Crystal dissolution-controlled release systems: I. Physical characteristics and modeling analysis

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Abstract

A novel class of phase-erosion, controlled release devices based on semicrystalline polymers was developed. For preparation of these systems, a drug was dissolved in a dilute polymer solution, the system was cast or molded and exposed to an annealing procedure leading to significant crystallization of the polymer carrier. Drug release from such systems is controlled by the rate of crystal dissolution in water or biological fluids. The degree of crystallinity of the polymer carrier can be varied by heat treatment and is the controlling factor of the drug release rate from such systems. A molecular interpretation of the overall release process is presented. A mathematical model is proposed to predict drug release rates from semicrystalline polymer systems, while taking into account the dissolution of the crystals when brought into contact with water.

Keywords: Controlled drug delivery; Swelling controlled release systems; Hydrogels; Crystallinity; Dissolution

1. Introduction

Controlled release of drugs, proteins or peptides reduces the amount of bioactive agent required for treatment by maintaining its concentrations in the body within therapeutic limits for longer periods of time [1,2]. In many cases, a constant drug release rate, or zero-order delivery is desired. This requires that the water transport and subsequent drug release be non-Fickian or anomalous in nature.

In his classic paper, Lee [3] has described how state-erosion or phase-erosion polymeric systems can be used to obtain non-Fickian release of drugs. Controlled release systems based on the principles of state or phase erosion rely on the thermodynamic state or phase changes occurring in the systems during water transport. A state erosion system typically involves a glassy polymer loaded with drug which is brought into contact with water [4–6]. The polymer swells and gradually transforms from a glassy to a rubbery state during the drug release. This swelling process, which occurs during the transition from glassy to a rubbery state, and more specifically the velocity of the moving front, controls the rate of drug release from such systems. Phase erosion systems [7] operate on a similar principle, the only difference being that they rely on phase...
rather than state changes. The most commonly known phase erosion systems, expertly modeled by Lee [3] are biodegradable and bioerodible systems.

A new class of phase erosion systems which have not been described until now are the crystal dissolution-controlled release systems, introduced here. In these systems, the release rate is controlled by the transformation of the crystalline phase to an amorphous phase.

The reasons for this unusual erosion behavior can be found in an analysis of solute diffusion in crystalline and non-crystalline polymers. The drug diffusion coefficient through the crystalline portion of the polymer is extremely low [8]. On the other side, diffusion through the amorphous portion of the polymer is substantial and can be described by classical free volume-based theory [9]. The overall diffusion process through semicrystalline polymers has been analyzed by various models of additive behavior, including the one by Harland and Peppas [8]. In this model, the crystalline regions are impermeable structures which are not affected by the presence of the solvent. In general, polymer crystals are relatively resistant to "melting out" in the presence of a thermodynamically compatible solvent, but may start dissolving by a molecular process consisting of crystal unfolding and disentanglement [10] as shown in Fig. 1. Transition from the crystalline to the amorphous phase is accompanied by a distinct moving front which controls the overall process.

Parameters controlling the phase transformation and thus the subsequent drug release are the polymer degree of crystallinity, crystal size distribution, molecular weight distribution of the polymer, degree of branching and the polymer-water interaction parameter. In this work we analyze the behavior of crystal dissolution controlled systems by appropriate molecular and mathematical models. A typical method of preparation and application in the biomedical field is described elsewhere [11]. The mathematical model takes into account the changes in the crystalline phase in the presence of water and its influence on the drug release rate. In general, samples with higher initial degrees of crystallinity exhibit a decreased rate of crystal dissolution resulting in slow drug diffusion.

2. Theory

In our previous work [10], we investigated and analyzed in some detail the mechanism of dissolution of semicrystalline polymers. We showed that in the presence of a thermodynamically compatible solvent, the crystals in the polymer unfold layer by layer and join the amorphous region around them. This is followed by chain disentanglement in the amorphous region, which leads to polymer dissolution shown in Fig. 1. In this work, the semicrystalline polymers are loaded with a drug and the release from this system is studied.

Drug release from drug-loaded, semicrystalline

![Fig. 1. Schematic representation of crystal unfolding and subsequent disentanglement in the presence of a solvent.](image-url)
polymeric devices exhibiting crystal dissolution-controlled behavior can be described by a simple mathematical model. The controlled release device is modeled in the form of a thin slab of thickness $2L_0$. The device swells initially as it absorbs water, and, depending on whether or not the polymer carrier is crosslinked, the thickness of the slab starts decreasing once the polymer starts dissolving as indicated in Figs. 2 and 3.

In our analysis, the amorphous portion of the polymer is in the rubbery state. Thus, the glassy/rubbery transition kinetics is assumed to be very fast.
in comparison with the dissolution kinetics, and transport is assumed to be one-dimensional. The water penetrates the slab, causing crystal dissolution, thereby increasing the amorphous portion of the polymer.

We denote by \( v_1, v_{2a}, v_{2c}, \) and \( v_d \) the volume fractions of water, the crystalline polymer portion, the amorphous polymer portion, and the drug, respectively. We assume volume changes upon mixing to be negligible, so that the sum of all these volume fractions is always equal to unity. Fig. 4 gives a simple representation of the typical phase equilibrium behavior of crystal dissolution-controlled systems. Typically, the crystalline portion (C) decreases from an initial value \( v_{2c} \) to a final value of zero at a characteristic time \( t_c \). The amorphous volume fraction \( v_{2a} \) increases and remains high due to crystal dissolution. The volume fraction of drug, \( v_d \), decreases as the drug (D) is released.

For crystal dissolution, a first order dependence on the concentration of the solvent may be assumed. Therefore, the expression for change in volume fraction of the crystalline portion of the polymer as a function of time can be written as

\[
\frac{\partial v_{2c}}{\partial t} = -k_1 v_1 H(v_{2c})
\]  

(1)

The negative sign is because the volume fraction of the polymer crystals decreases with time. The Heavyside function, \( H(v_{2c}) \) prevents the polymer crystal volume fraction from becoming negative as the crystal dissolution occurs for an extended period.

The term \( k_1 \) is the rate of unfolding of the crystals. Values of \( k_1 \) can be calculated for any polymer from knowledge of the degree of crystallinity of the polymer, average size of crystals, polymer molecular weight and polymer solvent interaction parameter as we have indicated before [12].

The expression for the rate of change of the amorphous portion has a classical diffusion term, characterized by a water diffusion coefficient, \( D_1 \), and an additional source term which accounts for the transformation of the crystalline phase to the amorphous phase during the unfolding process.

\[
\frac{\partial v_{2a}}{\partial t} = \frac{\partial}{\partial x}(D_1 \frac{\partial v_{2a}}{\partial x}) + k_1 v_1 H(v_{2c})
\]

(2)

In our work, the water diffusion coefficient was assumed to be dependent on the water volume fraction according to a Fujita equation [13] with a constant \( a_D \) which can be determined theoretically or calculated experimentally from spin echo NMR studies [14].

\[
D_1 = D_0 \exp(a_D v_1)
\]

(3)

The rate of change of the drug volume fraction is associated with the drug diffusion through the polymer system and is given by

\[
\frac{\partial v_d}{\partial t} = \frac{\partial}{\partial x}(D_d \frac{\partial v_d}{\partial x})
\]

(4)

The diffusion coefficient of the drug through the semicrystalline polymer, \( D_d \), depends not only on the volume fraction of the crystals [8] but also on the polymer tortuosity, \( \tau \).

\[
D_d = D_0 \left(1 - \frac{v_{2c}}{\tau}\right)
\]

(5)

Here \( D_0 \) represents the drug diffusion coefficient of the drug through the purely amorphous polymer. It has been shown by Harland and Peppas [8] that the value of \( \tau \) is equal to 3.0 for diffusion of small molecules through semicrystalline polymers, unless the volume fraction of the crystals is very low. In our studies, we have assumed, \( \tau = 1.0 \) when \( v_{2c} \leq 0.05 \), and \( \tau = 3.0 \) when \( v_{2c} > 0.05 \).

During the dissolution process, as the boundary moves the rate of change of the half thickness of the slab, \( L_{0c} \), with time is given by
When the polymer starts dissolving, the movement of the boundary inwards cannot be at a rate that is greater than the rate of unfolding of the chains of the crystal. Therefore, if there are crystals present at the boundary, the boundary does not move inward until all of the crystals have unfolded. This is mathematically represented by a Dirac delta function, \( \delta(v_{sc}) \), at the boundary which exists only when \( v_{sc} = 0 \). Here, \( k_2 \) is the disentanglement rate of the polymer which can be predicted using reptation theory as discussed by Narasimhan and Peppas [15].

The initial and boundary conditions for the above system of equations are as follows. Initially, the degree of crystallinity of the polymer is \( X \), the drug loading is \( W \), and there is no solvent present in the system. Therefore,

\[
\begin{align*}
t &= 0, \quad -L_0 \leq x \leq L_0 \quad v_{sc} = X \quad (7a) \\
v_{d} &= W \quad (7b) \\
v_{sc} &= 1 - X - W \quad (7c)
\end{align*}
\]

A symmetry condition is written at the center of the slab, represented as

\[
\begin{align*}
t &> 0, \quad x = 0, \quad \frac{\partial v_{sc}}{\partial x} = 0 \quad (8a) \\
\frac{\partial v_{d}}{\partial x} &= 0 \quad (8b)
\end{align*}
\]

At the polymer/solvent interface, a pseudo-equilibrium assumption is invoked, equating the solvent chemical potential on either side of the boundary. This concentration can be estimated by using thermodynamics of swollen networks [16].

\[
x = \pm L(t), \quad t > 0, \quad \frac{v_{sc}}{1 - v_{sc}} < 1 \quad (9)
\]

\[
x = \pm L(t), \quad t > 0, \quad v_{d} = v_{ds} \quad (10)
\]

where \( v_{ds} \) is a constant.

This completes the formulation of the moving boundary problem. The moving boundary problem was converted to a fixed boundary problem by using a Landau transform [17]. A normalized position, \( \xi \), was defined by

\[
\xi = x/L(t) \quad (11)
\]

The transformed differential equations were solved with finite difference approximations using the Thomas algorithm [18].

3. Results and discussion

Polymers used for these systems include poly-(ethylene oxide) and other hydrophilic materials. Simulations were performed to study the effect of the polymer degree of crystallinity and the crystal size on the release rate. Metronidazole release from dissolving semicrystalline poly(vinyl alcohol) (PVA) in water was used as a model system. Typical values of the various parameters used in the simulations are presented in Table 1. Typically our analysis was done with polymer degrees of crystallinity varying from 30 to 50%. As indicated by Peppas and Merrill [19], these are typical attainable degrees of crystallinity for PVA. The unfolding rate, \( k_1 \), was obtained by taking into account the free energy changes during crystal unfolding [12]. The values of \( D_0 \) and \( a_D \) were obtained from the Fujita analysis [13]. The values of disentanglement rates were obtained by using molecular arguments [15]. Drug diffusion coefficients were predicted using an analysis proposed by Lustig and Peppas [20]. For the initial solute loading, we used relatively low values of 2–4%, which would be appropriate for model peptide release systems.

Fig. 5 shows the amount of metronidazole released as a function of time from a PVA sample

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial degree of crystallinity, ( X )</td>
<td>0.3–0.6</td>
</tr>
<tr>
<td>Unfolding rate, ( k_1 )</td>
<td>( 10^{-5} ) x(^{-1})</td>
</tr>
<tr>
<td>( D_0 )</td>
<td>( 10^{-3} ) cm(^2) s(^{-1})</td>
</tr>
<tr>
<td>( a_D )</td>
<td>( ? )</td>
</tr>
<tr>
<td>Disentanglement rate, ( k_2 )</td>
<td>( 10^{-6} ) cm(^2) s(^{-1})</td>
</tr>
<tr>
<td>Drug diffusion coefficient, ( D_{ij} )</td>
<td>( 10^{-6} ) cm(^2) s(^{-1})</td>
</tr>
<tr>
<td>Initial drug loading</td>
<td>0.02–0.04</td>
</tr>
</tbody>
</table>
with $X=0.4$. It can be seen that 80% of the drug was released in 1 h. The corresponding profiles for the crystals and the drug as a function of normalized position are shown in Fig. 6 and Fig. 7, respectively. As expected, the polymer crystals and drug volume fractions are minimum near the polymer/water interface and increase as we move towards the center of the slab, which is farthest from the water. We also notice that in 1 h, the polymer crystal volume fraction has dropped from an initial value of 0.4 to about 0.28. We observe from Fig. 7 that in 1 h, the drug volume fraction has dropped to about $1.5 \times 10^{-4}$ from an initial value of 0.02.

The effect of the polymer degree of crystallinity on the release process is seen by comparing Fig. 5 with Fig. 8 and Fig. 9 respectively. In Fig. 8, the initial degree of crystallinity of the PVA sample was 0.6 whereas that in Fig. 9 was 0.3. It is seen that the amount of drug released increases with decreasing degree of crystallinity. This is to be expected as the
crystals act as barriers to drug diffusion and hence slow down the release process. In the sample with initial degree of crystallinity of 0.3, almost all the drug has been released in 1 h, while only about 25% of the drug has been released from the sample with $X = 0.6$.

Another interesting feature observed in the prediction of Fig. 8, i.e. the release kinetics of the PVA with initial degree of crystallinity of 0.6, is that a plateau occurs when the fraction of drug released reaches about 25%. This is attributed to the fact that the polymer is highly crystalline, as a result of which diffusion of most of the drug is hindered, leading to partial release of the drug before the plateau is reached.

The effect of the average polymer crystal size on the release was also studied. Fig. 10 shows the drug released as a function of time for a PVA sample with $X = 0.4$, and an unfolding rate that is 10 times the value that was used for the simulation of Fig. 5. It is observed that as the unfolding rate increases, a greater amount of the drug is released. This can be attributed to faster dissolution of the smaller crystals, which have lower unfolding rates, leading to faster drug release. As observed earlier [10], higher annealing temperatures and times lead to higher average crystal sizes, and hence slower drug release.

It can be observed from Fig. 5, Fig. 8 and Fig. 9 that the mechanism of drug release is predominantly non-Fickian. This is to be expected as the Fickian equation for solute transport has been modified by using concentration-dependent diffusion coefficients in our model.

### 4. Conclusions

In this work, we have introduced a new class of phase erosion systems, termed crystal dissolution-controlled systems, for drug delivery. The drug release rates from these systems is controlled by the rate of dissolution of the polymer crystals, which in turn can be controlled by a simple annealing process. The dissolution of the crystals causes an increase in the amorphous portion of the polymer, and as the crystals dissolve, the area available for drug diffusion constantly changes, leading to non-Fickian release of drugs.

A mathematical model was proposed to predict drug release rates from crystal dissolution-controlled systems. This was done by writing expressions for change of crystalline, amorphous and drug volume fractions as a function of time. The equations were solved numerically to obtain the fraction of drug released as a function of time as well as crystal and drug profiles within the polymer. Higher values of initial degrees of crystallinity, or larger crystal sizes were found to lead to slower drug release rates. The release was found to be non-Fickian.
Acknowledgments

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References