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Analyzing Drug Release Kinetics from Water-Soluble Polymers

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Analyzing Drug Release Kinetics from Water-Soluble Polymers

Abstract

The ability to develop predictive mathematical models of therapeutic release from pharmaceutical formulations has enormous potential to enhance our understanding of such systems and improve the controlled release of the payload. The current work describes the development and testing of a one-dimensional model of drug transport from amorphous, swelling/dissolving polymers. Model parameters such as the diffusivities of water and drug, the initial loading of the drug, the polymer dissolution rate, drug-polymer interactions, and the tablet thickness were varied, demonstrating the ability to tune the release to be controlled by either drug diffusion or polymer chain disentanglement. In addition, predictions of the concentration profiles of water and drug within the gel layer, the locations of the erosion and swelling boundaries, and gel layer thickness were obtained for diffusion- and disentanglement-controlled release. To highlight the generalizability of this model, multiple parameters were varied, and it was shown that increasing the diffusivities of water and drug and the initial drug loading and decreasing the polymer dissolution rate sufficiently resulted in diffusion-controlled release. The model was fit to experimental data for a model tablet system comprising of sodium diclofenac entrapped in a poly(vinyl pyrrolidone) matrix and yielded physically meaningful values of the model parameters. The work presented here demonstrates the predictive power of the model for rapid and rational design of future pharmaceutical formulations for controlled drug delivery.

Keywords

Polymer dissolution, mathematical modeling, controlled drug delivery, pharmaceutical formulation

Disciplines

Biochemical and Biomolecular Engineering | Biomedical Engineering and Bioengineering | Medicinal Chemistry and Pharmaceutics

Comments

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3 release to be controlled by either drug diffusion or polymer chain disentanglement. In
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7 addition, predictions of the concentration profiles of water and drug within the gel layer,
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10 the locations of the erosion and swelling boundaries, and gel layer thickness were
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25 was fit to experimental data for a model tablet system comprising of sodium diclofenac
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28 entrapped in a poly(vinyl pyrrolidone) matrix and yielded physically meaningful values of
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31 the model parameters. The work presented here demonstrates the predictive power of
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34 the model for rapid and rational design of future pharmaceutical formulations for
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37 controlled drug delivery.
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Introduction

The ability to develop predictive mathematical models to enhance our understanding of small molecule therapeutic release mechanisms from polymeric tablets and matrices is of paramount importance. Accurate and quantitative predictions of the characteristics of small molecule payloads released from polymer matrices will allow for rational *a priori* design of pharmaceutical drug-based formulations, resulting in both time and cost savings as well as the ability to tailor release kinetics based on desirable pharmacokinetic profiles. The sustained release of drugs from polymer-based tablets is a complex function of many parameters, including polymer concentration, drug loading, drug-polymer interactions, tablet dimensions, and dissolution media¹. Over the past fifty years, there have been significant strides in our ability to understand drug release mechanisms of various polymer-based delivery systems, allowing for mathematical models and better design principles²⁻¹⁸. A predictive model that considers this enhanced understanding of physical phenomena during polymer dissolution and that accounts for all of the above parameters would not only better our understanding of the fundamental phenomena that govern drug release, but more importantly, provide a generalizable design tool that can be valuable to the pharmaceutical industry.

There are many well-studied mechanisms of drug release from polymeric matrices^{5,19,20}, including: 1) Fickian diffusion from a porous polymer matrix; 2) diffusion following swelling

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3 of the polymer matrix; 3) release following swelling and subsequent dissolution of the
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7 polymer (either amorphous or semi-crystalline); and 4) erosion/degradation of the
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10 polymer matrix. The first two cases generally consider polymer matrices that are not
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14 soluble in a solvent, and therefore release of drug from the polymer matrix relies on a
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17 concentration gradient-driven Fickian diffusion of the drug through the matrix. Often times,
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21 however, the polymer matrix may be soluble in media, and there is now an increased
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24 understanding of all the phenomena that occur during polymer dissolution, based on both
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28 experimental advances as well as mathematical models^{1,10,15,16,20-26}. Models that account
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31 for the swelling and subsequent dissolution of the polymer matrix are of particular interest
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35 because the interplay between the diffusive flux of drug and polymer dissolution rate can
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38 allow for tighter control over the release profile of drugs.
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42 This enhanced understanding of polymer dissolution has led to the design of models of drug
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44 release, which attempt to capture observable phenomena^{5,7-9,17,18,20,23,24,27,28}, or more recently,
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46 statistical techniques, which attempt to develop quantitative structure-property relationships based
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48 upon experimental data²⁹. Various models have been developed that take into account
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50 experimental conditions such as pH and ionic strength³⁰, non-uniform drug distribution³¹, free
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52 volume³², and geometric effects³³. Narasimhan and Peppas⁷ developed one of the first one-
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3 dimensional models of drug release accounting for molecular level disentanglement mechanisms,
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5 based upon reptation theory. This model provided a quasi-steady state solution that could
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9 account for both diffusion- and disentanglement-controlled release and was validated with
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11
12 experimental data⁷. A focus of the current work is to extend the work of Narasimhan and
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15 Peppas by considering non-pseudo steady state solutions of drug release from
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18 swelling/dissolving amorphous polymers and validate the model predictions with
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21 experiments. The current model demonstrates the ability to accurately capture both
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24 diffusion- and disentanglement-controlled drug release, with control over parameters
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27 such as drug and water diffusivities, initial loading of drug, polymer dissolution rate, and
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30 equilibrium concentrations, therefore making it a valuable tool that can be employed for
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33 *a priori* design of pharmaceutical formulations.
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46 **Methods and Materials**

47 48 49 *Materials*

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4 Materials used for tablet fabrication and drug release experiments included sodium
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7 diclofenac, poly(vinyl pyrrolidone) (PVP; MW 40,000 Da and 360,000 Da) and cellulose
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10 acetate propionate, all of which were purchased from Sigma Aldrich (St. Louis, MO).
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14 *Tablet Preparation*

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19 A solid mixture of either 25% or 50% (w/w) sodium diclofenac in PVP (MW 40,000 Da or
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22 360,000 Da, depending on the system) was dissolved in isopropyl alcohol at a total solids
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26 concentration of 1 mg/mL. The solution was stirred until complete dissolution of the solids
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28
29 and the solution was dried in a vacuum oven. The dried product was then placed into a
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33 14 mm x 1 mm aluminum mold and pressed to approximately 258 psi on a Carver press
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35
36 (Model 4120, Wabash, IN). The tablets were coated on three sides with 15% (w/v)
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40 cellulose acetate propionate in acetone, which creates an impermeable barrier for water
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43 and reduces the dissolution of the tablet to one face of the tablet, leading to one-
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47 dimensional transport.
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51 *Polymer Dissolution and Drug Release*

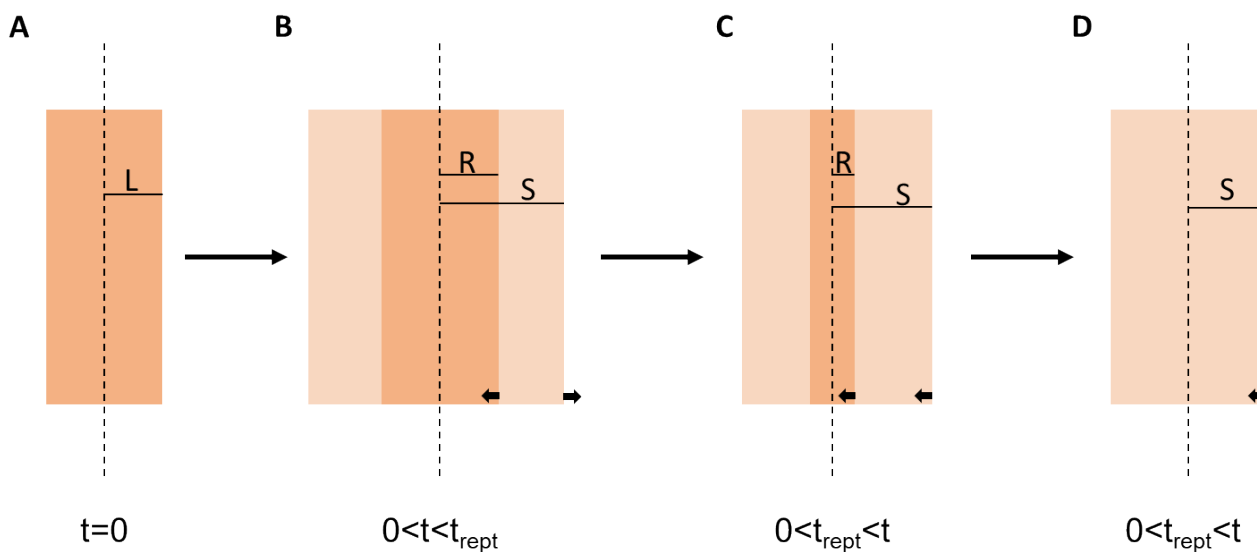
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4 Tablet dissolution experiments were conducted in a 1-L USP dissolution apparatus
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7 (Hanson Research, Chatsworth, CA) at 37 °C in ultrapure water (Milli-Q Advantage A10,
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10 resistivity 18.2 MΩ, TOC ≤ 5 ppb), with a 25 RPM stir rate. Aliquots were collected at 1,
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14 10, 20, 30, 40, 50, 60, 70, 90, 120, 150, and 180 minutes and the released sodium
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17 diclofenac concentration was measured at 275 nm with a UV spectrophotometer
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21 (SpectraMax M3, Molecular Devices, San Jose, CA). The background optical density
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24 (OD) of nanopure water was subtracted from each sample's OD measurement and the
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28 mass fraction of sodium diclofenac released was calculated as the OD at that specific
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31 time point divided by the OD of a sample following complete dissolution of the tablet. The
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35 experiments were performed in duplicate, with three tablets per formulation.
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43 **Model Description**

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47 The one-dimensional model of a drug-containing swelling/dissolving polymer tablet
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51 considers an amorphous polymer matrix in its glassy state prior to contact with solvent,
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55 with the drug uniformly distributed through the matrix (Figure 1A). Following initial contact
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4 with solvent, the portion of the polymer matrix that the solvent has penetrated into begins
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7 to relax and swell; this region is considered rubbery and is referred to as the gel layer of
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10 the polymer (Figure 1B). Solvent then continues to penetrate deeper into the glassy
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13 portion of the polymer matrix (as represented by the region between $x = 0$ and $x = R$)
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16 while the gel layer (as represented by the region between $x = R$ and $x = S$) continues to
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19 grow and expand outward, with the drug able to diffuse out of the swollen portion of the
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22 polymer and into the solvent. During this process, as the solvent continues to diffuse into
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25 the polymer, the polymer chains start disentangling. According to reptation theory³⁴, at
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28 the swollen front, when the mobility of the polymer chains increases, the chains will
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30
31 the swollen front, when the mobility of the polymer chains increases, the chains will
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33
34 disentangle by reptation and become free of the matrix after a characteristic time referred
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36
37 to as the reptation time (t_{rept}) and dissolve away from the bulk of the matrix and into the
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40 solvent. Once the polymer in the rubbery region begins to dissolve in the solvent, the
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43 swelling front ($x = S$) begins to move inward. In the case of steady state dissolution, the
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45
46 gel layer thickness ($S - R$) will remain constant over this period until the glassy front ($x = R$
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49) reaches the center of the tablet ($x = 0$). Once the solvent reaches the center of the tablet,
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52 the entire polymer matrix is rubbery and release of the drug from the tablet will be driven
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3 by a combination of diffusion out of the polymer matrix and release following dissolution
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7 of the polymer matrix.
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32 **Figure 1.** Schematic representation of the swelling/dissolving polymer model. L is the
33 thickness of the film/tablet. R is the thickness of the glassy front. S is the thickness of the
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35 swelling front.
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47 There are two controlling mechanisms of drug release from swelling/dissolving polymer
48 systems, namely drug diffusion- and polymer chain disentanglement-controlled
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51 release^{1,4,5,7}. In the first case, diffusion-controlled release occurs when the diffusive flux
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3 of drug is sufficiently high such that the release rate of drug is dominated by the diffusion
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6 of the drug out of the polymer matrix. This can occur through having higher diffusivities of
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9 drug (i.e., small molecule) and water or through increased loading of drug. In such
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12 systems, the Deborah number (De)³⁵ can be used to describe the characteristics of
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15 solvent penetration into the polymer matrix, and thus the release of drugs from diffusion-
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18 controlled systems. The De number is the ratio of chain relaxation time to solvent diffusion
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21 time into the polymer matrix; values of $De \ll 1$ or $De \gg 1$ result in classical Fickian-like
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24 diffusion while values of $De \approx 1$ results in non-Fickian, anomalous diffusion. In the second
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27 case, disentanglement-controlled release occurs when either the polymer dissolution rate
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30 is sufficiently high, or the diffusivities of water and drug are low enough, such that the rate
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33 of polymer dissolution at the swelling front dictates the rate of release of drug from the
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36 polymer matrix. This could be the case for highly soluble polymers, polymers of low
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39 molecular weight, or larger payloads such as proteins, but can also occur when the initial
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42 loading of the payload is low such that the flux through the gel layer is less than that of
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45 the polymer dissolution rate. The current work describes the development and testing of
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3 this one-dimensional model of drug transport from amorphous, glassy dissolving
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7 polymers using this phenomenological description.
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11 In previous work, Narasimhan and Peppas⁷ developed a pseudo steady state solution to
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13 the model equations, where the transport of water and drug through the gel layer was
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15 assumed to be at steady state throughout the entire release time period, resulting in linear
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17 concentration profiles through the gel layer as well as a linear increase in the gel layer
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19 thickness over time (in the case of disentanglement-controlled release). The current
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21 model does not make such assumptions, and hence the concentration profiles and gel
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23 layer thickness can exhibit non-linear profiles as a function of time.
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36 This model considers three components, i.e., water (component 1), polymer (component
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38 2), and drug (component d). The diffusion of drug and water are modeled according to
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44 Fick's 2nd law of diffusion as follows:
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48 Drug:
$$\frac{\partial v_d}{\partial t} = \frac{\partial}{\partial x} \left(D_d \frac{\partial v_d}{\partial x} \right) \quad (1)$$

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52 Water:
$$\frac{\partial v_1}{\partial t} = \frac{\partial}{\partial x} \left(D_1 \frac{\partial v_1}{\partial x} \right) \quad (2)$$

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Here v_i is the volume fraction of either the drug ($i = d$) or water ($i = 1$) and D_i is the diffusion coefficient of the drug or water. The polymer volume fraction can be obtained simply through:

$$v_2 = 1 - v_d - v_1 \quad (3)$$

The initial conditions for these mass balance equations are as follows:

$$@t = 0 \quad \forall x \quad v_1 = 0 \quad (4a)$$

$$@t = 0 \quad \forall x \quad v_d = v_{d,0} \quad (4b)$$

$$@t = 0 \quad \forall x \quad v_2 = v_{2,0} \quad (4c)$$

Here, $v_{d,0}$ and $v_{2,0}$ are initial loading of drug and water, respectively. To satisfy the boundary conditions, a mass balance at the moving boundary representing the glassy/rubbery interface ($x = R$) can be written as:

$$\text{For } t > 0: \quad (v_1^* + v_d^*) \frac{dR}{dt} = -D_1 \left. \frac{\partial v_1}{\partial x} \right|_{x=R} - D_d \left. \frac{\partial v_d}{\partial x} \right|_{x=R} \quad (5)$$

Here v_1^* is the equilibrium concentration of water and v_d^* is the equilibrium concentration of drug at the glassy/rubbery front ($x = R$). The initial condition for equation (5) is:

$$@t = 0 \quad R = l \quad (6)$$

Here l is the initial half-thickness of the tablet, or thickness of the film. At the glassy/rubbery front ($x = R$), the concentrations of water and drug can be determined by free volume theory³⁶.

The other boundary condition exists at the swelling front, representing the rubbery/solvent interface, where $x = S$. While $t < t_{rept}$, the swollen polymer matrix is still intact and since disentanglement is still ongoing, the polymer has not begun to dissolve into the solvent.

Writing a mass balance at this front yields:

$$0 < t < t_{rept} \quad (v_{1,eq} + v_{d,eq}) \frac{dS}{dt} = D_1 v_{1,eq} \frac{\partial v_1}{\partial x} \Big|_{x=S} + D_d v_{d,eq} \frac{\partial v_d}{\partial x} \Big|_{x=S} \quad (7)$$

However, once $t = t_{rept}$, disentanglement commences and the polymer chains at the swollen front begin to dissolve into the solvent. The flux of the dissolving polymer into the

solvent is balanced by the rate of disentanglement of the polymer chains and can be described as follows:

$$t > t_{rept} \quad x = S^+ \quad -D_2 \frac{\partial v_2}{\partial x} = k_d \quad (8)$$

Here k_d is the polymer chain disentanglement rate. According to Narasimhan and Peppas²⁴, the polymer chain disentanglement rate can be calculated as:

$$k_d = \frac{r_g}{t_{rept}} \quad (9)$$

Here r_g is the radius of gyration of the polymer. Applying this condition to the swollen front for $t > t_{rept}$ yields:

$$t > t_{rept} \quad (v_{1,eq} + v_{d,eq}) \frac{dS}{dt} = D_1 v_{1,eq} \left. \frac{\partial v_1}{\partial x} \right|_{x=S} + D_d v_{d,eq} \left. \frac{\partial v_d}{\partial x} \right|_{x=S} + k_d \quad (10)$$

The initial condition for equation (10) is:

$$@t = 0 \quad S = l \quad (11)$$

At the swollen front, the equilibrium concentrations of the water and drug can be estimated using the Flory-Rehner equation for the temporarily swollen network formed by the chain

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3 entanglements³⁷, according to Narasimhan and Peppas⁷. These are all of the equations
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7 necessary to define the swelling and release of drug from the polymer matrix. One
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10 important point to note is that this model assumes perfect mixing, hence there are no
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14 mass transfer limitations beyond the gel-liquid interface (@ $x = S^+$).
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18 The method to solving the two moving boundary Stefan problem is similar to that of Barry
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21 and Counce³⁸. This was done by first converting the moving boundaries to a fixed
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25 coordinate system by using a modified Landau transform:
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$$z = \frac{x - R}{S - R} \quad (12)$$

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34 Therefore, even though R and S vary as a function of time, z can only range from 0 to 1.
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37 Taking the partial derivative of z with respect to time and x yields:
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$$\frac{\partial v_i}{\partial x} = \frac{\partial v_i}{\partial z} \cdot \frac{1}{S - R} \quad (13)$$

$$\frac{\partial v_i}{\partial t} = \frac{\partial v_i}{\partial t} + \frac{\partial v_i \partial z}{\partial z \partial t} = \frac{\partial v_i}{\partial t} - \frac{(R' + (S' - R') \cdot z) \partial v_i}{S - R} \quad (14)$$

With the modified Landau transform, the diffusion equations and the boundary and initial conditions now take the following form:

$$\text{Drug: } \frac{\partial v_d}{\partial t} = \frac{1}{(S-R)^2} \frac{\partial}{\partial z} \left(D_d \frac{\partial v_d}{\partial z} \right) + \frac{(R' + (S' - R) \cdot z) \partial v_d}{S - R} \quad (15)$$

$$\text{initial condition: } t = 0 \quad \forall z \quad v_d = v_{d,0}$$

$$\text{R boundary condition: } t > 0 \quad z = 0 \quad v_d = v_d^*$$

$$\text{S boundary condition: } t > 0 \quad z = 1 \quad v_d = v_{d,eq}$$

$$\text{Water: } \frac{\partial v_1}{\partial t} = \frac{1}{(S-R)^2} \frac{\partial}{\partial z} \left(D_1 \frac{\partial v_1}{\partial z} \right) + \frac{(R' + (S' - R) \cdot z) \partial v_1}{S - R} \quad (16)$$

$$\text{initial condition: } t = 0 \quad \forall z \quad v_1 = v_{1,0}$$

$$\text{R boundary condition: } t > 0 \quad z = 0 \quad v_1 = v_1^*$$

$$\text{S boundary condition: } t > 0 \quad z = 1 \quad v_1 = v_{1,eq}$$

$$\text{Polymer: } v_2 = 1 - v_1 - v_d \quad (17)$$

$$\text{initial condition: } t = 0 \quad \forall z \quad v_2 = v_{2,0}$$

$$R \text{ boundary condition: } t > 0 \quad z = 0 \quad v_2 = 1 - v_d^* - v_1^*$$

$$S \text{ boundary condition: } t > 0 \quad z = 1 \quad v_2 = 1 - v_{d,eq} - v_{1,eq}$$

$$R \text{ Boundary Mass Balance: } t > 0 \quad (v_1^* + v_d^*) \frac{dR}{dt} = - \frac{D_1}{S-R} \frac{\partial v_1}{\partial z} \Big|_{z=0} - \frac{D_d}{S-R} \frac{\partial v_d}{\partial z} \Big|_{z=0}$$

(18)

$$\text{initial condition: } t = 0 \quad R = l$$

$$S \text{ Boundary Mass Balance: } 0 < t < t_{rept} \quad (v_{1,eq} + v_{d,eq}) \frac{dS}{dt} = \frac{D_1 v_{1,eq} \partial v_1}{S-R \partial z} \Big|_{z=1} - \frac{D_d v_{d,eq} \partial v_d}{S-R \partial z} \Big|_{z=1}$$

(19)

$$t > t_{rept} \quad (v_{1,eq} + v_{d,eq}) \frac{dS}{dt} = \frac{D_1 v_{1,eq} \partial v_1}{S-R \partial z} \Big|_{z=1} + \frac{D_d v_{d,eq} \partial v_d}{S-R \partial z} \Big|_{z=1} + \frac{D_2}{S-R} \frac{\partial v_2}{\partial z} \Big|_{z=1} \quad (20)$$

$$\text{initial condition: } t = 0 \quad S = l$$

An implicit backward Euler method was used to approximate the partial first derivatives of v with respect to time and position for the water and drug. A central difference equation

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3 was used to approximate the partial second derivative of v with respect to position for
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7 water and drug. Following substitution of the algebraic approximations into the set of
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10 equations for the mass balances of drug, water, and the moving boundary equations, the
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13 set of equations were rearranged into a tridiagonal matrix and the Thomas algorithm³⁹
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16 was used to solve for the concentration profile of drug, water, and polymer in the gel layer,
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19 the locations of the moving boundaries as a function of time, and the release profile for
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22 drug as a function of time. These model predictions were then tested by varying several
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25 parameters, including polymer molecular weight, chain disentanglement rate, drug
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28 diffusion coefficient, polymer-drug interactions, and the tablet dimensions. The
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31 predictions were also compared to experimental data on drug release rates for a model
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38 drug.
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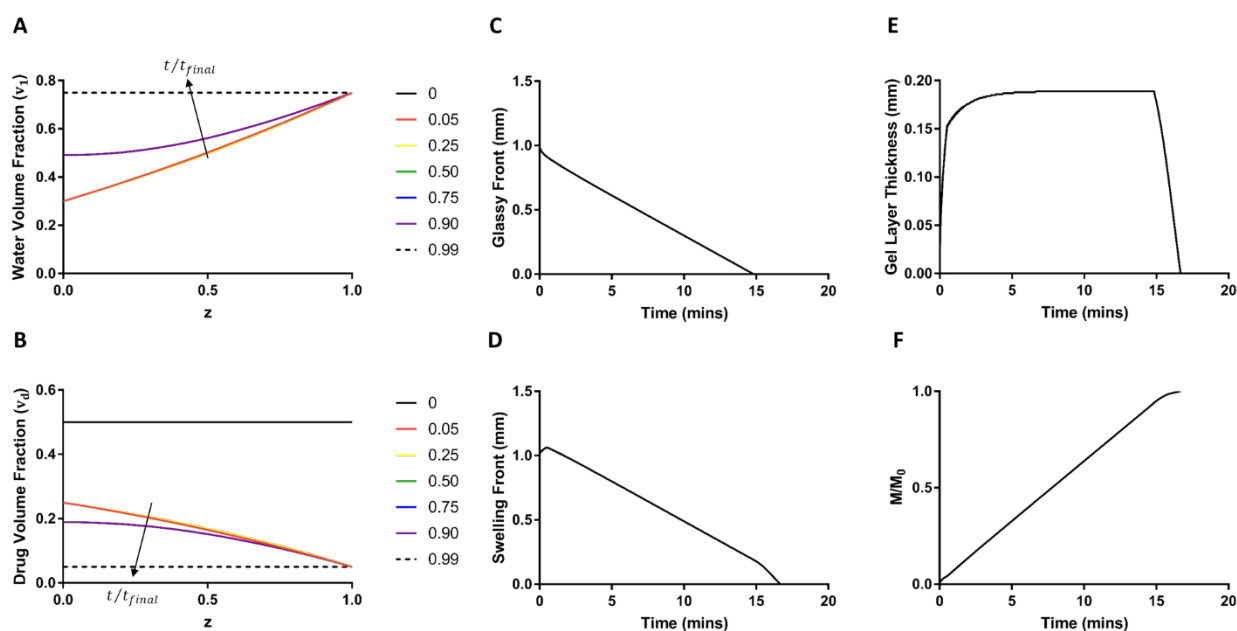
47 Results

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51 The model was assessed for its ability to capture the characteristics of swelling of the
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54 polymer matrix and subsequent chain disentanglement (i.e., locations of the boundaries
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4 *R* and *S*, the gel layer thickness, concentration profiles of drug and water, and drug release
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7 profile) for both disentanglement- (Figure 2) and diffusion- (Figure 3) controlled release
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10 of drug. First, the situation of disentanglement-controlled release was considered. As
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13 shown in Figure 2, the model demonstrates that at times just after water has contacted
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16 the glassy polymer matrix, an infinitesimally small gel layer is formed, with the
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19 concentration profile of drug and water across the gel layer being $v_{d,0}$ and $v_{1,0}$,
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22 respectively (Figure 2A and 2B, $t = 0$). Very shortly thereafter, as water penetrates deeper
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25 into the gel layer (Figure 2C), a concentration profile begins to emerge within the gel layer,
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28 with the concentrations at the boundaries *R* and *S* rapidly reaching their equilibrium
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31 concentrations (Figure 2A and 2B, $t/t_{final} = 0.05$). The glassy front *R* begins to penetrate
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34 inward towards the center of the film (Figure 2C), while the swollen front *S* begins to swell
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37 outward (Figure 2D). Once the reptation time has elapsed, the polymer chains begin to
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40 dissolve into the water and the swollen front starts to move inward (Figure 2D). Depending
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43 on the dissolution rate of the polymer (k_d) and the velocity of the glassy front, the gel layer
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46 thickness will either begin to shrink, continue to grow, or will reach a steady state, as is
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49 shown in Figure 2E. As time elapses, the normalized concentration profile of the drug and
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4 water remain relatively unchanged (Figure 2A and 2B, $t/t_{final} = 0.05$ to 0.75). This is
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7 because the gel layer thickness is at a steady state, as well as the fact that the diffusivity
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10 of the drug is not high enough for diffusion through the gel layer. During this period, with
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13 a constant gel layer thickness, a sufficiently high polymer dissolution rate or low diffusivity
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16 of drug and water, the release of drug is controlled by the disentanglement rate of the
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19 polymer at the swollen front, resulting in zero-order release (Figure 2F). Once the glassy
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22 front has reached the center of the film, the entirety of the polymer matrix is the gel layer,
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25 front has reached the center of the film, the entirety of the polymer matrix is the gel layer,
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28 and the release of drug is now dependent on a combination of drug diffusion and polymer
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31 dissolution at the swollen front.
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4 **Figure 2.** Disentanglement-controlled release example of the swelling/dissolving polymer
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7 model. Model parameters used for this case were $l = 1$ mm, $t_{rept} = 30$ sec, $k_d = -170 \times$
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10 10^{-8} m/s, $v_{d,0} = 0.50$, $v_d^* = 0.25$, $v_{d,eq} = 0.05$, $v_1^* = 0.30$, $v_{1,eq} = 0.75$, $D_1 = 4 \times 10^{-10}$ m²/s,
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12
13 and $D_d = 2.5 \times 10^{-10}$ m²/s. (A) Concentration profile of water through the gel layer over
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15
16 time, specifically 0, 5, 25, 50, 75, 90 and 99% of the release time frame. (B) Concentration
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19 profile of drug through the gel layer over time, specifically 0, 5, 25, 50, 75, 90 and 99% of
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21
22 the release time frame. (C) Location of the glassy front as a function of time. (D) Location
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25 of the swelling front as a function of time. (E) Thickness of the gel layer over time. (F)
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28 Mass fraction of drug released as a function of time.
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40 A similar prediction can be made for the diffusion-controlled drug release situation (Figure
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43 3 A and B), however as shown in Figure 3F, the release of the drug is not controlled by
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46 the chain disentanglement rate because of the increased diffusivity of water and drug
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49 compared to the polymer dissolution rate. In this scenario, the gel layer thickness does
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54 not develop at a steady state thickness over the time period of the drug release. This is
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3 because the increased diffusivity of water causes the glassy front to reach the center
4 before a steady-state gel layer could be achieved (Figure 3C-E), hence allowing the drug
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7 before a steady-state gel layer could be achieved (Figure 3C-E), hence allowing the drug
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10 to diffuse through the gel layer faster than the polymer can dissolve into the media,
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13 leading the drug to follow a square-root-of-time dependent release profile (Figure 3F).
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16 Therefore, the model demonstrates the expected characteristics of both disentanglement-
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19 and diffusion-controlled swollen/dissolving polymer systems, leading to different drug
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25 release profiles.

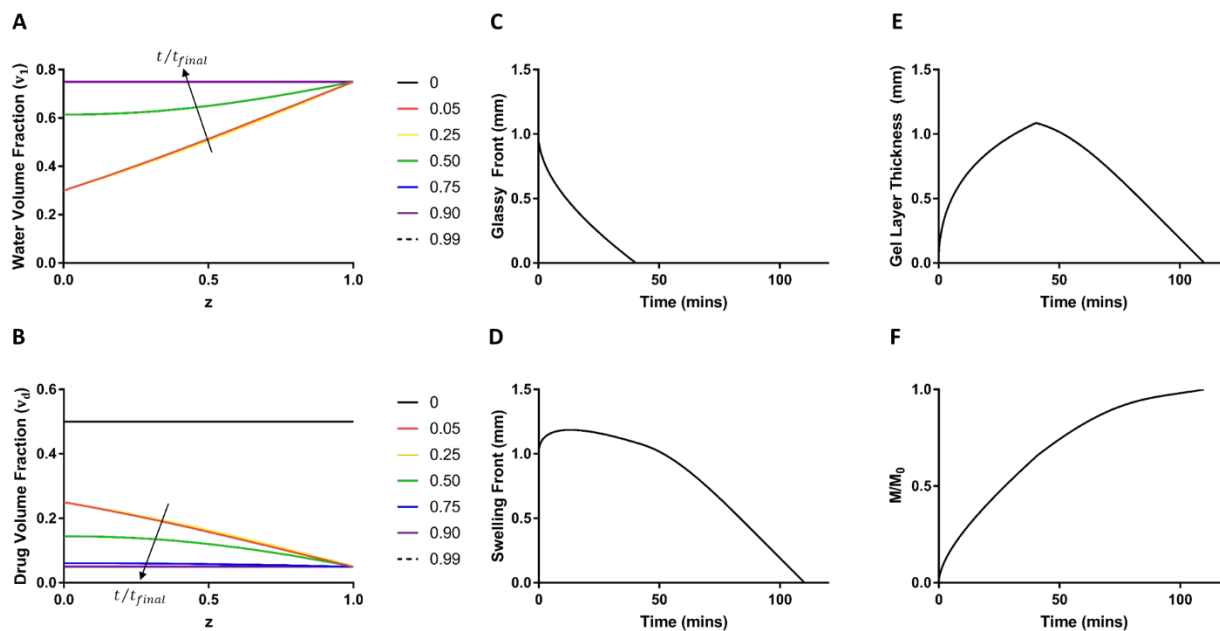


Figure 3. Diffusion-controlled release example of the swelling/dissolving polymer model.

Model parameters used for this case were $l = 1$ mm, $t_{rept} = 30$ sec, $k_d = -25 \times 10^{-8}$ m/s,

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4 $v_{d,0} = 0.50$, $v_d^* = 0.25$, $v_{d,eq} = 0.05$, $v_1^* = 0.30$, $v_{1,eq} = 0.75$, $D_1 = 5 \times 10^{-10} \text{ m}^2/\text{s}$, and $D_d = 3$
5
6
7 $\times 10^{-10} \text{ m}^2/\text{s}$. (A) Concentration profile of water through the gel layer over time, specifically
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9
10 0, 5, 25, 50, 75, 90 and 99% of the release time frame. (B) Concentration profile of drug
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12 through the gel layer over time, specifically 0, 5, 25, 50, 75, 90 and 99% of the release
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14 time frame (C) Location of the glassy front as a function of time. (D) Location of the
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16 swelling front as a function of time. (E) Thickness of the gel layer over time. (F) Mass
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18 fraction of drug released as a function of time.
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33 *Parametric effects on model predictions*

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37 As previously mentioned, the model is able to account for multiple types of release profiles
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39 for drugs, i.e., diffusion-controlled or disentanglement-controlled. Therefore, multiple
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41 model parameters were systematically varied in order to demonstrate the ability of the
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43 model to account for all of these phenomena in different drug-polymer systems. These
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45 results are described next.
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55 *Diffusion-controlled vs. disentanglement-controlled drug release*

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3 The model was tested for its ability to capture both diffusion-controlled and
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7 disentanglement-controlled release of the drug. The first case, diffusion-controlled
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10 release of drug, occurs when the diffusive flux of drug through the gel layer is greater than
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13 the dissolution rate of the polymer, either from an increased diffusivity of the drug and
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16 water or because of a high initial loading of the drug. Therefore, in order to account for
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19 these situations, conditions for diffusion-controlled release were first achieved for a set of
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22 model parameters and then the parameters k_d , $v_{d,0}$, D_1 , and D_d were varied in order to
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28 achieve disentanglement-controlled release of drug. As shown in Figure 4A, for a model
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31 system with an initial polymer dissolution rate of 25×10^{-8} m/s, an initial loading of 50%
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34 (v/v) drug, a water diffusivity of 5×10^{-10} m²/s, and a drug diffusivity of 3×10^{-10} m²/s (all
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37 reasonable values based on typical small molecule drug-based pharmaceutical tablet
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41 formulations), the release profile of drug demonstrated diffusion-controlled release (as
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44 demonstrated by fitting to a square-root-of-time dependence).
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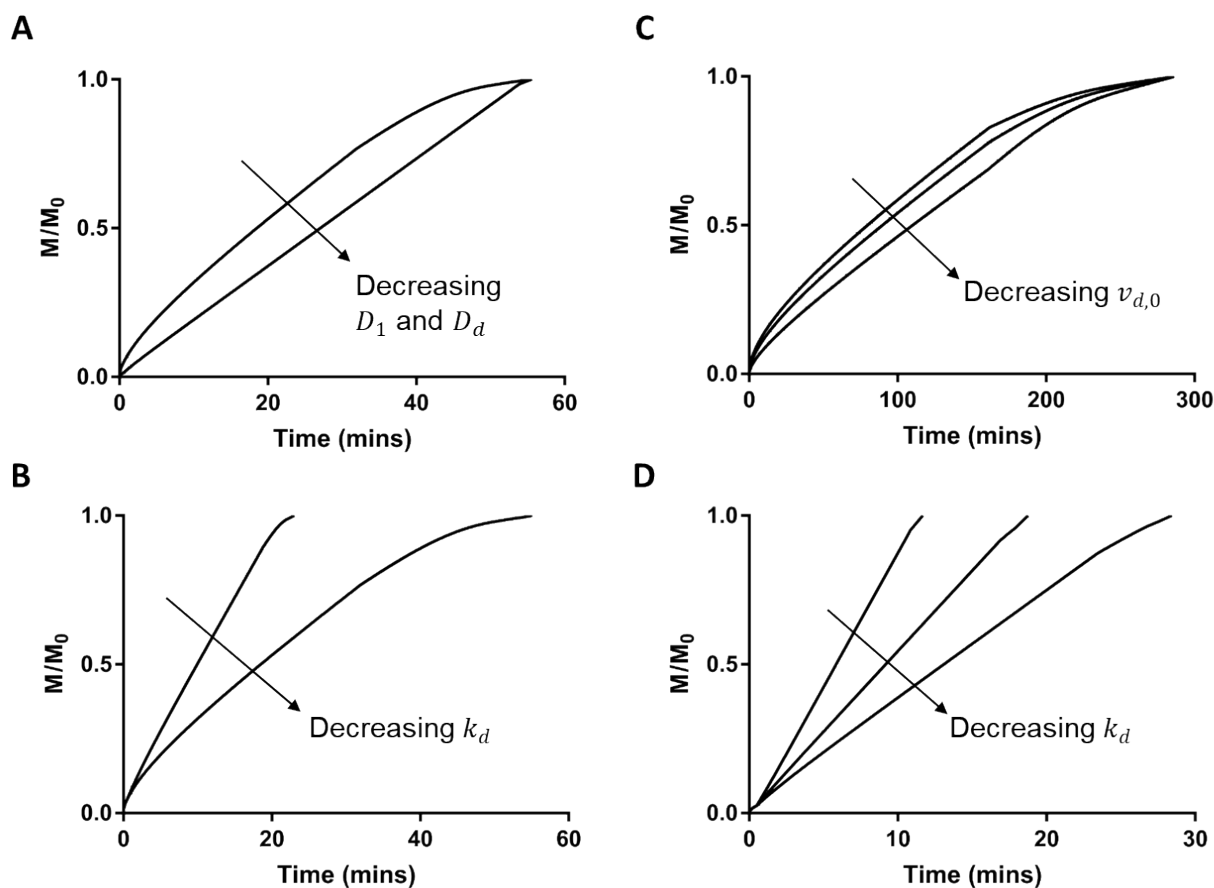
50 To achieve disentanglement-controlled release of drug, the model was first tested by
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53 decreasing the diffusivities of water and drug. When the diffusivities of drug and water
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3 were decreased to 1×10^{-10} m²/s, the release profile became linear over the entire time
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7 period (Figure 4A). The same result was observed when the polymer dissolution rate was
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10 increased from 25×10^{-8} m/s to 120×10^{-8} m/s (Figure 4B), or when the initial loading of
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13 the drug was decreased from 50% to 15% (v/v) (Figure 4C). Therefore, the model is able
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17 to predict both diffusion- and disentanglement-controlled release of drugs, and the model
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20 parameters k_d , $v_{d,0}$, D_1 , and D_d were shown to be the most important in order to achieve
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24 the expected changes in the drug release profile.
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28 *Effect of polymer molecular weight*

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33 As previously described²³, the reptation time of the polymer is inversely correlated with
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36 the dissolution rate of the polymer. Therefore, in the case of disentanglement-controlled
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39 release for polymers with higher molecular weight, it should be expected that the polymer
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42 dissolution rate, and therefore the release rate of drug, should be slower compared to
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45 that of the same polymer of lower molecular weight. In order to test this hypothesis, model
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48 simulations were performed maintaining the same boundary conditions, and same values
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51 of k_d , $v_{d,0}$, D_1 , and D_d was varied in order to observe the effect on the rate of drug release.
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As expected, decreasing k_d using values of 25×10^{-7} m/s, 15×10^{-7} m/s, and 10×10^{-7} m/s resulted in a decrease in the rate of release of drug over time scales of 10, 20, and 30 minutes, respectively (Figure 4D). Therefore, the model is able to accurately capture the effect of varying polymer molecular weight on the corresponding release kinetics of drugs from tablet formulations.



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4 **Figure 4.** Parametric variation of diffusion-controlled release to disentanglement-
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7 controlled release by varying k_d , D_1 , D_d , and $v_{d,0}$. (A) Case of decreasing water and drug
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10 diffusivities to $D_1 = 1 \times 10^{-10} \text{ m}^2/\text{s}$, and $D_d = 1 \times 10^{-10} \text{ m}^2/\text{s}$ using diffusion-controlled release
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13 parameters from Figure 3. (B) Case for increasing k_d to $125 \times 10^{-8} \text{ m/s}$ using diffusion-
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16 controlled release parameters from Figure 3. (C) Case for decreasing initial loading of
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19 drug from 45% to 25% (w/w) for the following parameters: $l = 1 \text{ mm}$, $t_{rept} = 30 \text{ sec}$, $k_d =$
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22 $-9 \times 10^{-8} \text{ m/s}$, $v_{d,0} = 0.45$, $v_d^* = 0.15$, $v_{d,eq} = 0.05$, $v_1^* = 0.45$, $v_{1,eq} = 0.75$, $D_1 = 1.4 \times 10^{-10}$
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25 m^2/s , and $D_d = 0.8 \times 10^{-10} \text{ m}^2/\text{s}$. (D) Case for decreasing k_d from $25 \times 10^{-7} \text{ m/s}$ to 10×10^{-7}
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28 m/s for the following parameters: $l = 1 \text{ mm}$, $t_{rept} = 30 \text{ sec}$, $v_{d,0} = 0.15$, $v_d^* = 0.10$, $v_{d,eq} =$
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32 0.05 , $v_1^* = 0.13$, $v_{1,eq} = 0.85$, $D_1 = 1 \times 10^{-10} \text{ m}^2/\text{s}$, and $D_d = 1 \times 10^{-10} \text{ m}^2/\text{s}$.
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43 *Effect of polymer-drug interactions*

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48 The rate of release of a drug from a polymer matrix is strongly dependent on miscibility
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51 of the drug within the polymer matrix. The miscibility of a drug within a polymer matrix is
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55 estimated by calculating the Flory-Huggins interaction parameter between the drug and
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3 polymer, χ_d . The lower χ_d is (generally negative or slightly positive), the more likely the
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7 drug is miscible with the polymer and less likely it readily diffuses away into the
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10 surrounding medium⁴⁰. Therefore, it is not surprising that, all things being equal, drug-
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13 polymer systems with increased χ_d will have a lower $v_{d,eq}$, as can be shown with the Flory-
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16 Rehner equation, and therefore will have increased rate of release of drug due to an
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19 increased diffusive flux through the gel layer. This effect is accurately captured by the
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22 model, where $v_{d,eq}$ was decreased to simulate an increase in χ_d , and this led to an
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25 increase in the rate of release of the drug as well as the curvature of the release profile
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31 over time (Figure 5A).

32 33 34 35 *Effect of tablet dimensions*

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40 As this model is designed for cases of one-dimensional transport, it is able to account for
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43 changes in the thickness of the polymer matrix. This is shown in Figure 5B for the base
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46 case of disentanglement-controlled release (Figure 2), where increasing the thickness of
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49 the matrix from 1 mm to 5 mm increased the time period of release of the drug
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54 proportionally from 16 minutes to 80 minutes.
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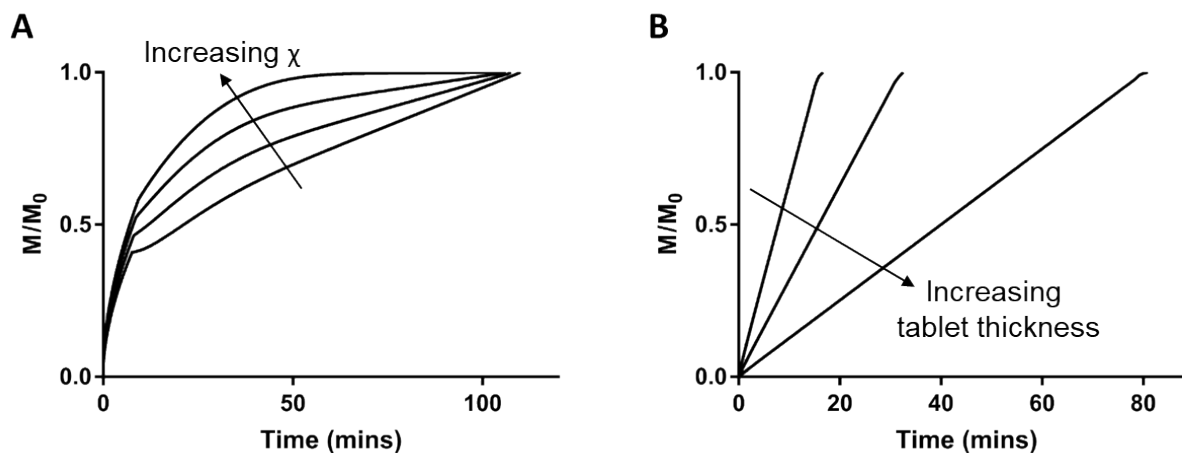


Figure 5. Parametric variation of drug release by varying χ_d and l . (A) Case of increasing χ_d demonstrated by decreasing $v_{d,eq}$ from 0.15 to 0.002 using the following parameters: $l = 1$ mm, $t_{rept} = 30$ sec, $k_d = 25 \times 10^{-8}$ m/s, $v_{d,0} = 0.50$, $v_d^* = 0.25$, $v_{d,eq} = 0.15$, $v_1^* = 0.30$, $v_{1,eq} = 0.75$, $D_1 = 25 \times 10^{-10}$ m²/s, and $D_d = 10 \times 10^{-10}$ m²/s. (B) Case of increasing l from 1 mm to 5 mm for disentanglement-controlled release base case represented in Figure 2.

Model validation

In order to validate the model, drug release experiments were performed using a model drug-polymer system. Release studies of sodium diclofenac were carried out with 14 mm

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4 x 1 mm tablets comprising of either 25% or 50% (w/w) sodium diclofenac entrapped in a
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7 PVP matrix with a molecular weight of either 40,000 g/mol or 360,000 g/mol, and the
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10 experimentally measured drug release kinetics were compared to model predictions. The
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14 model was then compared to the experimental data by initially defining the boundary
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17 conditions and diffusivities of the water and drug, and the polymer dissolution rate was
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20 used as a fitting parameter. It is expected for this polymer-drug system that varying the
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24 initial loading of the drug will not change the diffusivities of the drug and water. Thus, the
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28 drug release rate will primarily depend on the initial loading of the drug and the polymer
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31 dissolution rate – for a higher molecular weight polymer, k_d will decrease, hence the
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35 release rate should also correspondingly decrease.

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39 The results shown in Figure 6 for the low molecular weight PVP tablets and in Figure 7
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42 for the high molecular weight PVP tablets indicate a good fit between the model and
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46 experimental data for both low and high initial loadings of sodium diclofenac. The release
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50 profiles for both the 25% and 50% sodium diclofenac in low molecular weight PVP tablets
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53 exhibited diffusion-controlled release (Figure 6). The data were fit by the model using D_1
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4 = $4 \times 10^{-10} \text{ m}^2/\text{s}$, $D_d = 4 \times 10^{-10} \text{ m}^2/\text{s}$, with $k_d = -60 \times 10^{-8} \text{ m/s}$ for the 25% sodium diclofenac
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7 tablet formulation or $k_d = -80 \times 10^{-8} \text{ m/s}$ for the 50% sodium diclofenac tablet. For the high
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10 molecular weight tablets, a similar trend was observed with the higher loading of sodium
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13 diclofenac, however the 25% (w/w) sodium diclofenac tablet exhibited a linear release
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16 profile, indicating disentanglement-controlled release of the drug (Figure 7). This profile
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19 was also fit to the model using $D_1 = 0.5 \times 10^{-10} \text{ m}^2/\text{s}$, $D_d = 0.3 \times 10^{-10} \text{ m}^2/\text{s}$, and $k_d = 12 \times$
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22 10^{-8} m/s for the 25% sodium diclofenac tablet or $k_d = 28 \times 10^{-8} \text{ m/s}$ for the 50% sodium
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25 diclofenac tablet. The results of the model in this work meaningfully represent the
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28 phenomena of polymer swelling and gel layer formation as described in experimental
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31 studies^{21,22,25}. Additionally, values of k_d , $v_{d,0}$, D_1 , D_d , t_{rept} , and equilibrium volume
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34 fractions of drug, water, and polymer chosen to fit the experimental release data were
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42 consistent with ranges reported in the literature^{7,23,24,41-44}.
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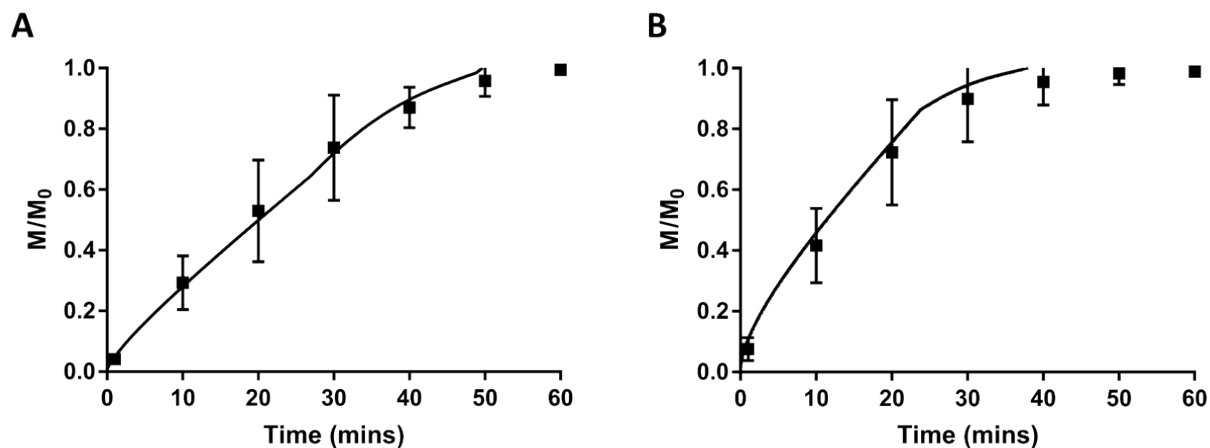


Figure 6. Normalized mass fraction of sodium diclofenac released over time from low molecular weight (40,000 g/mol) PVP tablets containing (A) 25% (w/w) sodium diclofenac and (B) 50% (w/w) sodium diclofenac. Base conditions used for the model were $l = 1$ mm, $t_{rept} = 30$ sec, $v_d^* = 0.15$, $v_{d,eq} = 0.05$, $v_1^* = 0.30$, $v_{1,eq} = 0.85$, $D_1 = 4 \times 10^{-10}$ m²/s, and $D_d = 4 \times 10^{-10}$ m²/s. Additional values used for the model were (A) $k_d = 60 \times 10^{-8}$ m/s, $v_{d,0} = 0.22$ and (B) $k_d = 80 \times 10^{-8}$ m/s, $v_{d,0} = 0.46$.

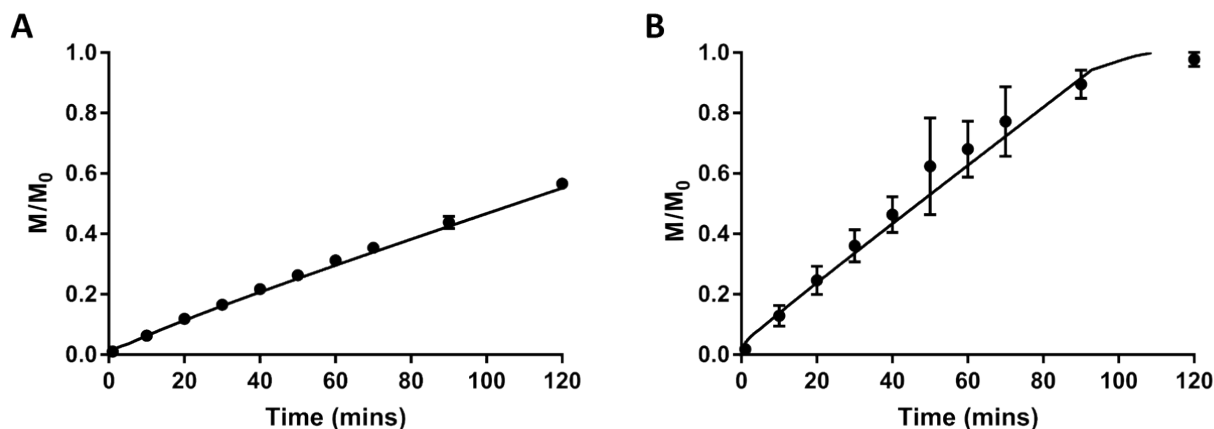


Figure 7. Normalized mass fraction of sodium diclofenac released over time from high molecular weight (360,000 g/mol) PVP tablets containing (A) 25% (w/w) sodium diclofenac and (B) 50% (w/w) sodium diclofenac. Base conditions used for the model were $l = 1$ mm, $t_{rept} = 300$ sec, $v_d^* = 0.15$, $v_{d,eq} = 0.05$, $v_1^* = 0.30$, $v_{1,eq} = 0.85$, $D_1 = 0.5 \times 10^{-10}$ m²/s, and $D_d = 0.3 \times 10^{-10}$ m²/s. Additional values used for the model were (A) $k_d = 12 \times 10^{-8}$ m/s, $v_{d,0} = 0.22$ and (B) $k_d = 28 \times 10^{-8}$ m/s, $v_{d,0} = 0.46$.

Discussion

The ability to accurately predict drug release kinetics from polymer matrices is an important component in the rational design of many pharmaceutical formulations;

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3 understanding how the components of the formulation interact with each other as well as
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7 with the solvent can not only result in significant time and cost savings, but also provide
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10 more accurate control over the release of the drug payload. The model developed in this
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13 work extended the work of Narasimhan and Peppas⁷, in which a pseudo steady state
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16 approximation of the above presented set of equations was used to describe drug release
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19 from swelling/dissolving polymer-drug systems. Despite the ability of previous models to
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22 successfully explain experimental data, the model developed by Narasimhan and
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25 Peppas⁷ was the first to take into account a molecular level understanding of drug release
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28 from amorphous dissolving polymer based on reptation theory. In their pseudo steady
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31 state model, the concentration gradient through the gel layer was approximated as being
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34 linear, which was reasonable based upon the concentration gradients calculated in this
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37 work (Figure 2A and 2B). The gel layer thickness predictions in the pseudo steady state
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40 model were such that disentanglement-controlled release resulted in a linear release
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43 profile, with gel layer characteristics mimicking those shown in Figure 2. For diffusion-
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46 controlled release, the release profile followed a square-root-of-time dependence with a
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49 linear increase in the gel layer thickness over time, similar to the scenario of diffusion-
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3 controlled release predicted by the current model (Figure 3), however the gel layer
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6 thickness tended to not increase linearly as the velocities of R and S were not constant,
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10 as assumed in the pseudo-steady state model.
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14 The current model was able to account for different types of drug release characteristics
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17 by systematic variation of model parameters. First, it was possible to demonstrate either
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21 diffusion- or disentanglement-controlled release of drug by varying k_d , $v_{d,0}$, D_1 , and D_d .
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25 Increasing the initial loading of the drug and the diffusivities of water and drug resulted in
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28 diffusion-controlled release of the drug from the polymer matrix (Figure 4A and 4C);
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31 conversely, increasing the polymer dissolution rate led to linear release of drug (Fig 4B).
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35 In addition, the slope of the release of the drug was shown to be highly dependent on k_d
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38 and $v_{d,0}$. This is expected for both, as the rate of drug released from the polymer matrix
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41 is dependent on the rate of polymer dissolution in the case of disentanglement-controlled
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44 release, and increasing the initial loading of the drug would increase the concentration
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49 gradient, and thus the flux of drug through the gel layer¹.
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4 There were a few observations from the experimental data that were taken into account
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7 in the model. As expected, an increase in the initial dose of the drug from 25% to 50%
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10 (w/w) led to a more rapid, and square-root-of-time release profile of the drug for both low
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13 and high molecular weight PVP tablets. This experimental observation was captured by
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16 the model, as increasing $v_{d,0}$ led to a higher release rate of drug that mimicked the square-
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19 root-of-time dependent release profile as indicated by the experimental data (Figures 6
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22 and 7). As the model would suggest, this could be due to the increased concentration
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25 gradient of drug in the gel layer, hence a higher rate of diffusion of the drug through the
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28 gel layer. Another expected trend observed was that the higher molecular weight PVP
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31 tablets (Figure 7) demonstrated prolonged release of the drug compared to the lower
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34 molecular weight PVP tablets (Figure 6), for both the 25% and 50% (w/w) drug loading.
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38 The model would suggest this could be due to a lower dissolution rate of the polymer,
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41 which is expected as k_d is inversely proportional to reptation time, and thus molecular
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44 weight. The model accurately captured this behavior because higher values of k_d were
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47 required for the low molecular weight PVP tablets than the high molecular weight PVP
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50 tablets to accurately fit the experimental data. In addition, values of the diffusivities of both
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4 water and drug were lower for the higher molecular weight polymer compared to the lower
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7 molecular weight polymer tablets. This could be due to higher entanglement of the
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10 360,000 Da PVP, resulting in a reduced effective diffusion of water and drug through the
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14 gel layer.
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18 The model can be employed for the purpose of simulating a variety of swelling/dissolving
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21 drug-polymer systems, including the choice of drug and polymer, for both diffusion- and
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25 disentanglement-controlled release. This can be accomplished by accounting for
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28 parameters such as the diffusivities of water and chosen drug, initial loading of the drug,
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31 polymer dissolution rate, polymer-drug interactions which would dictate the equilibrium
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34 concentrations at the R and S boundaries, and tablet dimensions, all of which are known
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37 to dictate the drug release kinetics of experimental systems¹. The ability of this model to
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40 capture the complex interplay between these parameters has the potential to be used for
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46 designing pharmaceutical formulations that provide controlled release of drug payloads.
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49 Further improvements to the model include accounting for excipients in the polymer
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53 matrix, polymer crystallinity, inhomogeneous drug distribution within the polymer matrix,
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3 concentration-dependent diffusivity of water and drug, solubility of the drug in the solvent,
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7 mass transfer limitations at the boundary layer, and multi-dimensional transport.
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15 **Conclusions**

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20 Developing models that accurately predict the release kinetics of small molecule payloads
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23 from polymeric tablets would greatly enhance our understanding of polymer-payload
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26 systems and enable rapid optimization of such systems. In this work a new model of
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29 swelling/dissolution of polymeric matrices was developed that could demonstrate both
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33 diffusion- and disentanglement-controlled release of a small molecular weight drug
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36 payload. The model could account for changes in the diffusivities of the drug and water,
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39 the polymer molecular weight, the initial dose of the drug, polymer-drug interactions, and
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43 tablet dimensions, therefore enabling greater control over predicting the effect of these
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47 multivariate parameters on different types of observed drug release profiles. Finally, the
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51 model was fit to experimental data on drug release and demonstrated the ability to
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55 accurately fit the release data using meaningful k_d , $v_{d,0}$, D_1 , and D_d values, indicating its
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3 value in terms of rationally (and rapidly) designing polymer-based pharmaceutical
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7 formulations for controlled drug delivery.
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38 **ABBREVIATIONS** 39

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41 De: Deborah number; OD: optical density; PVP: poly(vinyl pyrrolidone)
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