A Simultaneous Transport-Reaction Model for Controlled Drug Delivery from Catalyzed Bioerodible Polymer Matrices

A simultaneous diffusion-reaction model is presented for the analysis of the kinetics of a chemically eroding poly (orthoester) matrix incorporated with a bioactive agent and with a catalyst to promote the erosion. Simulation results are consistent with experimentally observed hollow residuals and provide a basis for analyzing various design options.

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SCOPE

Chemically eroding polymer systems constitute a potentially important class of controlled drug delivery devices since they obviate the need for surgical removal after the delivery is complete. Mathematical modeling of these systems is complex due to the variety of physicochemical processes occurring when the device is exposed to an aqueous environment. In the present study, a transport-reaction model is developed for a poly (orthoester)-based controlled drug delivery system.

Mathematical models that include both transport and chemical kinetics have been extensively applied to the modeling of gas-solid reactions which occur in a variety of chemical process industries. The major applications are found in extractive metallurgy, coal gasification and combustion, and catalyst manufacture. The application of these models to drug delivery systems is relatively new (Korsmeyer and Peppas, 1983; Thombre and Himmelstein, 1983).

Numerical simulations using the model developed here lead to quantitative description of the physical processes and their interactions that govern the kinetics of release of the active agent. Also, the model permits the assessment of the relative contributions of various factors to the overall delivery process. Many of the processes under consideration in this study, in particular the use of diffusion-reaction equation sets to develop mathematical models, are applicable to a wide variety of situations involving solid phase reacting systems.

CONCLUSIONS AND SIGNIFICANCE

In this study a simultaneous transport-reaction model has been proposed which enables an analysis of the proesses leading to the release of a bioactive agent from a poly (orthoester) matrix. The polymer matrix is subjected to catalytically induced chemical erosion by incorporating an acid anhydride in the matrix. This feature leads to a versatile device for the purpose of administering a drug at a controlled rate. Numerical simulations using the proposed model indicate that the performance of the delivery device, judged by the rate of release of the active agent and the extent of hydrolysis of the poly (orthoester), can be controlled by suitable design of the device.

The model shows that changes in the matrix properties with time caused by chemical erosion are the key phenomena responsible for the release kinetics of the active agent. The changes in the matrix properties correspond to the extent of hydrolysis of the polymer. The varying matrix properties are reflected in the varying diffusion coefficients of the species involved in the degradation process as well as that of the active agent. The amount of acid anhydride incorported in the matrix, and to some extent the partition coefficient of water relative to the matrix, are under the control of the device designer. The model indicates that there is a range of values for these parameters that result in an optimum performance of the device. The fact that the release of the active agent proceeds at a constant rate over most of the delivery period enhances the potential of the device for its use as a controlled delivery vehicle.

The model also predicts incomplete erosion leading to the formation of hollow residuals. The formation of these residuals depends on the external mass transfer conditions in the surrounding aqueous medium.

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INTRODUCTION

There is considerable interest in the development of controlled drug delivery devices in which the polymer constituting the matrix is subject to chemical erosion. A number of reviews on controlled drug delivery (Langer, 1980; Nakano, 1979; Wood, 1980) address the delivery from such chemically controlled systems. Several features of chemically erodible devices make them an extremely attractive class of controlled drug delivery devices.

If a drug has a minimum concentration below which the drug is ineffective and a maximum concentration above which the drug may be toxic, it may be desirable that the drug be delivered at a constant rate, independent of the surrounding environment. This "zero-order" release is important since it represents maximum drug delivery at therapeutically effective levels with a minimum amount of drug. Nonerodible, matrix-type devices from which the active agent is released by a diffusion-dissolution mechanism have been analyzed by Higuchi (1963); it is well-established that the rate of release of an active agent from such inert matrices is inversely proportional to the square root of time. In contrast, it is possible to deliver the drug at a relatively constant rate from an erodible matrix having a slab geometry at low drug loadings since the effect of the decreasing concentration gradient may be offset by the decrease in the physical dimensions of the matrix due to the erosion process.

An erodible device that shrinks with time and eventually disappears is particularly suitable in controlled drug delivery because it is not necessary to remove such a device from its site of application in the body once the delivery role is complete. Since the products of degradation are eventually absorbed by the body, the polymer must degrade into toxicologically innocuous products.

A controlled release system which uses poly (orthoester)s as biodegradable matrices has been shown by Heller et al. (1983) to be promising for the controlled release of drugs. These hydrophobic orthoesters are relatively stable under alkaline or neutral conditions but readily hydrolyze in acidic media. Nguyen et al. (1984) investigated the hydrolysis of some poly (orthoester)s in homogeneous solution; their results indicate that the hydrolysis reaction is catalyzed by acid. Shih et al. (1984) reported that the catalytic degradation of poly (orthoester)s can be utilized effectively to control the rate of degradation of the polymer by incorporating an acid-producing species, such a acid anhydride, into the hydrophobic polymer matrix along with the active agent. The catalytic content in the matrix can be controlled, giving the device the potential for releasing the active agent at a constant, controlled rate.

Mathematical formulations for bioerodible systems have not been developed to the same extent as they have for diffusion-controlled nonerodible systems. Hopfenberg (1976) considered situations where surface erosion is the only factor permitting drug release. Characterizing the erosion kinetics by a single empirical rate constant, he showed that the rate of release of the incorported active agent is constant if the surface area of the device remains constant. Lee (1980) analyzed the diffusive release of a drug from an erodible device by formulating two moving boundaries, a moving diffusion front and a moving erosion front. However, he too assumed the erosion to be strictly surface erosion charaterized by a zero-order rate constant. A physically different but mathematically similar situation exists in drug release from swelling controlled systems. Such systems have been analyzed by Korsmeyer and Peppas (1983). The mathematical similarity is due to the fact that both erosion as well as swelling involve changes in the matrix dimensions with time. Also, in both cases, the diffusion of the solvent into the polymer matrix is important and the diffusivities are likely to be concentration-dependent.

The aim of the present study is to develop a mathematical model that simulates the performance of a catalyzed poly(orthoester)-based drug delivery system. The active agent incorporated in the polymer matrix is released by a diffusive mechanism, under the influence of a concentration gradient. However, due to the degradation process occurring concurrently, the matrix phase through which the diffusion takes place changes continuously as a function of the extent of hydrolysis of the poly (orthoester). Therefore, the diffusivity of the active agent within the matrix cannot be considered to be constant. Rather, it is a function of the extent of hydrolysis. The extent of hydrolysis of the poly (orthoester) in turn depends on a number of transport and kinetic parameters such as the partitioning and diffusion of water into the matrix, the concentration of the acid catalyst in the matrix, and the rate of the catalytic degradation of the polymer.

Some experimental data on the rate of release of an active agent from a poly (orthoester) system are available (Shih et al., 1984); however, the present model is envisioned to be of primary utility prior to extensive laboratory experimentation. Various design parameters, such as amount of incorporated anhydride, are under the control of the device designer and can be varied to optimize the performance of the delivery system with respect to achieving a constant rate of release and complete degradation of the matrix by the end of the delivery period. Results from numerical simulations with various parameter values aid this rational design process by providing the sensitivity of the system to various model parameters. Also, it enhances the understanding of the interactions of the physical processes and chemical reactions that occur simultaneously during the delivery period. In the case of certain parameters, such as the diffusivity changes with respect to matrix properties, experimental determination is difficult; in such situations, a mathematical simulation is the only way to estimate them.

DEVELOPMENT OF THE MODEL

A schematic diagram of the poly (orthoester)-based drug delivery system is shown in Figure 1. A slab geometry is considered with the origin, $x = 0$, at the center of a matrix of total thickness $2a$. This choice of coordinates enables the development of the model equations for half of the matrix due to the obvious symmetry about $x = 0$. The matrix consists of polymer which is uniformly mixed with an acid anhydride and a bioactive agent. Exposure of this device to water triggers a series of physical processes and chemical reactions. Water A partitions at the surface of the hydrophobic matrix and then diffuses into the matrix under the influence of the concentration gradient. Reaction R1 is the hydrolysis of the acid anhydride B; it is assumed to be an elementary bimolecular reaction. The corresponding acid produced by this reaction is assumed to be active catalytically itself or to dissociate instantaneously to yield hydrogen ions which are responsible for the catalytic degradation of the polymer. In the first step of the polymer degradation, reaction R2, the catalytic species C (henceforth called the "acidic species" or "active catalyst") reacts reversibly with the active sites of the poly (orthoester) molecule D to form an intermediate species, termed "ester*" D^*. The intermediate species then reacts with water, reaction R3, to regenerate the acidic species and form the final products, an ester and an alcohol.

It is important to note the simplifying assumptions that are made in the above description of the degradation process. The dissociation of the acid corresponding to the anhydride actually depends

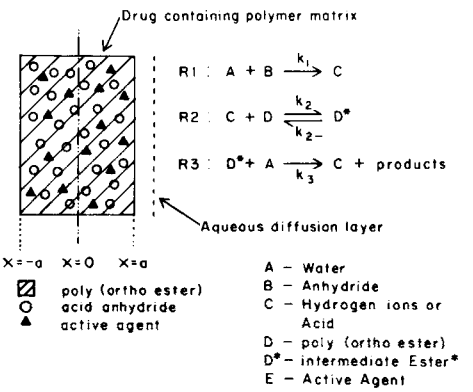

Figure 1. Schematic diagram of the diffusion-reaction model for poly-(orthoester)-based drug delivery system.

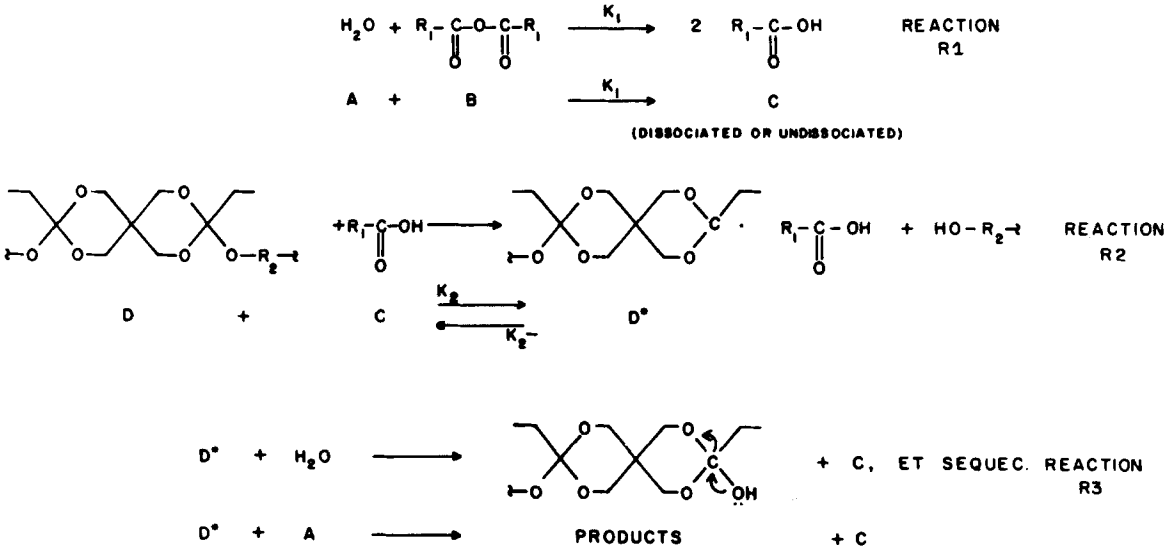

Figure 2. Mechanism of chemical erosion of poly (orthoester)s.

on a dissociation constant which is a function of the particular acid under consideration. Also, there is evidence (Nguyen et al., 1984) of general acid catalysis as well as specific acid catalysis. However, in the present model the catalysis is assumed to be solely due to the acid generated by R1. The acid-catalyzed hydrolysis of orthoesters has been extensively studied (Bunton and DeWolfe, 1965; Cordes and Bull, 1974) and proceeds via a three-stage reaction shown schematically in Figure 2. The first and rate-determining step is the generation of a dialkoxycarbonium ion and an alcohol moiety following the initial cleavage of the ecocyclic alkoxy group. The carbonium ion hydrates readily in the second step to an unstable intermediate, hydrogen ortho ester, which finally breaks down to give an ester and an alcohol as end products. Although the proposed kinetic scheme takes a simplified view of this degradation process, it adequately describes the essential features of poly (orthoester) hydrolysis. Specifically, it accounts for the catalytic activity of the acid because it is regenerated. Also, it is important to note that since water is a reactant in R3, the end products will not form in the absence of water.

The surrounding bulk aqueous medium is assumed to be a perfect sink, and the loss of anhydride and acid due to diffusion away from the matrix is considered. Although the experimental conditions of agitation are such that the external mass transfer resistances are negligible, provision is made to consider them in the model should they prove to be significant in future *in vivo* studies. The diffusion of the polymeric species, D and D^*, is neglected in the present model, which is a reasonable assumption considering their very large molecular weights. The end products of this degradation are not modeled; they are assumed to diffuse away without influencing the kinetics of degradation as well as the kinetics of drug release. Under typical *in vivo* conditions, cellular as well as enzymatic attack could be potentially important factors. Also, plasticization by biological materials is likely to occur. However, in absence of *in vivo* performance data, these effects are not considered in the present model.

As a result of the various chemical reactions occurring within the matrix, the transport properties—the diffusivities of the species—cannot be considered to be constant for the entire duration of release. Experimental data is not available for diffusivities as a function of matrix properties. However, the diffusivities are limited at the lower end by diffusivities through the polymer and at the higher end by the diffusivities in water. Therefore, diffusion coefficients are assumed to increase with the local extent of hydrolysis of the polymer. Fujita (1961) has reported that diffusion coefficients of species in polymers vary in a linear or exponential fashion with the concentration of the diffusing species. In the present model, the diffusivities of all the species under consideration are related to the concentration of the poly (orthoester) in the matrix rather than the diffusing species. The extent of the hydrolysis simulates the disappearance of the polymer; i.e., the conversion is considered to be a marker with respect to the physical integrity of the matrix. Hence, transport properties such as the diffusivities of various components of the system, which are functions of the matrix properties, are assumed to be dependent on the extent of hydrolysis of the poly (orthoester). Since the polymer backbone undergoes continual transformation, the solubility of water may also be dependent on the extent of hydrolysis. However, this is not taken into account in the present model.

It is emphasized that the structural integrity of the matrix and the extent of hydrolysis of the polymer, although related, are two distinct phenomena. Nguyen et al. (1984) show that although the bonds at the polymer chain ends may be slightly more reactive than the intermediate linkages, the overall reaction proceeds to a large extent via random scission. As a consequence of the hydrolysis reaction, there is a molecular weight distribution of the poly (orthoester). It is conceivable that the smaller polymer fragments would be removed from the matrix before all the sites on such fragments are hydrolyzed. Thus, it is possible that the loss of physical integrity occurs before all the sites on such fragments are hydrolyzed. Also, it is recognized that the hydrolysis of the acid anhydride contributes to the change in the permeability of the matrix. However, in view of the fact that the anhydride is less than 5% w/w of the polymer, this contribution is neglected.

The release of the active agent from the matrix is considered to be solely by diffusion, albeit through a medium that is rapidly changing. The loading of the active agent in the matrix is assumed to be low enough so that it does not form a second phase; consequently, there is no need to account for a moving diffusion front within the matrix. As a result of the loss of integrity of the matrix, a leaching mechanism would contribute to the delivery of the active agent. Here the diffusion coefficient of the active agent also approaches the value of its diffusion coefficient in water, simulating the leaching process.

The major assumptions made in the development of the present model are summarized in Table 1. The model equations are obtained by considering unsteady-state mass balances for all species subject to diffusion and reaction:

$$\frac{\partial C_i}{\partial t} = \frac{\partial}{\partial x} D_i \frac{\partial C_i}{\partial x} + r_i; \qquad 0 < t, 0 < x < a \tag{1}$$

where the subscript i denotes the species (A, B, C, D, D^*, E) and r_i represents the rate of generation of the ith species. The rate expression r_i is a sum of elementary first and second order reactions based on the reactions R1, R2, and R3.

The boundary condition $x = 0$ is that of symmetry, or

TABLE 1. ASSUMPTIONS MADE IN PROPOSED MODEL FOR THE POLY-(ORTHO ESTER)-BASED DELIVERY SYSTEM

Hydrodynamics
- Perfect sink
- External mass transfer resistances

Transport
- Fickian diffusion
- Diffusivities depend on the extent of hydrolysis of the poly (orthoester)

Reaction
- Instantaneous and complete ionization of acid if specific acid catalysis
- Catalysis by hydrogen ions or acidic species

Equilibrium
- Partitioning of water into the hydrophobic polymer matrix

$$D_i \frac{\partial C_i}{\partial x}(0,t) = 0; \qquad 0 < t, i = A,B,C,E \tag{2}$$

The condition at the outer edge of the matrix, $x = a$ is represented in terms of the external mass transfer coefficients, k_i,

$$D_i \frac{\partial C_i}{\partial x}(a,t) = k_i(C_{i,\text{bulk}} - C_i(a,t)); \quad 0 < t, i = B,C,E \tag{3}$$

For water, the relation is in terms of the partition coefficient K:

$$C_A(a,t) = KC_A^\circ \tag{4}$$

where C_A° is the concentration of water in the bulk of the aqueous surrounding.

The initial conditions for the above set of equations are given by

$$\begin{aligned} C_i(x,0) &= 0; \qquad 0 < x < a, i = A,C,D^* \\ C_i(x,0) &= C_i^\circ; \quad 0 < x < a, i = B,D,E \end{aligned} \tag{5}$$

where C_i° represents the initial, uniform concentration of the ith species in the matrix. The diffusion coefficients are related to the local extent of hydrolysis of the polymer by the expression

$$D_i = D_i^\circ \exp[\alpha_i(C_D^\circ - C_D)/C_D^\circ]; i = A,B,C,E \tag{6}$$

where α's are constants and D_i°'s are the diffusivities when the polymer is not hydrolyzed.

The model equations, 1–6, are normalized by defining a set of dimensionless quantities, Table 2. The transformed equations are presented in Table 3 with all the required auxiliary conditions.

TABLE 2. DIMENSIONLESS QUANTITIES IN THE PRESENT MODEL

Quantity	Notation	Definition
Concentrations	θ_A	C_A/C_A°
	θ_B	C_B/C_B°
	θ_C	C_C/C_B°
	θ_D	C_D/C_D°
	θ_D^*	C_D^*/C_D°
	θ_E	C_E/C_E°
Distance	ξ	x/a
Time	τ	$D_A^\circ t/a^2$
Thiele Modulus	ϕ_1	$a(k_1C_B^\circ/D_A^\circ)^{1/2}$
	ϕ_2	$a(k_2C_D^\circ/D_A^\circ)^{1/2}$
	ϕ_{2-}	$a(k_{2-}/D_A^\circ)^{1/2}$
	ϕ_3	$a(k_3C_D^\circ/D_A^\circ)^{1/2}$
Biot Numbers for External Mass Transfer	Bi_{mB}	k_Ba/D_B°
	Bi_{mC}	k_Ca/D_C°
	Bi_{mE}	k_Ea/D_E°
Others	α	C_A°/C_B°
	β	C_B°/C_D°
	γ_B	D_B°/D_A°
	γ_C	D_C°/D_A°
	γ_E	D_E°/D_A°

NUMERICAL METHOD

Equations similar to those presented in Table 3 are frequently encountered in the modeling of gas-solid reactions occuring in

TABLE 3. DIMENSIONLESS EQUATIONS OF THE PRESENT MODEL

$$\frac{\partial\theta_A}{\partial\tau} = \exp[\alpha_A(1-\theta_D)]\frac{\partial^2\theta_A}{\partial\xi^2} - \alpha_A\exp[\alpha_A(1-\theta_D)]\frac{\partial\theta_D}{\partial\xi}\frac{\partial\theta_A}{\partial\xi} - \phi_1^2\theta_A\theta_B - \phi_3^2\theta_A\theta_D$$

$$\frac{\partial\theta_B}{\partial\tau} = \xi_B\exp[\alpha_B(1-\theta_D)]\frac{\partial^2\theta_B}{\partial\xi^2} - \alpha_B\gamma_B\exp[\alpha_B(1-\theta_D)]\frac{\partial\theta_D}{\partial\xi}\frac{\partial\theta_B}{\partial\xi} - \alpha\phi_1^2\theta_A\theta_B$$

$$\frac{\partial\theta_C}{\partial\tau} = \gamma_C\exp[\alpha_C(1-\theta_D)]\frac{\partial^2\theta_C}{\partial\xi^2} - \alpha_C\gamma_C\exp[\alpha_C(1-\theta_D)]\frac{\partial\theta_D}{\partial\xi}\frac{\partial\theta_C}{\partial\xi} + \alpha\phi_1^2\theta_A\theta_B$$
$$- \phi_2^2\theta_C\theta_D + (\phi_{2-}^2/\beta)\theta_D^* + \alpha\phi_3^2\theta_A\theta_D^*$$

$$\frac{\partial\theta_D}{\partial\tau} = -\beta\phi_2^2\theta_C\theta_D + \phi_{2-}^2\theta_D^*$$

$$\frac{\partial\theta_D^*}{\partial\tau} = \beta\phi_2^2\theta_C\theta_D - \phi_{2-}^2\theta_D^* - \alpha\beta\phi_3^2\theta_A\theta_D^*$$

$$\frac{\partial\theta_E}{\partial\tau} = \gamma_E\exp[\alpha_E(1-\theta_D)]\frac{\partial^2\theta_E}{\partial\xi^2} - \alpha_E\xi_E\exp[\alpha_E(1-\theta_D)]\frac{\partial\theta_D}{\partial\xi}\frac{\partial\theta_E}{\partial\xi}$$

Initial Conditions

$$\theta_A = 0; \theta_B = 1; \theta_C = 0; \theta_D = 1; \theta_D^* = 0; \theta_E = 1; \tau = 0, 0 < \xi < 1$$

Boundary Conditions

$$\frac{\partial\theta_A}{\partial\xi} = \frac{\partial\theta_B}{\partial\xi} = \frac{\partial\theta_C}{\partial\xi} = \frac{\partial\theta_E}{\partial\xi} = 0; \quad \xi = 0, 0 < \tau$$

$$\theta_A = K; \quad \xi = 1, 0 < \tau$$

$$\frac{\exp[\alpha_B(1-\theta_D)]}{Bi_{mB}}\frac{\partial\theta_B}{\partial\xi} + \theta_B; \quad \xi = 1, 0 < \tau$$

$$\frac{\exp[\alpha_C(1-\theta_D)]}{Bi_{mC}}\frac{\partial\theta_C}{\partial\xi} + \theta_C; \xi = 1, 0 < \tau$$

$$\frac{\exp[\alpha_E(1-\theta_D)]}{Bi_{mE}}\frac{\partial\theta_E}{\partial\xi} + \theta_E; \quad \xi = 1, 0 < \tau$$

various chemical process industries. It has been shown (Bischoff, 1963; King and Jones, 1979) that the pseudosteady-state assumption, which is frequently employed in such cases, leads to significant error if used for liquid-solid diffusion-reaction systems. The model equations are therefore solved simultaneously using an implicit finite-difference approximation technique (Carnahan et al., 1969), without making the pseudosteady-state assumption.

The numerical procedure employed is illustrated for the case of the equation describing the concentration of the acid anhydride as a function of distance and time:

$$\frac{\partial\theta_B}{\partial\tau} = \gamma_B \exp[\alpha_B(1-\theta_D)]\frac{\partial^2\theta_B}{\partial\xi^2} - \alpha_B\gamma_B \exp[\alpha_B(1-\theta_D)]\frac{\partial\theta_D}{\partial\xi}\frac{\partial\theta_B}{\partial\xi} - \alpha\phi_1^2\theta_A\theta_B \quad (7)$$

The various partial derivatives of θ_B are represented by their finite-difference approximations; a forward difference for the derivative with respect to τ, and central differences for the derivatives with respect to ξ. Thus,

$$\frac{\partial\theta_B}{\partial\tau} \simeq \frac{u_{Bi,n+1} - u_{Bi,n}}{\Delta\tau} \quad (8)$$

$$\frac{\partial\theta_B}{\partial\xi} \simeq \frac{u_{Bi+1,n+1} - u_{Bi-1,n+1}}{2\Delta\xi} \quad (9)$$

$$\frac{\partial^2\theta_B}{\partial\xi^2} \simeq \frac{u_{Bi-1,n+1} - 2u_{Bi,n+1} + u_{Bi+1,n+1}}{(\Delta\xi)^2} \quad (10)$$

where $u_{Bi,n}$ denotes the approximation to θ_B at the grid point (i,n).

The coefficients of the three terms on the righthand side of the equality in Eq. 7 are functions of θ_D, its derivative with respect to ξ, and θ_A, respectively. Rather than values at the known time level τ_n, their values at the time level τ_{n+1} are assigned. Since these values are unknown, an iteration parameter (k) is introduced. To start the iteration process, the coefficients are assigned their values at the beginning of the time step, i.e., at τ_n, and all the model equations are solved. This yields the concentrations to be used for the next iteration across the time step. Thus Eq. 7 is represented by

$$\frac{u_{Bi,n+1} - u_{Bi,n}}{\Delta\tau} = \gamma_B \exp[\alpha_B(1-u_{Di,n+1})] \times \left[\frac{u_{Bi-1,n+1} - 2u_{Bi,n+1} + u_{Bi+1,n+1}}{(\Delta\xi)^2} - \alpha_B\gamma_B \exp[\alpha_B(1-u_{Di,n+1})]\left[\frac{u_{Bi+1,n+1} - u_{Bi-1,n+1}}{2\Delta\alpha}\right]\right] - \alpha\phi_1^2 u_{Ai,n+1}u_{Bi,n+1} \quad (11)$$

Equation 11 represents a set of linear equations in the unknowns $u_{Bi,n+1}^{(k+1)}$ for all the space grid points at the time level τ_{n+1}. In addition, there are two equations corresponding to the two associated boundary conditions. Rearranging these equations, it is apparent that the coefficient matrix is a tridiagonal matrix. Similar sets of linear equations are obtained for all other species. These equations are solved for the unknown time level and the iteration process is continued until the concentrations at τ_{n+1} for all species and at all the space grid points converge to within a desired accuracy. This yields the concentrations as a function of distance and time. At any time, the concentration profiles are integrated to obtain the amount of species within the matrix. In dimensionless quantities this corresponds to the fractional amount of species in the matrix as a function of time.

TABLE 4. PARAMETER VALUES FOR FIGURE 3

Parameter	Value
ϕ_1	7.91
ϕ_2	15.7
ϕ_{2-}	0
ϕ_3	157.0
α	1.36
β	0.076
$\alpha_A = \alpha_B = \alpha_C = \alpha_E$	9.21
γ_B	0.43
γ_C	0.97
γ_E	0.19
$Bi_{mB} = Bi_{mC} = Bi_{mE}$	∞

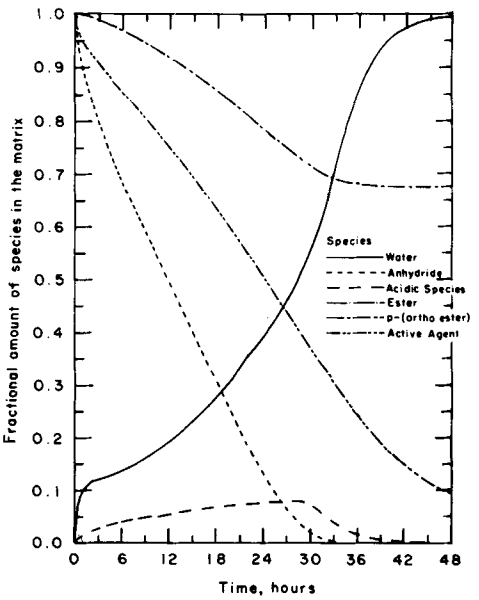

Figure 3. Fractional amount of species in the matrix as a function of time.

RESULTS AND DISCUSSION

In this section, simulation results are presented which demonstrate the effect of the amount of acid anhydride incorporated in the matrix, the water-polymer partition coefficient, and the degree of structural changes in the matrix on the performance of a poly (orthoester) controlled-delivery device. For all simulations, a device of thickness 0.2 cm (a = 0.1 cm) is considered. 2% w/w of the device, which has a total weight of 500 mg, is a marker compound of molecular weight 500 that simulates the action of the bioactive agent. The remainder of the matrix consists of an acid anhydride of molecular weight 98.06, which corresponds to maleic anhydride, and a poly (orthoester). Each monomeric unit of the polymer has a molecular weight of 350 and has two sites where hydrolysis can

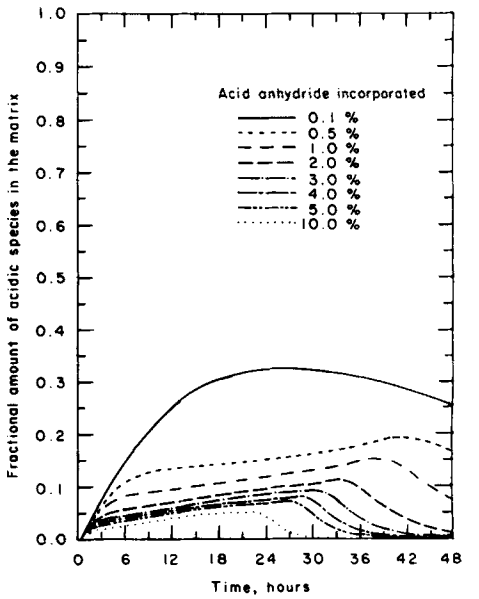

Figure 4. Effect of incorporated acid anhydride on the accumulation of active catalyst in the matrix.

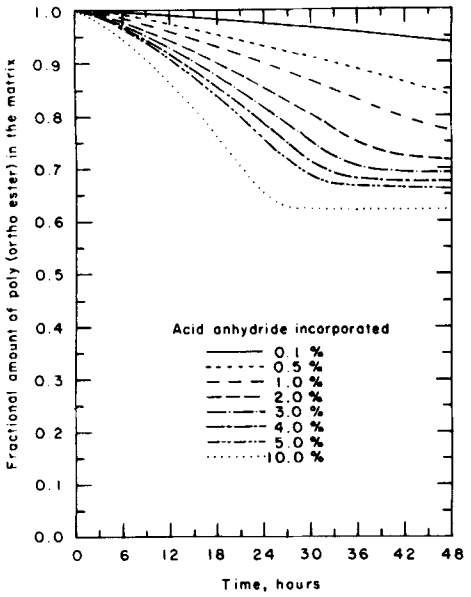

Figure 5. Effect of incorporated acid anhydride on the hydrolysis of poly (orthoester).

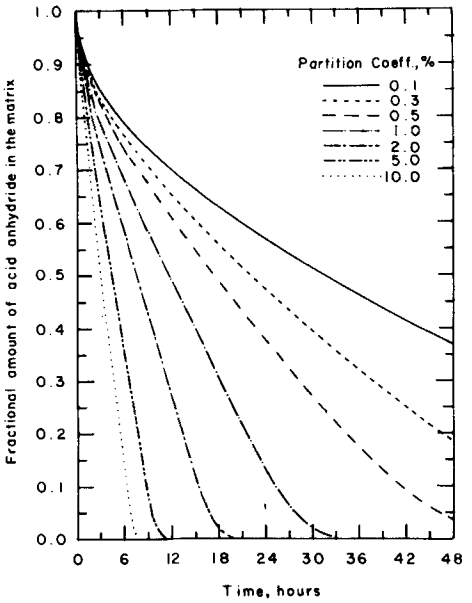

Figure 7. Effect of water-polymer partitioning on the hydrolysis of the acid anhydride.

occur. The density of the device is taken as 1.15 g/cm^3, giving the device a volume of 0.435 cm^3, independent of the amount of incorporated anhydride. The diffusion coefficient of water at zero time is fixed at 3.0×10^{-8} cm^2/s (Nguyen, 1984) and the diffusion coefficients of all other species are computed assuming that the diffusivity is inversely proportional to the square root of the molecular weight. For the purpose of this computation, each hydrogen ion is assumed to be associated with one molecule of water. The reaction rate constants k_1, k_2, and k_3 are assigned to values 0.4, 0.12, (Nguyen et al., 1984) and 12 cm^3/mol/s respectively. The reaction rate constant for the reverse reaction, k_{2-}, is taken to be zero for all the simulations. The values for the density of the matrix, the diffusivity of water, and the dimensions of the device are based on *in vitro* studies on poly (ortho-ester)-based devices (Shih et al., 1984; Nguyen et al., 1984). The values of the reaction rate constants k_1 and k_3 are chosen arbitrarily.

Results for a typical set of parameter values (Table 4) are presented in Figure 3, which shows the fractional amount of each species in the matrix as a function of time. The profiles indicate three regions that can be thought of as three phases in the delivery scheme. The first phase, apparent from the profile for water, is the rapid initial uptake of water by the matrix. The second phase of delivery corresponds to the hydrolysis of the acid anhydride. In this phase there is a buildup of the active catalyst which is responsible for the catalytic hydrolysis of the poly (orthoester). It is in this phase that a major fraction of the active agent is released. The third phase begins when the matrix is rendered free of all the acid anhydride via the diffusion and hydrolysis occurring in the first two phases. In this phase, the generation of new catalyst is stopped and hence its amount in the matrix steadily decreases. Over the entire delivery period, the amount of ester* in the matrix is low, primarily due to its rapid conversion to the products of degradation. It is seen from the result that the amount of active agent in the matrix decreases in an approximately linear fashion, indicating that its rate of release is reasonably constant over most of the delivery period which corresponds to "zero-order" delivery desired in controlled drug delivery applications.

The amount of acid anhydride incorporated in the matrix is expected to have a significant influence on the performance of the poly(orthoester)-based controlled delivery system since it is the acid anhydride that provides the catalyst vital to the degradation process. Simulations are performed with various levels of incorporated acid anhydride ranging form 0.1 to 10%. Figure 4 shows the amount of active catalyst in the matrix for various amounts of in-

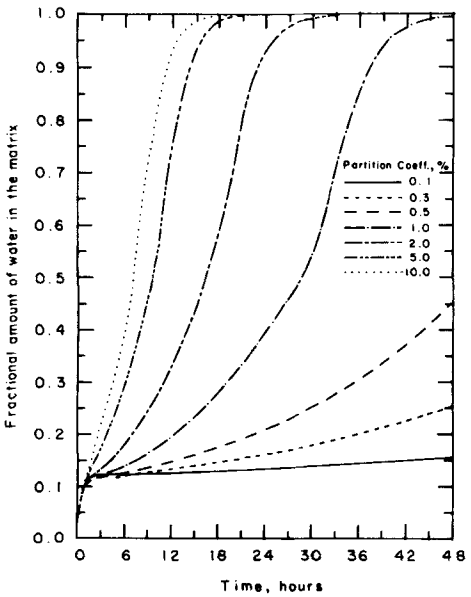

Figure 6. Effect of water-polymer partitioning on the amount of water uptake by the matrix.

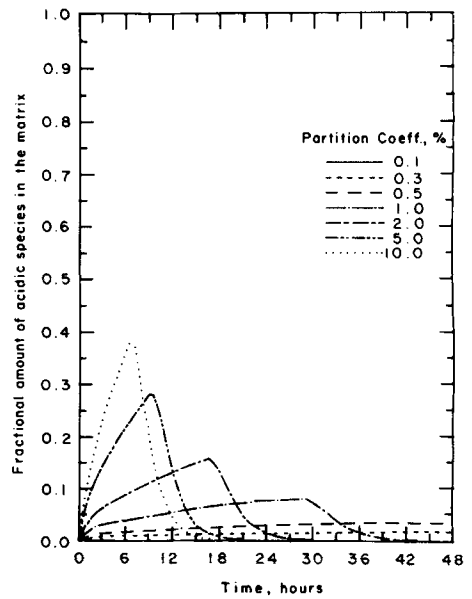

Figure 8. Effect of water-polymer partitioning on the accumulation of active catalyst in the matrix.

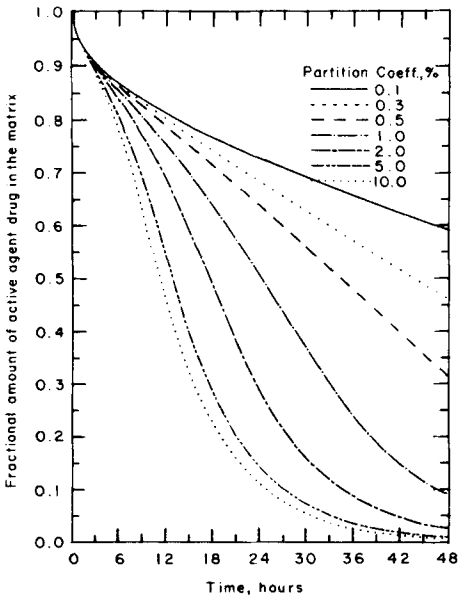

Figure 9. Effect of water-polymer partitioning on the release of the active agent.

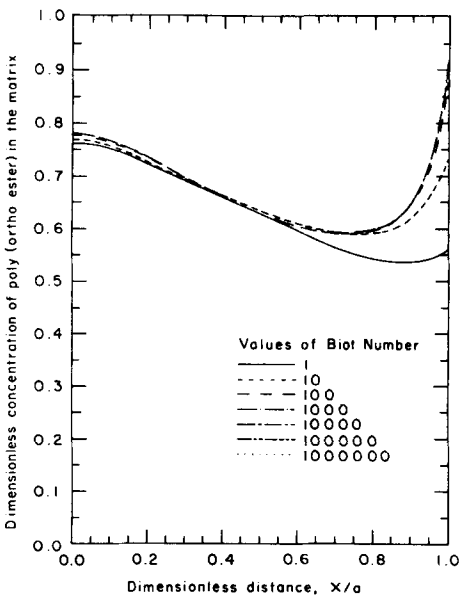

Figure 11. Influence of external mass transfer resistance on the 48-hour concentration profile of poly (orthoester).

corporated anhydride. It is apparent from the profiles that for low amounts of incorporated acid anhydride, the hydrolysis is rapid and there is a significant build-up of the active catalyst within the matrix. However, as seen in Figure 5, the poly (orthoester) hydrolyzes at a significantly lower rate, hindering the erosion of the matrix. Since the erosion rate is low, the diffusivities of species remain low for longer time periods. Thus a low level of anhydride incorporation leads to relatively long delivery periods.

In contrast, if a large amount of acid anhydride is incorporated in the matrix, the matrix properties change rapidly, resulting in enhanced transport of all species, including the catalyst, away from the matrix. This leads to an early initiation of the third phase of the delivery and relatively short delivery periods. It is emphasized that an early loss of the catalyst also slows down any further erosion of the polymer matrix, which may not be always desirable. In fact, a desirable goal may be to make the disappearance of the device coincide with complete delivery of the active agent.

The partition coefficient of water into the matrix can be controlled, although to a lesser extent, by varying the hydrophobicity of the matrix by proper choice of polyol. It is also probable that the partitioning behavior depends on the extent and nature of additives in the polymer matrix. As mentioned earlier, the variation of the partition coefficient with the extent of hydrolysis is not considered in the present model. As shown in Figure 6, the amount of water uptake by the matrix is drastically lowered for low values of the water partition coefficient. Under these circumstances, the hydrolysis of the anhydride is hindered leading to a delay in the initiation of the third phase of delivery. If the device is being designed to deliver in a certain specific period of time, there may be some amount of unhydrolyzed acid anhydride at the end of the delivery period, Figure 7. Figure 8 shows that for high values of the partition coefficient of water, the catalyst has peaks at earlier times, leading to a rapid release of the active agent, as shown in Figure 9. Also, the delivery is not at a constant rate. Thus there is an optimum value for the partition coefficient of water relative to the matrix which yields desirable performance. The partition coefficient of water into the poly (ortho ester) matrix is experimentally found to be 0.3% (Nguyen, 1984) and the simulations were performed in the range from 0.1 to 10%.

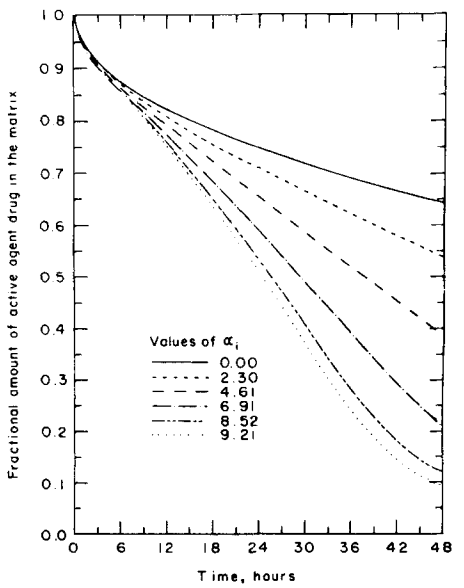

Figure 10. Effect of the degree of structural change on the release of the active agent.

As discussed in an earlier section, it is difficult to determine experimentally the diffusion coefficients of the species as a function of the extent of hydrolysis of the poly (ortho ester). Simulation studies with various values of α_i's (Eq. 6) show that the fractional amount of the active agent in the matrix is very sensitive to the choice of α_i. As seen in Figure 10, significantly higher amounts of the active agent are released for large changes of diffusion coefficients. It is suggested that as more experimental data are made available, the data on the amount released from the system be fitted to determine the most appropriate value of α_i. As discussed earlier, the diffusivities are bounded; the value of 9.21 for α_A increases the diffusivity of water to approximately 3×10^{-6}, or 100-fold when the local extent of hydrolysis of the poly (ortho ester) is 0.5, and the increase is 10,000-fold when the polymer is completely hydrolyzed. Therefore, the values used in the present simulations are realistic. Simulations were also performed using a linear correlation for the diffusivities and the results obtained are qualitatively similar to those presented here.

It is interesting to note that the model predicts that the peak in the catalyst concentration occurs near the outer boundary of the device, and steadily moves towards the center of the device before the ultimate decay when the third phase is reached. This is due to the slow diffusion and relatively fast reaction rates typical of a poly (ortho-ester) system. It is for this reason that more polymer is hydrolyzed near the outer edge of the device than at the center. However, the model predicts no degradation at the outer boundary, $x = a$. This phenomenon occurs, Figure 11, for large values of the Biot number for external mass transfer. This fact is consistent with some experimental studies on the poly (orthoester) system. Figure 12 is a photograph of poly (orthoester) devices taken at the end of

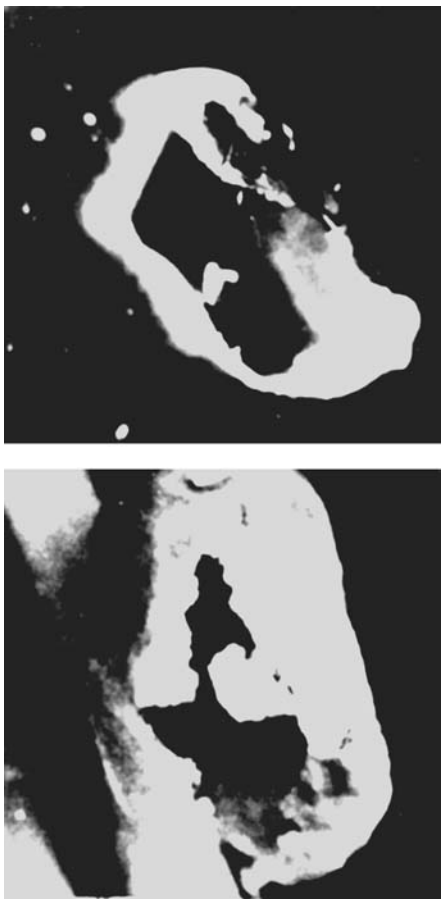

Figure 12. Poly (orthoester) devices at the end of an *in vitro* dissolution experiment.

the delivery of a marker compound in a dissolution experiment conducted *in vitro*. The stirring conditions in the dissolution runs were such that the mass transfer resistances were low. Due to the extremely brittle nature of the residue it is not always possible to extract the residue from the apparatus. The hollow residuals indicate that the interior of the device has been completely eroded, leaving behind the hollow shells seen in the photographs. Analysis of the residuals using FTIR spectroscopy indicates that the residual has the same composition as the initial polymer confirming that the polymer at the outer boundary is not degraded. As seen in Figure 11, for finite values of the external mass transfer resistances some hydrolysis is predicted at $x = a$. However, the maximum conversion of the polymer occurs within and not at the boundary of the matrix, predicting, qualitatively, the possible formation of hollow residuals.

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NOTATION

a	= half thickness of the device
Bi_m	= Biot number for external mass transfer
C	= concentration
C°	= concentration at time zero
D	= diffusion coefficient
D°	= diffusion coefficient at time zero
k_1,k_2,k_{2-},k_3	= reaction rate constants
k_B,k_C,k_E	= external mass transfer coefficients
K	= partition coefficient of water
t	= time elapsed
x	= distance from center of device
X	= extent of hydrolysis of polymer

Greek Letters

α	= C_A°/C_B°
$\alpha_A,\alpha_B,\alpha_C,\alpha_E$	= coefficients in Eq. 6
β	= C_B°/C_D°
γ	= ratios of diffusivities, Table 3
θ	= dimensionless concentrations, Table 3
ϕ	= Thiele-type moduli, Table 3
τ	= dimensionless time
ξ	= dimensionless distance

Subscripts

A	= water
B	= acid anhydride
C	= catalytic species
D	= poly (orthoester)
D^*	= unstable intermediate
E	= active agent

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