and lens used to focus the beam; the laser beam exciting the probe in the sample cuvette; the masks on the lens system used to collect the same solid angle of emission at each position; and the monochromator and photomultiplier tube (PMT) used to detect the fluorescence signal.

grated fluorescent intensities are reported as a relative measure of microviscosity.

To determine the effect of convection on the dissolution of PEG, a star magnet was placed in each cuvette and a small stirring motor was mounted directly on the sample stage in order to keep the stir bar at a consistent height toward the top of the cuvette well above the surface of the PEG slab throughout the experiment. For experiments in which the dissolution was monitored in an unstirred environment, the stir bar was not activated until the end of the experiment at which time rapid stirring was used to completely dissolve the PEG to form a homogeneous solution. In each of these cases the fluorescence intensities at all heights converged to a single value corresponding to a single bulk viscosity. For experiments in which the dissolution was monitored in stirred enviromnents, slow, moderate and rapid stirring speeds were assessed qualitatively.

5. Results and discussion

Poly(ethylene glycol), PEG, is well known as a dissolution enhancing excipient. However, the viscosity of aquesous PEG solutions has the potential to impede the dissolution and release of drugs in its matrix. These two statements appear to be contradictory. Indeed, the effect of PEG molecular weight on its ability to enhance the dissolution of several drugs is reportedly inconsistent (Ford, 1984). It is hypothesized that there is a microviscous layer that surrounds the dissolving drug-PEG matrix which also affects the rate of release of drug from the matrix. An understanding of the dynamics that occur in this layer can ultimately be used to explain previous inconsistent data and predict the effect of various molecular weight PEGs on the enhancement of drug dissolution. To test our hypothesis and to begin to understand the dynamics occuring near the surface of dissolving PEG, an apparatus was designed to monitor continuously the properties of heterogeneous media by exciting only those probe molecules found in specific regions of the medium during the brief period of excitation. The heterogeneous medium investigated here is the dissolution medium above a sample of PEG 1450. The fluorescent probes, JMN and CMN are dissolved homogeneously throughout the dissolution medium.

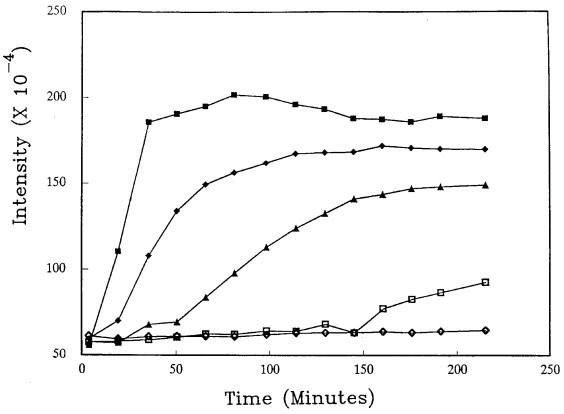

Fig. 3. Profiles of integrated fluorescent intensities of the viscosity-sensitive probe, JMN (2.0×10^{-5} M), in an unstirred medium of 20% v/v ethanol in water in the presence of a dissolving slab of PEG 1450. (■) 0 mm, (◆) 0.635 mm, (▲) 1.27 mm (□) 2.54 mm and (◇) 5.08 mm above the surface of the dissolving PEG solid slab.

When the medium above the dissolving PEG 1450 slab is unstirred, the fluorescent probes report an initial rapid rise of microviscosity measured near the surface of the PEG sample (Fig. 3). The fluorescent intensities emitted from the dissolved probe molecules located at various heights above the PEG surface all approach a maximum and remain constant over time. As the laser excites probes further from the surface, it can be seen that the rise in fluorescent intensity occurs at later times than the rise in intensity of probes closer to the surface. In addition, the rate of the rise is lower further from the surface. Lastly, it should be pointed out that the maximum fluorescent intensity of the plateau is lower for probe molecules found further from the surface. Generally, the development of a plateau in concentration, viscosity or any other property with respect to time indicates that either equilibrium or steady-state has been reached. An equilibrium exists when and only when the solution is homogeneous. The fact that the plateaus were different each height (Fig. 3) indicates that equilibrium solubility was not reached. This is supported by the obser-

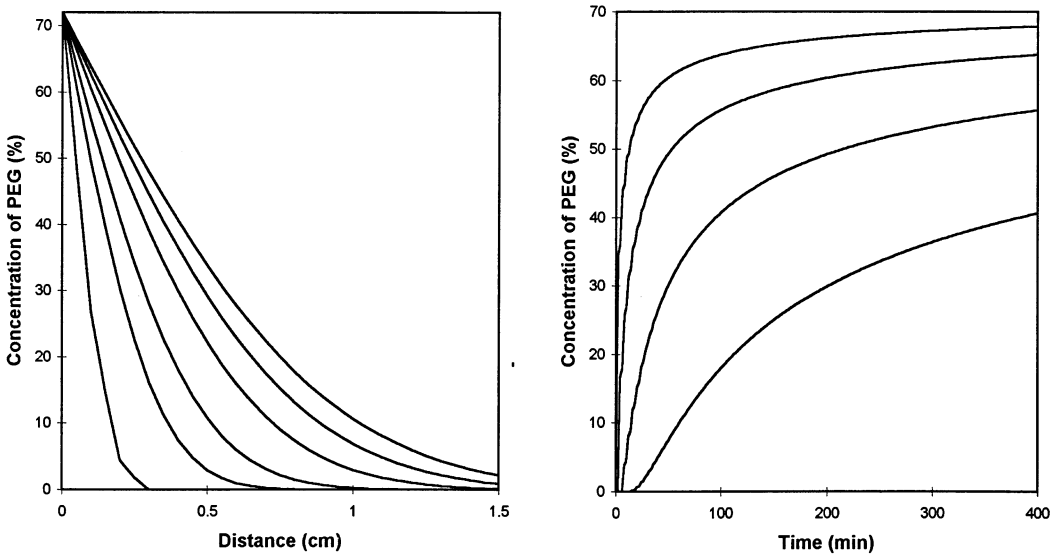

Fig. 4. (a) Simulated concentration gradients of a small molecule with a constant diffusion coefficient of 10^{-5} cm^2/s dissolving from a surface into a stagnant medium. From lowest to highest, the profiles correspond to 10, 50, 100, 200, 300 and 400 min. The profiles were obtained using a finite difference approximation to Eq. (1) with $\Delta t = 120$ s and $\Delta x = 0.05$ cm. At a distance of 2.5 cm from the surface the boundary condition was set at conc = 0. (b) Simulated profiles of concentration versus time of a small molecule with a constant diffusion coefficient of 10^{-5} cm^2/s dissolving from a surface into a stagnant medium. From lowest to highest, the profiles correspond to 0.5, 1.0, 2.0 and 4.0 mm above the dissolving surface. The profiles were obtained using a finite difference approximation to Eq. (1) with $\Delta t = 120$ s and $\Delta x = 0.05$ cm. At a distance of 2.5 cm from the surface the boundary condition was set at conc = 0.

vation that at the end of the experiment, when stirring was initiated, the PEG dissolved rapidly and completely. A steady-state, on the other hand, results from a constant source which exists in this experiment and a constant sink which does not exist here. In an unstirred medium, such as that employed here, the establishment of a steady-state profile seems counter-intuitive. Certainly we would have expected there to be a concentration gradient of PEG in the medium leading to an unsteady-state profile. Thus, neither equilibrium nor true steady-state conditions were adhered to in these experiments. The reasons for the apparent steady-state microviscosity profile became clear upon examining the mathematical simulations of a viscosity-inducing solid such as PEG.

The ability of a dissolved molecule to diffuse to the next layer of medium is dependent on its concentration gradient and diffusivity. For cases in which Eq. (2) is applicable, at any point, it is only the concentration gradient that changes. The diffusivity is constant throughout the medium. In these cases, the concentration gradient near the surface is very steep during the initial phase of dissolution (Fig. 4a). In addition, the concentration gradient changes with distance from the surface. There can be no steady-state in the presence of the changing concentration gradients. Therefore, there is no plateau in the concentration versus time profiles until the solution approaches saturation, an equilibrium condition (Fig. 4b).

In contrast, for viscosity-altering molecules such as PEG for which Eq. (6) is more applicable, the transport of the diffusant is dependent upon not only the concentration gradient, but also the diffusivity at any point. During the initial phase of dissolution of PEG 1450, the concentration gradient is very steep, similar to the profile where diffusivity is constant. However, the diffusivity is much lower than that in the bulk due to the high

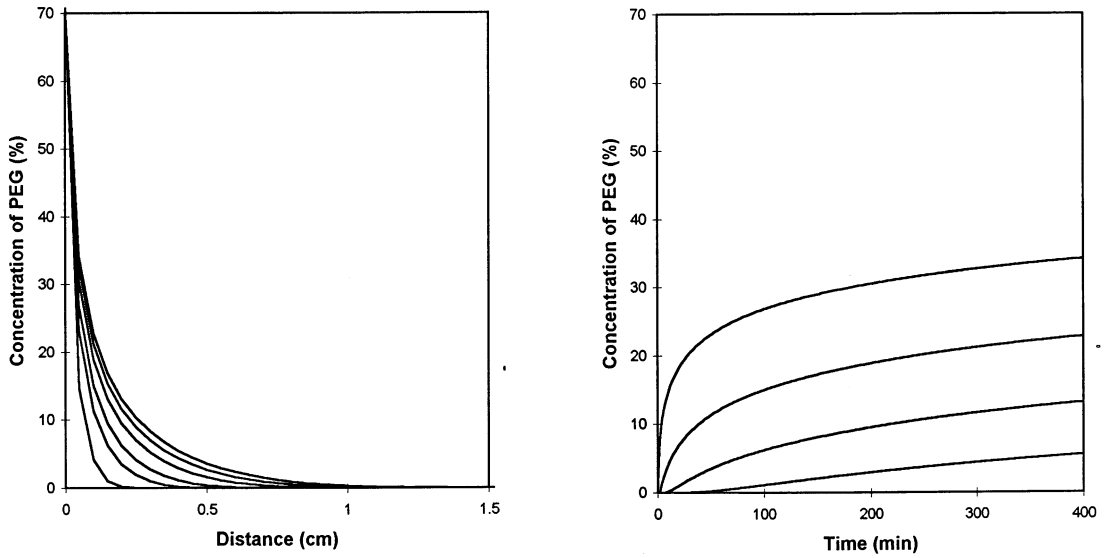

Fig. 5. (a) Simulated concentration gradients of PEG 1450 dissolving from a slab into a stagnant medium. From lowest to highest, the profiles correspond to 10, 50, 100, 200, 300 and 400 min. The profiles were obtained using Eq. (6) and the diffusion coefficient described by Eq. (9) with $\Delta t = 120$ s and $\Delta x = 0.05$ cm. At a distance of 2.5 cm from the surface the boundary condition was set at conc = 0. (b) Simulated profiles of concentration versus time of PEG 1450 dissolving from a slab into a stagnant medium. From lowest to highest, the profiles correspond to 0.5, 1.0, 2.0 and 4.0 mm above the dissolving surface. The profiles were obtained using Eq. (6) and the diffusion coefficient described by Eq. (9) with $\Delta t = 120$ s and $\Delta x = 0.05$ cm. At a distance of 2.5 cm from the surface the boundary condition was set at conc = 0.

viscosity in the region of concentrated PEG. The low local diffusivity near the surface is the result of the high concentration of dissolved PEG 1450 and reduces the transport of PEG molecules away from the dissolving solid. Thus, the concentration gradient close to the dissolving surface remains steep for a longer period of time (Fig. 5a). In regions close to the dissolving solid, the concentration begins to plateau with time well before it reaches saturation (Fig. 5b).

The apparent steady-state condition seen as a plateau in Fig. 5b results from the product of the diffusivity gradient and the concentration gradient. For the purposes of this discussion, we will refer to the mid-point of a volume element that molecules diffuse into and out of as position. The diffusivity approaching each position is less than the diffusivity leaving that position. Thus, from the viewpoint of diffusivity alone, it is easier for the solute to arrive than to leave from any position close to the surface where this phenomenon is operating. However, the concentration gradient decreases at positions further from the surface. So, while it is easier to leave a certain position than it was to arrive there, there is less of a driving force (i.e. concentration gradient) to leave. The concentration gradient normally regarded as a driving force for diffusion is, in this case, op-

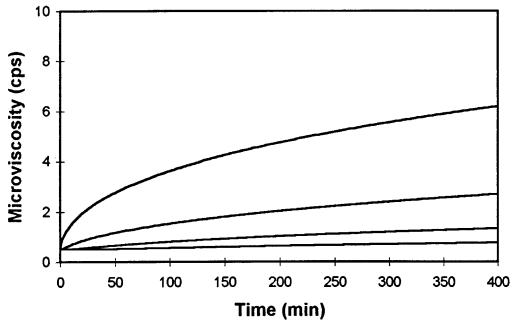

Fig. 6. Simulated profiles of microviscosity versus time of PEG 1450 dissolving from a slab into a stagnant The profiles were obtained by transforming the concentration data in Fig. 5b into microviscosity using Eq. (8).

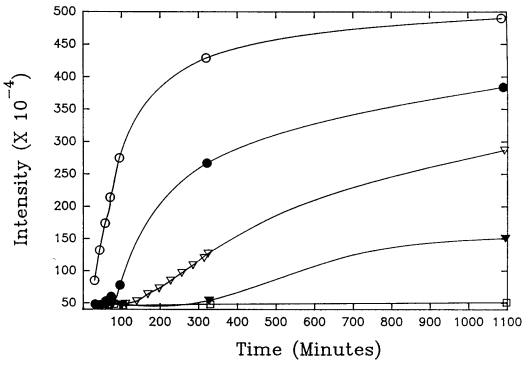

Fig. 7. Profiles of integrated fluorescent intensifies of the viscosity-sensitive probe, CMN (1.8×10^{-5} M), in an unstirred medium of 1% v/v ethanol in water in the presence of a dissolving slab of PEG 1450. (○) 0 mm, (●) 1.27 mm, (▽) 2.54 mm and (▼) 5.08 mm above the surface of the dissolving PEG solid slab.

posed by a diffusivity gradient in the opposite direction. This effect leads to an apparent steady-state microviscosity (and PEG concentration) even in the presence of a high concentration gradient near the surface.

Fig. 6 shows the local microviscosities that develop over time calculated from the concentration versus time profiles in Fig. 5b. Very close to the surface of the dissolving PEG solid, the simulation suggests that the viscosity can reach 6 cps. Thus, as dissolution occurs, it is slowed by an increasing resistance to diffusion offered by the dissolving molecules themselves. The release of any codissolving solute would also be impeded by this viscous layer. The simulation and the laser induced fluorescence show similar evidence of a series of plateaus developing. Consistent with the experimental data, the simulated plateaus are lower and appear later at further distances from the dissolving surface. At distances further form the surface, the solute arrives later and at a lower concentration. The delay in arrival is a function of the diffusivity of the medium integrated over the path of the solute and over the period of delay. The lower plateaus in microviscosity at successive distances form the surface are due to lower concentration gradients and lower viscous resistances. At distances far from the dissolving surface (1–5 mm), the fluorescent intensity approaches zero as the viscosity approaches 1 cps (Figs. 3 and 7). Thus, the region over which the viscosity profile develops remains close to the surface just as indicated in the simulation in Fig. 6. While these comparisons are only qualitative, the similarities are striking. Further work will be done to obtain a more quantitative comparison of the theory with the experimental results.

When the dissolution medium over the PEG slab is stirred slowly, the fluorescence emitted from the probes located at 1 mm from the surface did not rise initially, but remained low for the first 100 min (Fig. 8). However, very near the surface at a nominal distance of 0 mm, an increase in apparent microviscosity was seen. In addition, the characteristic plateaus seen in Figs. 3 and 7 are not present. Instead, there is a somewhat steady rise in viscosity with time. The profiles seen under unstirred conditions collapsed due to convective flow of the solution induced by the stirring bar in the dissolution medium. Convection carries away elements of solution laden with viscosity-inducing solute and replaces them with fresh low viscosity medium. This can occur more easily at distances further from the surface where there is little viscous resistance to convective flow. At positions in which the solute begins to accumulate, the higher viscosity resists convective flow and allows the slower diffusive process to develop a viscosity profile. However, convection reduces the distance to which the viscosity gradient can develop and also modifies the shape of the viscosity profile.

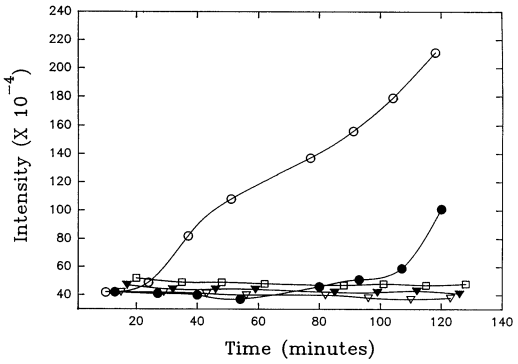

Fig. 8. Profiles of integrated fluorescent intensities of the viscosity-sensitive probe, CMN (1.8×10^{-5} M), in a slowly stirred medium of 1% v/v ethanol in water in the presence of a dissolving slab of PEG 1450. (○) 0 mm, (●) 1.27 mm, (▽) 2.54 mm, (▼) 5.08 mm and (□) 10.2 mm above the surface of the dissolving PEG solid slab.

In summary, an experimental technique for determining the viscosity of heterogeneous systems has been described. The technique was used to determine the microviscosity of dissolving PEG 1450. The data agree qualitatively with the proposed mathematical model which describes both the viscosity and concentration gradients of the dissolving sample. Experimentally determined viscosity profiles near the surface of dissolving PEG 1450 slabs were explained in terms of both diffusion and convection in the dissolution media.

The results suggest that polyethylene glycol, a widely regarded dissolution enhancing excipient, also has the ability to slow its own release by creating a viscous barrier. This has implications for the co-release of drugs from PEG solid dispersions. In particular, it is expected that the viscous resistance to dissolution resulting from higher molecular weight PEGs with their higher viscosities will accentuate the viscosity profiles shown here in Figs. 3, 7 and 8. However, it is insufficient to consider only the viscosity effects of PEG. Rather, the effects of PEGs on the local dielectric constant and other properties of the solution will also play significant roles in predicting and understanding the drug release from PEG solid dispersions.

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