Diffusion-Controlled Polymer Dissolution and Drug Release

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ABSTRACT: A model is formulated for diffusion-controlled polymer dissolution and simultaneous drug release for amorphous, uncrosslinked polymers. Calculated fractional drug release versus time curves are similar to experimental curves reported in the literature. Solutions of the transport equations provide a way of illustrating how polymer type and molecular weight can be used in an attempt to approach a constant drug release rate. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 93: 92–99, 2004

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INTRODUCTION

The ability to supply materials such as drugs at prescribed rates can often be facilitated by utilizing a polymer matrix as a binder in which the drug is molecularly dispersed or dissolved. The dissolution behavior of the polymer can then be used to control the rate of drug release. In general, the following three classes of polymeric materials can be used in an attempt to control the drug release process: (1) crosslinked polymers; (2) semicrystalline polymers; (3) amorphous, uncrosslinked polymers.

For crosslinked polymers, the release of a drug can be regulated by adjusting the degree of polymer crosslinking. However, crosslinking agents are often toxic and can cause adverse interactions in the body after the drug is released. For semicrystalline polymers, drug release can be controlled by the appropriate choice of polymer type, polymer molecular weight, degree of crystallinity, and crystallite size. A modeling analysis of drug release by using a semicrystalline polymer is complicated by the need to consider transport processes in a heterogeneous material and to include a crystal dissolution process in the formulation of the pertinent transport equations. For amorphous, uncrosslinked polymers, drug release rates can be controlled by varying the polymer type and/or polymer molecular weight. No toxic crosslinking agents are involved, and the transport analysis is somewhat simpler than that for semicrystalline polymers. Thus, amorphous, uncrosslinked polymers were chosen as the basis for this study.

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The principal objective of this article was to formulate a model for diffusion-controlled polymer dissolution and simultaneous drug release for amorphous, uncrosslinked polymers. In addition, solutions of the transport equations were used to illustrate how polymer type and molecular weight can be varied to approach a constant drug release rate (zero-order delivery). The calculated fractional drug release versus time runs obtained from the model are similar in shape to experimental curves reported in the literature.[1–4]

The basic approach used in the investigation to model simultaneous polymer dissolution and drug release is similar to the approach utilized in analyzing the dissolution of rubbery and glassy polymers.[5] In that previous study, the dissolution process was analyzed by using a single liquid phase, which consisted of a binary liquid mixture of solvent and polymer. Previous mathematical models for polymer dissolution and drug delivery were reviewed by Narasimhan,[6] and the present investigation presents a somewhat different analysis of the polymer dissolution and drug release processes than previously presented in the literature. Note that the components of the ternary system considered here will be referred to as follows: drug-component, 1; polymer–component, 2; solvent–component, 3.

ASSUMPTIONS OF MODEL

The following assumptions and restrictions are used to define the transport process in this model:

1. The polymer is an amorphous, uncrosslinked polymer, and both glassy and rubbery regions of the system contain no crystals.
2. The polymer, drug, and solvent are assumed to be completely miscible so that the entire system

comprises a single liquid phase.[5] The drug will have been dissolved initially in the polymer matrix at a concentration below the solubility limit.

3. The diffusion process is isothermal; there are no chemical reactions, and the effect of pressure on liquid density is negligible.
4. The polymer is initially in the glassy state but gets converted to a rubbery state as the solvent diffuses into the polymer matrix. For the rubbery state, it is assumed that the partial specific volumes of the polymer-drug-solvent system are independent of composition. For the glassy state, the addition of solvent leads to structural rearrangements in the polymer matrix, and the partial specific volumes of the system effectively become concentration dependent.[7,8] Hence, for the rubbery polymeric system, the volume average velocity $\boldsymbol{v}^{\ddagger}$ is described by the equation

$$\nabla \cdot \boldsymbol{v}^{\ddagger} = 0 \tag{1}$$

but, for the glassy polymeric system, the following result is applicable:

$$\nabla \cdot \boldsymbol{v}^{\ddagger} \neq 0 \tag{2}$$

For a glassy polymer, therefore, there can be a velocity field induced by the nonequilibrium volumetric properties of the glass. This induced velocity field can have a significant effect on the overall mass transfer process. For integral sorption in a glassy polymeric film, in which there are two immiscible liquid phases, the combination of the induced velocity field and the moving phase boundary produces a term which cannot be neglected and which changes the character of the mass transfer process.[8] However, for the dissolution of a glassy polymer which consists of a single liquid phase, the effect of the induced velocity is small and can be neglected.[5] Consequently, for our single liquid phase model, we can assume that eq. (1) will adequately describe variations of the volume average velocity in the dissolution process for both glassy and rubbery regions of the system.

5. The diffusion process in the drug release system is considered to be a one-dimensional transport process in which a pure solvent is put into contact with a drug-containing polymer film of initial thickness L_0. For simplicity in the analyses, it is also assumed that the drug–polymer combination initially is adjacent to a solid, stationary wall. Consequently, the diffusion field extends from the solid wall at $x = 0$ to $x = \infty$, where x is the distance variable in the diffusion direction.
6. For this polymer-drug-solvent system, the diffusion Deborah number will be either high or low for most of the diffusion field.[5] Consequently, it is assumed (as a first approximation) that there is a Fickian diffusion process with concentration-dependent diffusion coefficients essentially everywhere in the system.
7. There is no external flow in the fluid surrounding the dissolving polymer-drug film. Our investigation of a static system should thus provide maximum polymer dissolution and drug release times for a particular polymer-drug-solvent system at a given temperature.
8. In general, a ternary system of components 1, 2, and 3 can be analyzed by using four mutual diffusion coefficients D_{11}, D_{12}, D_{22}, and D_{21}. We assume that the cross-term diffusion coefficients (D_{12} and D_{21}) are very small and that the main-term diffusion coefficients (D_{11} and D_{22}) depend on concentration:

$$D_{12} \approx 0 \tag{3}$$

$$D_{21} \approx 0 \tag{4}$$

$$D_{11} = D_{11}(\rho_1, \rho_2) \tag{5}$$

$$D_{22} = D_{22}(\rho_1, \rho_2) \tag{6}$$

Here ρ_1 is the mass density of the drug and ρ_2 is the mass density of the polymer. Although the assumption that cross-diffusion effects are small for the polymer-drug-solvent system appears to be reasonable, there seems to be no diffusion coefficient data which can provide justification for this assumption.

The above assumptions are used to formulate appropriate species continuity equations in the next section of the article. Before this is done, the simplifications that are introduced by the assumption that the diffusion problem is a one-dimensional transport process should be discussed. Because eq. (1) is utilized for both glassy and rubbery regions in the system, the following result is valid for a one-dimensional diffusion process in rectangular coordinates:

$$\frac{\partial v_x^{\ddagger}}{\partial x} = 0 \tag{7}$$

Here, $v_x^{\ddagger}$ is the x component of the volume average velocity. Because the solid wall at $x = 0$ can be considered to be impermeable, we can write

$$v_x^{\ddagger} = 0, \quad x = 0, \quad t \geqq 0 \tag{8}$$

where t is time. It thus follows from eqs. (7) and (8) that

$$v_x^{\ddagger} = 0 \tag{9}$$

everywhere in the diffusion field (both glassy and rubbery regions) for all time. It can also be shown that the radial component of the volume-average velocity is zero when there is only radial diffusion in cylindrical and spherical geometries which extend to the origin of the coordinate system. For these two geometries, eq. (8) is replaced by the requirement that the volume-average velocity is bounded at the origin of the coordinate system. Consequently, if pressure effects on the diffusion process can be considered to be negligible for the polymer-drug-solvent system, then the species continuity equations for the drug and the polymer can be solved for ρ_1 and ρ_2. There are no convective terms in the species continuity equations because $v_x^{\ddagger} = 0$. The single remaining equation of motion and the thermal equation of state can then be used to determine the pressure field and the distribution of the total mass density of the mixture, ρ, in the system. However, the pressure and density calculations are not actually needed for the one-dimensional diffusion process considered here because the species continuity equations are not coupled to the x component of the equation of motion.

It is sometimes stated in the literature that the assumption of one-dimensional diffusional transport can be easily relaxed to include two- and three-dimensional transport processes. This statement is not generally true. For example, when considering a three-dimensional diffusion process, it is not correct to conclude simply that $\boldsymbol{v}^{\ddagger} = \mathbf{0}$ even if there are solid walls in the system. Although eq. (1) is valid everywhere in the system, no direct information about the three velocity components can be obtained from this equation only because there are three unknowns in a single equation. Consequently, the convective terms in the species continuity equations cannot in general be set equal to zero, and, therefore, the species continuity equations will be coupled with eq. (1) and with the three equations of motion. Thus, for a three-dimensional diffusion problem for a ternary system, it is necessary to solve seven equations [two species continuity equations, eq. (1), three equations of motion, and a thermal equation of state] for seven unknowns (ρ_1, ρ_2, ρ, three components of velocity, and pressure). Clearly, changing from one to three spatial dimensions is not trivial. Often what has been done for three-dimensional problems is that the convective terms in the species continuity equations are ignored without comment. We do not believe that these convective terms can be excluded without justification.

FORMULATION OF TRANSPORT EQUATIONS

Species continuity equations for the drug and polymer can be formulated for the one-dimensional transport problem by excluding cross-diffusion effects and by using the fact that $v_x^{\ddagger} = 0$ to eliminate the convective terms. The dimensionless forms of the species continuity equations and corresponding boundary conditions for the drug and polymer subsequently can be written as:

$$\frac{\partial C_1}{\partial \tau} = \frac{\partial}{\partial \xi}\left(\frac{D_{11}}{D_{s2}}\frac{\partial C_1}{\partial \xi}\right) \tag{10}$$

$$\frac{\partial C_1}{\partial \xi} = 0, \quad \xi = 0, \quad \tau \geqq 0 \tag{11}$$

$$C_1 = 0, \quad \xi = \infty, \quad \tau \geqq 0 \tag{12}$$

$$C_1 = 1, \quad \tau = 0, \quad 0 \leqq \xi < 1 \tag{13}$$

$$C_1 = 0, \quad \tau = 0, \quad 1 < \xi \leqq \infty \tag{14}$$

$$\frac{\partial C_2}{\partial \tau} = \frac{\partial}{\partial \xi}\left(\frac{D_{22}}{D_{s2}}\frac{\partial C_2}{\partial \xi}\right) \tag{15}$$

$$\frac{\partial C_2}{\partial \xi} = 0, \quad \xi = 0, \quad \tau \geqq 0 \tag{16}$$

$$C_2 = 0, \quad \xi = \infty, \quad \tau \geqq 0 \tag{17}$$

$$C_2 = 1, \quad \tau = 0, \quad 0 \leqq \xi < 1 \tag{18}$$

$$C_2 = 0, \quad \tau = 0, \quad 1 < \xi \leqq \infty \tag{19}$$

$$D_{11} = D_{11}(C_1, C_2) \tag{20}$$

$$D_{s1} = D_{11}(0, 0) \tag{21}$$

$$D_{22} = D_{22}(C_1, C_2) \tag{22}$$

$$D_{s2} = D_{22}(0, 0) \tag{23}$$

$$C_1 = \frac{\rho_1}{\rho_{10}} \tag{24}$$

$$C_2 = \frac{\rho_2}{\rho_{20}} \tag{25}$$

$$\xi = \frac{x}{L_0} \tag{26}$$

$$\tau = \frac{D_{s2}t}{L_0^2} \tag{27}$$

Here, ρ_{10} is the initial mass density of the drug in the polymer film and ρ_{20} is the initial mass density of polymer in the polymer film. Also, D_{s1} and D_{s2} refer to values of D_{11} and D_{22} in an infinite sea of solvent.

The above set of equations can be solved numerically if expressions for the concentration dependencies of D_{11}/D_{s2} and D_{22}/D_{s2} are known. In this study, we use a weighted residual method to obtain an approximate analytical solution, and we use free-volume theory to suggest forms for the concentration dependencies of the diffusion coefficients. Equations based on the free-volume theory of diffusion[9–11] can be written for D_1, the self-diffusion coefficient for the drug, and D_2, the self-diffusion coefficient for the polymer:

$$D_1 = D_{01}\exp\left[-\frac{\left(\omega_1\hat{V}_1^* + \omega_2\hat{V}_2^*\frac{\xi_{13}}{\xi_{23}} + \omega_3\hat{V}_3^*\xi_{13}\right)}{\hat{V}_{FH}/\gamma}\right] \quad (28)$$

$$D_2 = D_{02}\exp\left[-\frac{\left(\omega_1\hat{V}_1^*\frac{\xi_{23}}{\xi_{13}} + \omega_2\hat{V}_2^* + \omega_3\hat{V}_3^*\xi_{23}\right)}{\hat{V}_{FH}/\gamma}\right] \quad (29)$$

$$\frac{\hat{V}_{FH}}{\gamma} = \frac{\omega_1 f_1\hat{V}_1^0}{\gamma_1} + \frac{\omega_2 f_2\hat{V}_2^0}{\gamma_2} + \frac{\omega_3 f_3\hat{V}_3^0}{\gamma_3} \quad (30)$$

Here, D_{0I} is the preexponential factor for component I, ω_I is the mass fraction of component I, f_I is the fractional hole free volume of pure component I at the diffusion temperature, $\hat{V}_I^0$ is the specific volume of pure component I at the temperature of interest, $\hat{V}_I^*$ is the specific critical hole free volume of component I required for a jump, $\hat{V}_{FH}$ is the average hole free volume per gram of mixture, γ is the average overlap factor for the mixture which is introduced because the same free volume is available to more than one jumping unit, γ_I represents the overlap factor for the free volume of pure component I, and ξ_{I3} represents the ratio of the critical molar volume of a jumping unit of component I to the critical molar volume of the jumping unit of the solvent. Equations (28) and (29) should be used at a single temperature because the effective energy per mole that a molecule needs to overcome attractive forces has been incorporated in the preexponential factor for each component.

We now use the above free-volume formulation for self-diffusion coefficients to suggest reasonable approximate concentration dependencies for the two mutual diffusion coefficients, D_{11} and D_{22}. To facilitate the analysis of our one-dimensional transport problem, we introduce the following four assumptions:

1. It is assumed that
$$D_{s1} = D_{s2} = D_s \quad (31)$$
so that the time scales for polymer dissolution and drug release are comparable. It seems preferable to have the polymer dissolution and drug release processes occur simultaneously. Because D_{s2} represents the polymer diffusion coefficient in an infinite sea of solvent, D_{s2} is a function of polymer molecular weight.[12] Consequently, the equality of eq. (31) can be achieved by appropriate choice of the molecular weight of the polymer.
2. It is assumed that the jumping units of the drug and polymer are very nearly the same so that
$$\frac{\xi_{13}}{\xi_{23}} \approx 1 \quad (32)$$
Because many drugs are large molecules, this appears to be reasonable.
3. It is assumed that the concentration dependencies of D_{11} and D_{22} can be ascertained from the concentration dependencies of D_1 and D_2. Free-volume theory gives equations only for the dependencies of D_1 and D_2 on ρ_1 and ρ_2. It does not directly give equations for the dependencies of D_{11} and D_{22} on ρ_1 and ρ_2. However, it seems reasonable to expect that free-volume theory will suggest a general form for the dependencies of D_{11} and D_{22} on ρ_1 and ρ_2.
4. It is assumed that the concentration dependencies of the mutual diffusion coefficients are similar in both the glassy and the rubbery states of the polymer. This assumption was utilized implicitly in the dissolution investigation,[5] and it appears to be a reasonable approximation to use in an initial study of the present transport problem. In general, a stronger concentration dependence would be expected for glassy polymer-penetrant systems because the free volume for such systems is generally lower. However, illustrative free-volume calculations[11] of the concentration dependence of penetrant self-diffusion coefficients indicate that a wide variety of behavior is possible for the concentration dependence because of structural rearrangements in the glassy region when penetrant is added. Additionally, at the glass transition temperature, the concentration derivative for the self-diffusion coefficient is greater in the rubbery state.[13] These variations in behavior do not exclude the possibility of similar behavior in both glassy and rubbery states.

Utilization of the above four assumptions produces the following result for the two mutual diffusion coefficients:

$$\frac{D_{11}}{D_s} = \frac{D_{22}}{D_s} = \frac{D_{01}}{D_s}\exp\left[-\frac{(\omega_1\hat{V}_1^* + \omega_2\hat{V}_2^* + \omega_3\hat{V}_3^*\xi_{13})}{\hat{V}_{FH}/\gamma}\right] \quad (33)$$

Because the solvent has more free volume than the drug and the polymer ($f_3 > f_1, f_3 > f_2$), it follows from eq. (30) that

$$\frac{\partial(\hat{V}_{FH}/\gamma)}{\partial\omega_1} < 0 \tag{34}$$

$$\frac{\partial(\hat{V}_{FH}/\gamma)}{\partial\omega_2} < 0 \tag{35}$$

From an examination of eqs. (33)–(35), it is reasonable to expect that D_{11}/D_s and D_{22}/D_s will decrease with increasing ρ_1 and ρ_2 and that some form of an exponential concentration dependence will be operative. Consequently, as an approximate representation of the above trends, we propose the following exponential-type dependence in which D_{11}/D_s and D_{22}/D_s decrease with increasing C_1 and with increasing C_2:

$$\frac{D_{11}}{D_s} = \frac{D_{22}}{D_s} = \exp[-(A_1C_1 + A_2C_2)] \tag{36}$$

Here, A_1 and A_2 are positive constants. Note that expressions of the form of eq. (36) are not a direct result of free-volume theory, as is stated sometimes in the literature. The form of eq. (36) was chosen and is used here because it facilitates the analysis and because it is consistent with the characteristics of the free-volume theory of diffusion. Note that in eq. (36) the concentration dependence of the diffusion coefficients appears in the numerator of the argument of the exponential, whereas in free-volume theory the major part of the concentration dependence of self-diffusion coefficients appears in the denominator of the argument of the exponential. Consequently, although eq. (36) is consistent with free-volume theory, the exact form of the concentration dependence is different.

It follows from eqs. (10)–(19) and eqs. (31) and (36) that

$$C_1(\xi, \tau) = C_2(\xi, \tau) \tag{37}$$

so that the dimensionless concentrations of drug and polymer are identical in the diffusion field. Consequently, for the present analysis, eq. (36) can be rewritten as

$$\frac{D_{11}}{D_s} = \frac{D_{22}}{D_s} = \exp[-kC_1] \tag{38}$$

where the positive constant k is simply

$$k = A_1 + A_2 \tag{39}$$

It is evident from the above analyses that both C_1 and C_2 can be determined by solving eqs. (10)–(14) by using eq. (38) for the concentration dependence of the diffusion coefficient D_{11}/D_s.

SOLUTION OF TRANSPORT EQUATIONS

Although an analytical solution to eqs. (10)–(14) and (38) can be obtained for the case $k = 0$ (constant diffusion coefficient), it is not possible to derive an exact, analytical solution for the case $k > 0$ because the partial differential equation is nonlinear. Consequently, we follow the procedure used in an earlier investigation[5] and use a weighted residual method (the method of moments) to obtain an approximate solution to the nonlinear diffusion problem. The following trial function is used for C_1, the concentration field for the drug,[5]

$$C_1 = \frac{1}{2}\left[\operatorname{erf}\left(\frac{\xi+1}{2\tau^{1/2}\beta}\right) - \operatorname{erf}\left(\frac{\xi-1}{2\tau^{1/2}\beta}\right)\right] \tag{40}$$

where the function $\beta(\tau)$ must be determined from the moment equations. The time dependence of β is given by the expression[5]

$$\int_0^{\gamma_0} \frac{k \operatorname{erf}\left[\frac{1}{2\bar{\gamma}^{1/2}}\right] d\bar{\gamma}}{1 - \exp\left[-k \operatorname{erf}\left(\frac{1}{2\bar{\gamma}^{1/2}}\right)\right]} = \tau \tag{41}$$

where

$$\gamma_0 = \beta^2\tau \tag{42}$$

The function $\gamma_0(\tau)$ and, hence, $\beta(\tau)$ can be determined from eq. (41) by using a straightforward numerical integration procedure. It is convenient to define the amount of drug retained in the polymer matrix as the mass M_1 of drug per unit area still in the region $0 \leqq x \leqq L_0$. Consequently, it can be shown[5] that

$$\frac{M_1}{M_{10}} = \int_0^1 C_1 d\xi \tag{43}$$

where M_{10} is the initial mass of drug per unit area in the region $0 \leqq x \leqq L_0$. Finally, it can be shown[5] from eqs. (40) and (43) that the fraction of drug that has been released, $1 - (M_1/M_{10})$, can be determined by using the following expression:

$$1 - \frac{M_1}{M_{10}} = 1 - \operatorname{erf}\left(\frac{1}{\tau^{1/2}}\right) - \left(\frac{\tau}{\pi}\right)^{1/2}(e^{-(1/\tau)} - 1) \tag{44}$$

The concentration field for the polymer, $C_2(\xi, \tau)$, can be calculated directly from eqs. (37) and (40)–(42) and the

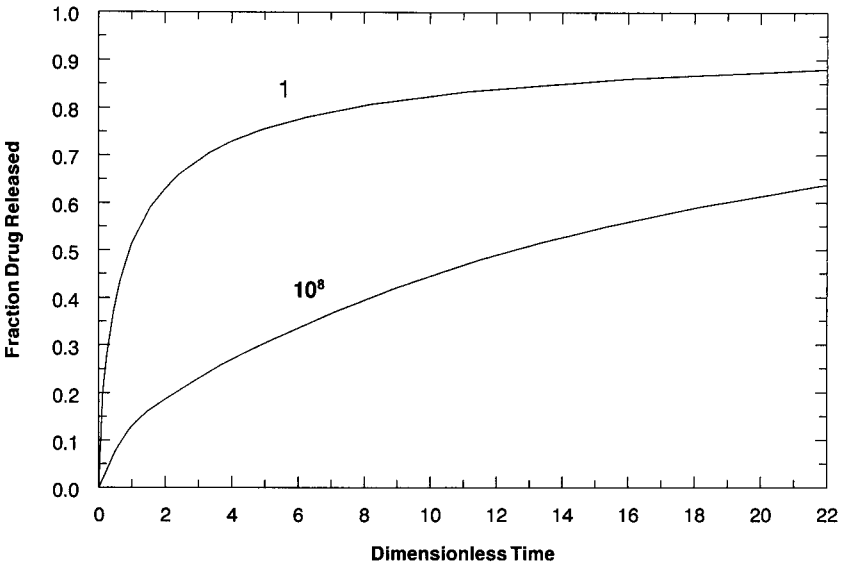

Figure 1 Fractional drug release curves for two values of r, the diffusivity ratio defined by eq. (45).

fraction of polymer dissolved can be determined from eq. (44) by replacing M_1 and M_{10} with M_2 and M_{20}.

RESULTS AND DISCUSSION

As indicated above, the time scales for polymer dissolution and drug release can be made comparable by adjusting the molecular weight of the polymer so that $D_{s1} = D_{s2} = D_s$. In addition, the strength of the concentration dependence for D_{11}/D_s (and thus for D_{22}/D_s) can be adjusted by choice of polymer type. A polymer with a lower fractional hole free volume should lead to stronger concentration dependence. The strength of the concentration dependence can be characterized by the diffusivity ratio r:

$$r = \frac{D_{11}(C_1 = 0)}{D_{11}(C_1 = 1)} = e^k \tag{45}$$

Fractional drug release curves can be constructed by plotting the fraction of drug that has been released [based on eq. (44)] versus the dimensionless time. Fractional drug release curves for $r = 1$ (constant diffusivity) and $r = 10^8$ (strong concentration dependence) are presented in Figure 1. These curves also represent the fraction of polymer that has dissolved. The curves presented here are similar in shape to experimental fractional drug release curves found in the literature, including the following references with pertinent figure numbers given for each reference: ref. 1 (Fig. 1b); ref. 2 (Figs. 7a and 8a); ref. 3 (Fig. 17); and ref. 4 (Fig. 8). The two curves in Figure 1 of our study present a range of shapes which essentially includes the shapes of curves presented in refs. 1–4. Also, Figure 16 of ref. 3 includes a curve of the fractional amount of polymer that has dissolved for the lowest molecular weight polymer used. This curve is similar in shape to the curves of Figure 1 of our study. Furthermore, this experimentally obtained polymer dissolution curve for the lowest molecular weight is quantitatively not much different than the experimental drug release curve also presented in ref. 3. In the theoretical model proposed here, the polymer dissolution and drug release curves are taken to be identical. However, for the higher molecular weights, there are significant differences between the experimental fractional polymer dissolved and fractional drug released curves of ref. 3. It is not clear what causes the significant differences at the higher molecular weights because there are two complicating factors in the experiments of this reference. First, the experimental system contained a large amount of a filler component in addition to the drug, polymer, and solvent. Second, the experimental system was not static because a magnetic stirrer was employed. Consequently, it is possible that these complicating factors contributed to the molecular weight effects observed in the experiments of ref. 3.

A constant drug release rate (zero-order delivery) is of course achieved if the curves of fraction of drug released versus time are linear. Visual examination of the drug release curves in Figure 1 indicates that the curves appear to become more linear as r and k increase (stronger concentration dependence). A constant rate of drug release can be achieved for all time only if the second time derivative of a fractional drug release curve is zero everywhere. This, of course, cannot be achieved for a diffusion-dominated transfer process, but it can be shown theoretically that the second time derivative at a given level of fractional

TABLE I
Dependence of Half-Times on Diffusivity Ratio

Diffusivity ratio, r	Dimensionless half-time
1	0.950
10	1.96
10^6	9.80
10^8	12.5

drug release decreases in magnitude for sufficiently large k as k undergoes a further increase. Consequently, linear behavior can be approached for sufficiently large k, and large k values can be obtained by an appropriate choice of polymer type. Polymers with small fractional hole free volumes should lead to large values of k because there will be large changes in the fractional hole free volume of the entire system when a low hole free-volume polymer is mixed with a high hole free-volume solvent. Note that the only input data needed for the proposed model are the diffusion coefficients D_{11} and D_{22}.

Finally, it is useful to report half-time values for the polymer dissolution or drug release processes because such values provide a measure of the time scales of these processes. The half-time for the dissolution or drug release process can be defined as the dimensionless time when the fraction dissolved or released is equal to one-half. The dependence of the half-time for the present system on diffusivity ratio r is presented in Table I. It is evident that the time scale of the dissolution and release processes is only moderately sensitive to the strength of the concentration dependencies of the mutual diffusion coefficients. The results in Table I were previously presented in Figure 3 of ref. 5, but the ordinate of the graph should have been designated as $(\text{half-time})^{1/2}$, not half-time.

CONCLUSION

The contributions of this paper can be summarized as follows:

1. A new analysis was formulated for the drug release and polymer dissolution processes.
2. It was shown that appropriate choice of polymer molecular weight can be used to achieve comparable time scales for polymer dissolution and drug release.
3. It was shown that a constant drug release rate can be approached by choice of polymer type, namely by using amorphous, uncrosslinked polymers with small fractional hole free volumes.
4. It was shown that calculated theoretical fractional drug release versus time curves are similar in shape to a very representative sample of experimental fractional drug release curves found in the literature.

In the formulation and solution of the transport equations, a thin film geometry was utilized, and it was assumed that there was no external flow in the fluid surrounding the dissolving polymer-drug system. Also, some additional assumptions were introduced in the formulation of the theoretical diffusivity—concentration relationships. All of the above assumptions are not necessary and were introduced simply to facilitate the analysis. Furthermore, the purpose of this article was *not* a direct comparison of theory with experimental data but rather the illustration of a new method of analysis and the utilization of this method to suggest an optimal formulation for the drug-polymer system.

In *in vitro* experiments which are used to mimic *in vivo* conditions, drug dosages are usually cylindrical or spherical in shape; a well-stirred surrounding fluid is utilized, and materials with very specific mutual diffusion coefficient-concentration relationships are utilized. The analysis presented here can easily be extended to cylindrical or spherical geometries and to any concentration dependencies for the mutual diffusion coefficients. Taking into account the effect of an external flow field is more difficult because geometric details of the particular apparatus utilized must be included in the analysis and the resulting flow field is often very complex. Because it is not clear that a well-stirred surrounding fluid actually is an acceptable representation of *in vivo* conditions, it perhaps is better to carry out experiments on a static system (if possible) because such experiments are easier to analyze and will provide maximum polymer dissolution and drug release times for a given polymer-drug-solvent system. Note that because complete mutual diffusion data and all necessary details of the external flow field have not been provided, we do not believe that it is possible to carry out a direct quantitative comparison of our theory with experimental data currently available in the literature.

Finally, for drug release using an amorphous, uncrosslinked polymer, it appears to us that both drug release and polymer dissolution are largely controlled by drug and polymer diffusion. Thus, an analysis such as that presented here is useful in selecting a polymer type and molecular weight to approach a constant drug release rate.

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References

1. Conte, U.; Colombo, P.; Gazzaniga, A.; Sangalli, M. E.; La Manna, A. Biomaterials 1988, 9, 489.

2. Ju, R. T. C.; Nixon, P. R.; Patel, M. V. J Pharm Sci 1995, 84, 1455.
3. Ju, R. T. C.; Nixon, P. R.; Patel, M. V.; Tong, D. M. J Pharm Sci 1995, 84, 1464.
4. Siepmann, J.; Kranz, H.; Bodmeier, R.; Peppas, N. A. Pharm Res 1999, 16, 1748.
5. Vrentas, J. S.; Vrentas, C. M. J Polym Sci, Polym Phys Ed 1998, 36, 2607.
6. Narasimhan, B. Adv Drug Delivery 2001, 48, 195.
7. Vrentas, J. S.; Vrentas, C. M. Macromolecules 1996, 29, 4391.
8. Vrentas, J. S.; Vrentas, C. M. Chem Eng Sci 1998, 53, 629.
9. Vrentas, J. S.; Duda, J. L.; Ling, H.-C. J Polym Sci, Polym Phys Ed 1984, 22, 459.
10. Vrentas, J. S.; Vrentas, C. M. Macromolecules 1994, 27, 4684.
11. Vrentas, J. S.; Vrentas, C. M. Macromolecules 1994, 27, 5570.
12. Vrentas, J. S.; Duda, J. L. J Appl Polym Sci 1976, 20, 1125.
13. Vrentas, J. S.; Vrentas, C. M. J Appl Polym Sci 2003, 89, 1682.