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Cellular automata model for swelling-controlled drug release

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ABSTRACT

A cellular automata approach for modeling swelling-controlled drug release is presented. In the model, a drug release device is divided into a square grid space. Each cell in the grid contains information about the material, drug, polymer or solvent in that domain. Cells are allowed to change their state according to statistical rules designed to mimic physical phenomena. Diffusion and swelling are modeled by a random walk of mobile cells, and kinetics of chemical or physical processes by probabilities of conversion from one state to another. The model is applied to drug release from a swelling binary polymer/drug device. The effect of simulation parameters on the drug release profiles and the locations of erosion and diffusion fronts are considered. The model was able to produce realistic simulations and is proposed as a new tool for the design of controlled release devices.

1. Introduction

Controlled release of drugs from polymeric tablets or implants is a technologically and therapeutically important field. In order to create and plan new dosage forms efficiently, it is important to be able to design the release characteristics of the drug. These characteristics are influenced by a plethora of factors, such as geometry and solubility of the polymer used. All the factors are chosen so that the resulting drug will behave in a desired manner. In several cases it is requested that the drug can be released at a constant release rate. One way to tune the release characteristics towards this profile is to use swelling polymers or hydrogels. In these swelling-controlled systems, the polymer absorbs water and swells as the water penetrates further into the device. Drug release is controlled by the thickness and permeability of the hydrogel layer and in some cases even zero-order release can be achieved (Colombo et al., 2000, Colombo, 1993; Narasimhan, 2000; Gupta et al., 2002; Peppas et al., 2000; Siepmann et al., 2007).

Modeling the behavior of these systems is challenging, since it involves the movement of several different fronts: erosion, diffusion and swelling. Erosion front is the outer radius of the systems and is defined as the water/gel interface where the polymer is eroded. Diffusion front is the location of the solid drug/dissolved drug interface and swelling front is the location of solid polymer/gel interface inside the device. For drug release purposes, the most important parameter is the gel layer thickness, i.e. the difference between the erosion and diffusion fronts (Colombo et al., 2000). Drug diffusion and concentration gradient in this phase ultimately define the release rate. In most hydrogel systems, a period where the gel layer thickness is constant is observed. During this period the drug release profile is usually assumed to be linear. As all these interfaces can move independently of each other and the relevant diffusion problem must be simultaneously solved, the differential equations for a general swelling case cannot be solved in a closed form, and must be solved numerically. Although this is not difficult, it means that each drug release system must be solved individually, as the geometry of the device affects the boundary conditions of the system. Nevertheless, several approaches have been proposed in the literature (Colombo et al., 2000; Siepmann and Peppas, 2001; Peppas and Khare, 1993; Bernik et al., 2006; Lin and Peng, 2005). It is very common that the simple Peppas equation (Korsmeyer et al., 1983; Peppas and Gurny, 1985) (released fraction is defined as: $M/M_\infty = at^n$) is used to classify the system, where the n of that equation defines the transport mechanism. Fickian systems will have $n = 0.5$ and for anomalous systems $n > 0.5$ will be observed. For drug administration reasons, a zero-order release is often desired, for which a system where $n = 1$ would be optimal.

Here, a new approach for swelling-controlled drug release based on a cellular automata model is proposed. Similar models have been used by Badiali et al. to model corrosion of metal surfaces (Lafage et al., 1998; Saunier et al., 2004) and to model drug release from eroding polymeric matrices (Siepmann and Peppas, 2001; Göpferich and Langer, 1995; Barat et al., 2006a,b; Zygourakis, 1990; Zygourakis and Markenscoff, 1996). In this model a 2D representation of the release device is divided into a grid space, where each cell represents a small part of the whole system. Each cell is connected to 4

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neighboring cells and can interact with them according to a simple set of rules designed to model the physics and chemistry of drug release. For example, diffusion is modeled by allowing drug cells to randomly move into adjacent water cells but not into other drug cells. Diffusion inside permeable membranes is modeled in the same manner, but with a lower diffusion coefficient. The idea behind the model is to consider microscopic domains of the release device and treat them statistically instead of considering molecular interactions directly. For each physical or chemical reaction possible in the system, a probability for that occurrence is given.

As in our previous study (Laaksonen et al., 2009), here we assume no arbitrary lifetimes for drug and polymer regions, but instead link these directly to erosion kinetic constants and diffusion coefficients. As the diffusion in the model is based on random walk, this also eliminates the need to solve Fick's law for the system since it is modeled directly. We show that this simple system leads to simulations which are able to adequately mimic real-life drug release from swelling-controlled devices.

2. Theoretical section

The model divides a planar representation of a drug release device, e.g. a tablet, into a 2D array of square cells. In a typical simulation presented below, each unit cell is assumed to be ca. 100 μm wide, with the whole device considered being ca. 1 cm in size. The state of each cell represents the physical contents of that part of the tablet. The states can be e.g. water, polymer or drug. Each cell represents a domain of the release device, not single molecules or even groups of molecules. In swelling-controlled release, special attention is paid to whether each cell is dry or wet, as they will have fundamentally different behavior. Solid drug cells are immobile, whereas dissolved drug cells are able to diffuse through a wet polymer matrix. In a typical system, a water cell layer surrounds a continuous matrix of polymer and drug cells, i.e. the drug release device is suspended in water. During the simulations, cells are allowed to interact with the 4 adjacent cells and change their state according to a simple set of rules. A dissolved drug filled domain is always assumed to be at the saturation concentration and concentration is represented by the density of these cells. Each cell has defined probabilities to behave according to the set rules, such as to move to a neighboring cell or to be converted into another type of a cell. The time taken in one calculation step is defined by the fastest process. In most cases, this will be the diffusion speed of drug in water. The probability for its movement is set to 1 and all other probabilities are relative to this. A high probability means that the occurrence it models has a high rate constant and vice versa.

While different drugs could have very different behavior, for the purposes of the present model, only the diffusion coefficient and the estimation of drug solubility are used. Solubility is taken into account by considering the volume difference of the solvated and solid drug. This parameter, θ, is equivalent to the concentration ratio between solid drug and saturated drug solution. In the implementation of the model, each initial solid drug cell contains θ mobile drug cells. The case $\theta = 1$ means that the drug is initially dispersed as a saturated solution. Higher values mean that the surface of the particle erodes in an increasingly slower pace as it takes longer time for the diffusion to transfer the solvated drug away from the solid drug or that the solution is initially supersaturated. The parameter can be used to model the difference between two compounds with different saturation solubilities. A low solubility drug will have a higher value for θ. Drug load extent is partly included in this value. If the empty space inside of the device would only be filled to 50% of the maximum possible, θ of that case would be only half of the situation where the device would be completely filled. If the state of a cell changes, the cell either keeps its original θ value or changes it according to the rules shown in Table 1.

Polymer has four characteristics in the model: permeability to drug (and water), swelling potential, swelling probability and erodability. Swelling potential, γ, is defined as the volume increase the polymer would have if it would have taken in the maximum amount of water. The case $\gamma = 1$ means that the polymer will not change its size in water, e.g. a non-swelling system. Other characteristics of the simulation arise from the way the drug and polymer cells are mixed and the maximum dimensions. If the state of a cell changes, the cell either keeps its original γ value or changes it according to the rules shown in Table 1.

The model allows each cell to have one of six different states and has different rules for each state. These are listed in Table 1.

Each cell is checked in random order during each calculation cycle and the rules above are applied. Fig. 1 illustrates how this works in practice. W cells do nothing, while D cells are automatically converted into d cells if adjacent to water like in the case of

Table 1
Cell states considered in the model and the cellular automata rule applied for each cell state in the simulations.

Cell state and symbol		Cellular automata rule	θ and γ values
Water	W	No rules.	$\theta = 0$, $\gamma = 0$
Solid drug	D	When in contact with a W, p or O will convert into a mobile drug cell. This is to say that drug cells are not allowed to diffuse except through water.	$\theta = \theta_0$. θ is initially the same for all D cells.
Mobile drug (dissolved)	d	Will randomly move to any nearby water cell and convert it into a d cell. Can also move into a wet polymer cell with a probability p_p thus forming an O cell.	If a transfer takes place, the θ value of this cell is decreased by one and θ of the receiving cell is increased by one.
		Will be removed from the simulation if it reaches the boundary of the simulation area. Removed d cells are counted and a release profile is formed by dividing this by the initial sum of θ_0.	Converts into a W cell if θ is reduced to 0.
Polymer	P	Will become a p cell when in contact with water with a probability p_w. Polymer cells are assumed to be passive unless they come into contact with water.	$\gamma = \gamma_0$. γ is initially the same for all P cells.
Wet polymer	p	Can swell with a probability p_s if $\gamma > 1$.	If swelling takes place, the cell will increase the γ of a nearby cell by one and lower its own γ by one. Erosion decreases γ by one.
		Has a probability p_e to be eroded. The probability is higher if there are more water cells adjacent to it, i.e. hydrolysis is faster in water rich regions.	Converts into a W cell if γ is reduced to 0.
Wet polymer with drug	O	Obeys the same rules as d and p cells.	If θ falls to zero, this cell is converted into a p cell. If γ falls to zero, this cell is converted into a d cell.

For clarification, rules for applying θ and γ values are explained separately.

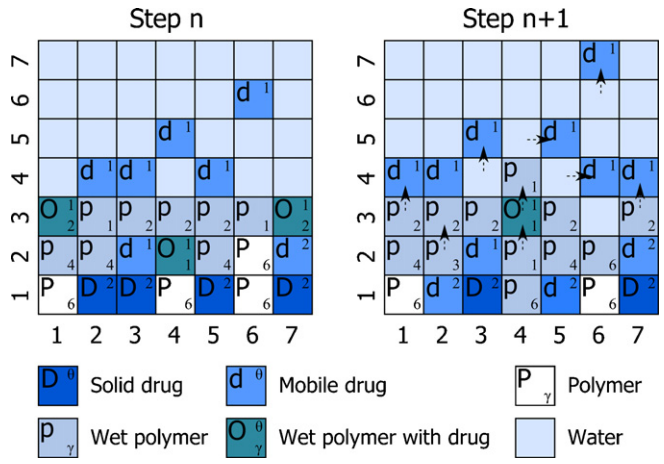

Fig. 1. Schematic illustration of the model in action. All cells follow the rules given in Table 1. Arrows indicate the flow of either θ or γ.

the cell at (2,1). Wet polymer cells (p) can be eroded, like at (6,3), or cause swelling as at (4,4). P cells can be wetted by wet polymer cells as is seen at (6,2). Mobile drug cells move to random directions. In practice, there are two somewhat separate phenomena going on in the simulations. The state of each cell changes according to the rules and, at the same time, there is a flux of the parameters θ and γ from high values to low values. The two fluxes mimic diffusion and swelling that occurs in the swollen gel phase of the device.

Mobile drug cells are allowed to move randomly to W or p cells. This leads to a random walk behavior, and intrinsically creates a diffusion field in the simulation. Convection inside or close to the device is not considered. The relationship between the simulation time step Δt, diffusion coefficient D and the lattice size of the simulated matrix a is shown in Eq. (1) (Saunier et al., 2004).

$$D = \frac{1}{4}\frac{a^2}{\Delta t} \tag{1}$$

Probability p_p indicates the permeability of the polymer to the drug, i.e. the solubility of the drug into the polymer matrix. For the solid polymer phase this is 0. For the permeable gel phase it is dependent on the diffusion coefficient of the drug inside the swollen polymer ($D_{polymer}$), as per Eq. (2). Similarly, p_w measures how fast water can penetrate or wet the polymer.

$$p_p = \left(\frac{D_{polymer}}{D}\right)^{1/2} \tag{2}$$

Swelling probability p_s models the swelling rate of wet polymer. Here, swelling is assumed to proceed as by diffusion. Solid polymer cells are wetted by water or other wet cells. The gradient of γ values in the wet polymer phase creates a kind of stress field which pushes the wet polymer phase outwards. When the wet polymer would move into a water cell, or more precisely when the rules would indicate an increase of the γ of a W cell by one, it creates a new wet polymer cell in that location. This extends the wet polymer phase, thus increasing the thickness of the hydrogel layer. In reality, the uncoiling of polymer would push the whole gel outwards, but a diffusion type approach was assumed here for simplicity reasons. The end-results look realistic with this approach and were deemed to adequately mimic real behavior.

Polymer erosion parameter (p_e) indicates the probability that a p/O cell is destroyed during each calculation cycle. The rate constant of disintegration (k) can be obtained from Eq. (3) when p_e is known (Saunier et al., 2004). The model assumes different values for p_e depending on how many W cells neighbor it. More water means higher mobility for the polymer and less support from neighboring polymer cells leading to a higher probability for erosion. In the simulations below, a $p_e = An$ dependency is assumed, where n is the number of neighboring water cells and A is a constant.

$$k = \frac{p_e a}{\Delta t} \tag{3}$$

Two dimensionless parameters describing swelling have been proposed in the literature (Vrentas et al., 1975; Peppas and Franson, 1983): the Swelling interface number (Sw) and the Deborah number (De). Sw is defined as the relation between solvent penetration and drug diffusion inside the gel layer (Eq. (4)). In the equation, v is the velocity of the swelling front and δ is the thickness of the gel layer. $D_{polymer}$ can be derived from Eq. (2), but the term $v\delta$ is unfortunately defined by all the parameters of the present model. Nevertheless, it can be said that for low values of p_p, Sw $\ll 1$ and the system will be Fickian. If Sw is ca. 1, an anomalous behavior will be observed and the parameter n of the Peppas equation will be >0.5. In the following, we focus on the systems with anomalous transport mechanisms, since those are the most interesting systems and because they are the most difficult to model with traditional approaches. It is good to note that in the cellular automata model, no assumptions about velocities of different boundaries are made, such as the parameter v, as these arise from the assumed diffusion and wetting rates.

$$\mathrm{Sw} = \frac{v\delta}{D_{polymer}} \tag{4}$$

Another common dimensionless parameter is the Deborah number, De. It is defined as the ratio between polymer swelling rate and water penetration rate and is shown in Eq. (5). D_w is the diffusion coefficient of water inside the polymer matrix, τ is the characteristic water diffusion time, and λ is the characteristic relaxation time of the polymer. Both parameters are dependent on many of the parameters presented above. For very high and low values of De, the system will be Fickian since diffusion controls the release. De values around 1 will lead to anomalous transport and, again, this is the focus of the simulations presented below.

$$\mathrm{De} = \frac{\lambda}{\tau} = \frac{\lambda D_w}{\delta^2} \tag{5}$$

Radiuses of the two important fronts, erosion and diffusion, were estimated from the simulated matrices. Outer radius, or erosion front, was assumed to be located at the circular arch where more than 50% of the cells were other than water cells. Core radius was estimated to be located at the circular arch where more than 50% of the initial solid drug cells were left. A drug cell was assumed to be solid if it had $\theta > 1$. Thickness of the gel layer is the difference between these two fronts.

The initial conditions were randomly set according to a predetermined drug/polymer volume ratio. Simulations were done for a circular matrix, but could have been done for other geometries as well, as there are no built-in assumptions about the shape of the device in the cellular automata model. Simulations were run with different probability constants and values of θ and γ. All calculations were done with standard mathematical software (MATLAB). The simulations were run on a 125×125 grid. The area with the release matrix was a 100 cell wide disc. Each simulation was run for 15,000 steps and all simulations for each individual parameter set were repeated 10 times. An average of these runs was taken as a representative of each parameter set.

3. Results and discussion

Drug release curves were simulated with the cellular automata model for various parameters in order to see how it behaves in different situations. To get comparable simulations, a basic set of parameters was determined. Each parameter was studied individ-

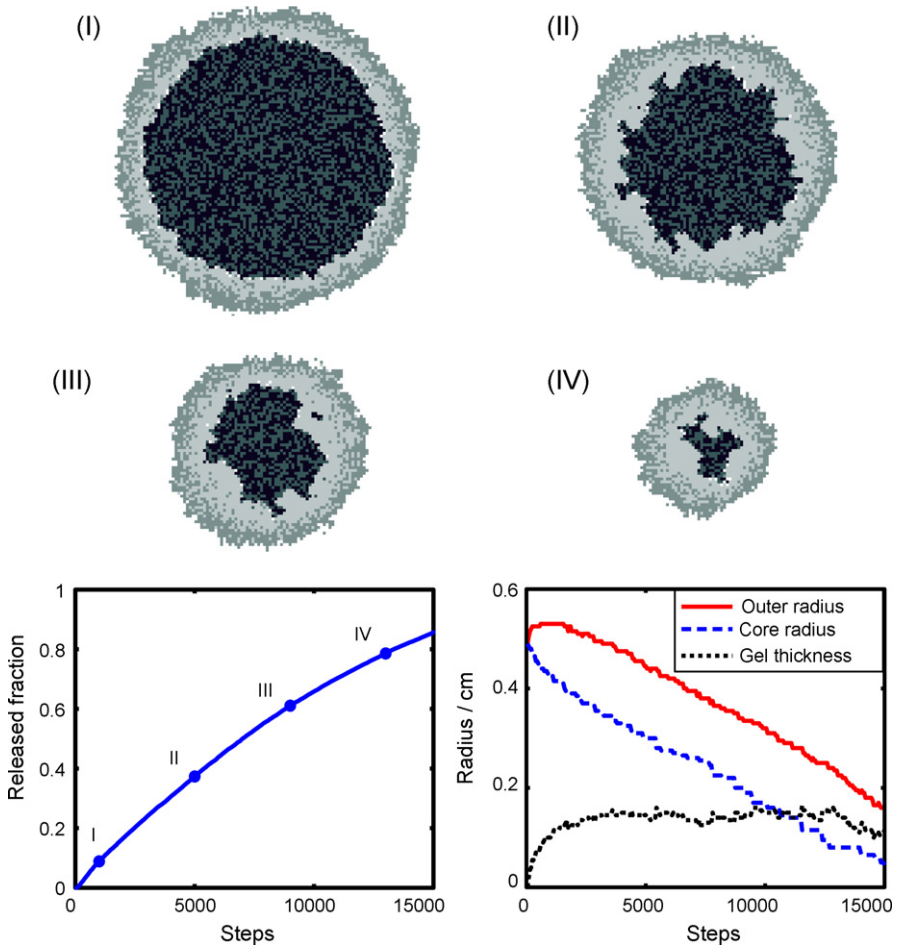

Fig. 2. Illustration of a single simulation run for a swelling-controlled drug release system. The status of the drug release matrix in different time points during the simulation is shown above. The release curve and the location of the different fronts during the simulation are shown below. Black spots represent polymer, dark gray spots represent solid drug, gray spots represent wet polymer and light gray spots represent wet polymer with drug cells.

ually while keeping the others constant in this basic set. These parameters were: $\theta = 4$, $\gamma = 6$, $p_e = 0.005n$, $p_p = 0.10$, $p_s = 0.30$, and $p_w = 0.10n$. The drug was assumed to be initially in the solid state, as is implied by the parameter θ. The values were determined so that running a simulation with the basic set would give a representative "text book" example of swelling-controlled release. The result of such a simulation is shown in Fig. 2. As can be seen, the typical near zero-order release profile is seen for most of the release time as the thickness of the hydrogel layer stays constant throughout the dissolution (Colombo et al., 2000). In all the simulations below, if a parameter value is not stated it is taken from the basic set.

In the first case, the effect of varying drug fraction was studied. Larger volume fraction means that of the overall volume of the device, larger portion is taken up by the drug phase. It is not,

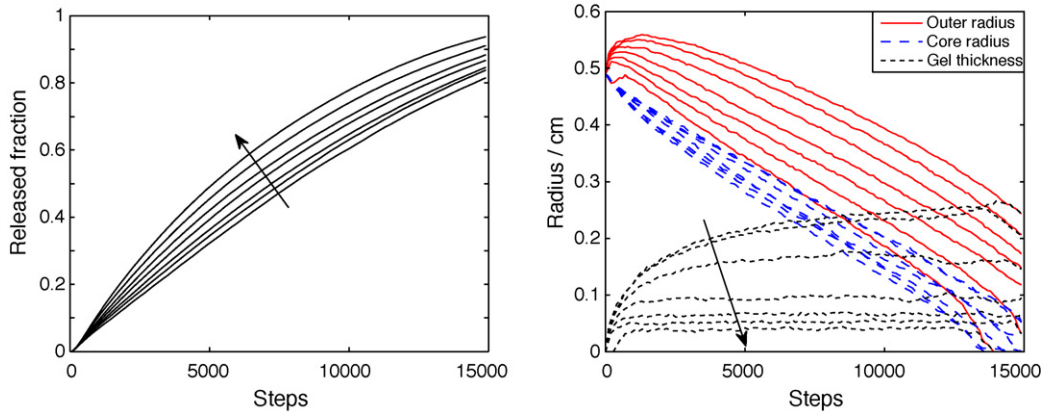

Fig. 3. (Left) Release curves for a simulated swelling-controlled drug release system. Parameters were as follows: $\gamma = 6$, $\theta = 4$, $p_p = 0.10$, $p_s = 0.30$, $p_w = 0.10n$ and $p_e = 0.005n$ for n flanking W cells. Volume fraction of D cells was varied from 20% to 80% with 10% increments. (Right) Locations of erosion and diffusion fronts and the thickness of the hydrogel layer during the same simulations. (Both) Arrows indicate the effect of increasing volume fraction on the release curve and hydrogel thickness. Each curve is an average of 10 simulation runs.

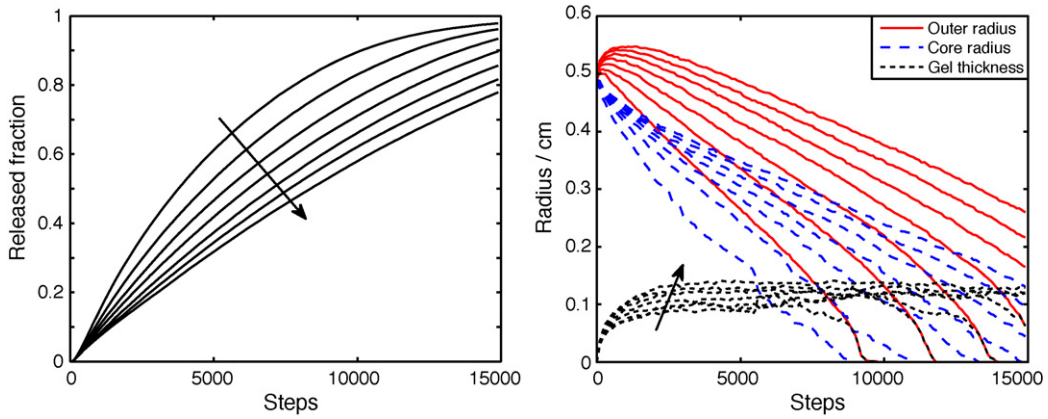

Fig. 4. (Left) Release curves for a simulated swelling-controlled drug release system. Parameters were as follows: $\theta = 4$, $p_p = 0.10$, $p_s = 0.30$, $p_w = 0.10n$ and $p_e = 0.005n$ for n flanking W cells. Volume fraction of D cells was 45%. Parameter γ was varied from 2 to 8. (Right) Locations of erosion and diffusion fronts and the thickness of the hydrogel layer during the same simulations. (Both) Arrows indicate the effect of increasing γ on the release curve and hydrogel thickness. Each curve is an average of 10 simulation runs.

however, directly related to the density or concentration of the drug, as these could be affected by other factors as well, such as the load extent of the drug. Volume fraction was varied from 20% to 80% and the results are shown in Fig. 3.

Larger drug fractions showed faster release, as there was less polymer to bind the drug into the gel phase. This is also apparent from the radius data, where the gel phase is considerably larger for polymer fractions exceeding 60%. Peppas equation (Korsmeyer et al., 1983; Peppas and Gurny, 1985) was used to estimate the linearity of the release for drug fractions up to 60%. Highest amount for the n in the equation obtained for these simulations was 0.96 for the 20% drug fraction case. Although the gel phase thickness is not as constant for low load rates as for the higher ones, it seems to be a good condition for obtaining constant release from swelling-controlled systems. The trend is contrary to what was observed by Siepmann and Peppas (2001), who observed that increasing the drug amount initially slowed down the release rate, but when the drug amount was further increased the release rate was increased. This was suggested to be due to the increasing presence of solid drug phase. In the current study, release rate was increased for all drug amounts. This is because here the drug was initially above its saturation limit ($\theta > 1$).

Parameter γ simulates the swelling potential of the polymer, i.e. the maximum volume the swollen polymer can attain without erosion is γ times the initial volume. Here, γ values of 2–8 were studied. The simulation results are shown in Fig. 4. Larger values cause lower release of the drug as expected, as the swollen layer is thicker and offers a spatially larger diffusion barrier for the drug. This is also reflected in the radius results. For all cases the hydrogel layer thickness was constant for large portions of the release curve. The highest n of the Peppas equation was 0.93 for the case of $\gamma = 6$. Therefore, a polymer that has a high swelling potential seems to be the best choice for obtaining constant release profiles.

Fig. 5 shows the same analysis as above for the simulations run for different values of θ. As would be expected, increase in θ, i.e. a decrease in saturated solubility, decreases the rate of release. For the case of $\theta = 2$, the gel layer thickness was very large. In that case water penetration into the polymer matrix was faster as the dissolving drug provided little resistance for the diffusion of water. The most linear release profile was obtained with $\theta = 8$, where n of the Peppas equation was 0.97. Therefore, swelling-controlled release would seem to be most beneficial for low solubility drugs to reach zero-order release profiles.

The next parameter considered was permeation probability p_p. As this defines how fast the drug cells move in the gel phase, it also defines how fast the solid drug core of the systems erodes and, therefore, the location of the diffusion front. As the distance between the erosion and diffusion fronts fundamentally defines the release kinetics from the swelling-controlled release systems, factors that directly affect this distance are very important. Simu-

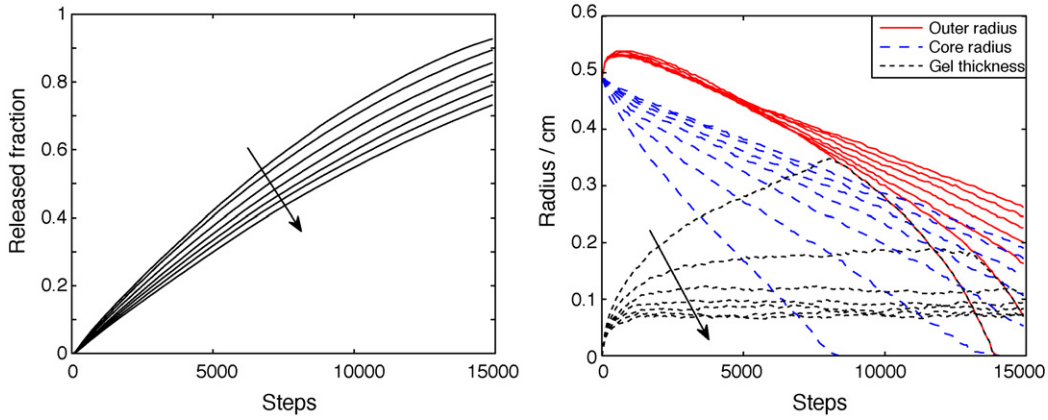

Fig. 5. (Left) Release curves for a simulated swelling-controlled drug release system. Parameters were as follows: $\gamma = 6$, $p_p = 0.10$, $p_s = 0.30$, $p_w = 0.10n$ and $p_e = 0.005n$ for n flanking W cells. Volume fraction of D cells was 45%. Parameter θ was varied from 2 to 8. (Right) Locations of erosion and diffusion fronts and the thickness of the hydrogel layer during the same simulations. (Both) Arrows indicate the effect of increasing θ on the release curve and hydrogel thickness. Each curve is an average of 10 simulation runs.

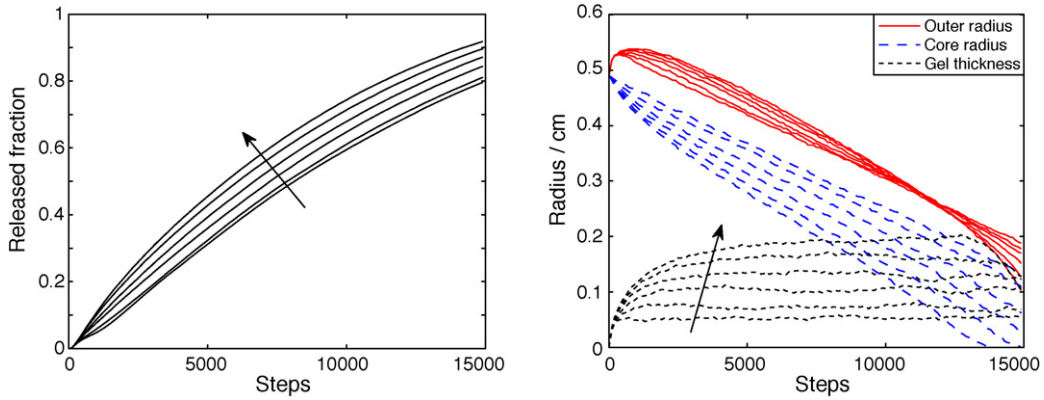

Fig. 6. (Left) Release curves for a simulated swelling-controlled drug release system. Parameters were as follows: $\gamma = 6$, $\theta = 4$, $p_s = 0.30$, $p_w = 0.10n$ and $p_e = 0.005n$ for n flanking W cells. Volume fraction of D cells was 45%. Parameter p_p was varied from 0.01 to 0.20 with 0.04 increments. (Right) Locations of erosion and diffusion fronts and the thickness of the hydrogel layer during the same simulations. (Both) Arrows indicate the effect of increasing p_p on the release curve and hydrogel thickness. Each curve is an average of 10 simulation runs.

lations are shown in Fig. 6. Naturally, a lower p_p resulted in lower release rate as diffusion constant in the gel layer was decreased. This is the same result as was observed by Narasimhan (2000) in studies on the effect of drug diffusion coefficient on the release profile. Lower probability also caused the release to be more linear, with the best n being 1.00 for the case of $p_p = 0.04$. The effect on the location of the erosion front was minimal, but changing p_p did have a strong influence on the core radius, i.e. the location of the diffusion front. Lower permeation probability decreased the rate of core shrinking and, therefore, decreased the hydrogel layer thickness during the release.

Swelling probability parameter, p_s, is directly related to the erosion front movement rate, and together with p_p and p_e, defines the gel layer thickness during the drug release simulations. Higher probability means that the swelling is faster and erosion front radius is increased. Results of the simulations where p_s was varied are shown in Fig. 7. Higher probability caused a more linear but slower release, with $p_s = 0.70$ having a Peppas equation parameter $n = 1.00$. The parameter had little effect on the core radius, but a stronger effect on the outer radius of the device. In the beginning a high p_s causes a rapid increase in the size of the device and in the end a more rapid decline. This stabilizes the gel layer thickness so that for a quickly swelling polymer the gel layer maintained constant thickness for the longest time. This would be a desired quality in real drug release systems. Considering the Deborah number defined in the Eq. (5), increasing the value of p_s increases the characteristic relaxation time of the polymer and, thus, also the Deborah number. Therefore, the response moves away from the Fickian behavior with already relatively low values of p_s, and the parameter set chosen had a De ~1 and exhibited anomalous transport (Colombo et al., 2000).

The last parameter that was studied was water permeability parameter p_w. The results of these simulations are shown in Fig. 8. Water penetration naturally has a larger effect on the inner radius of the system than on the outer one, as a higher p_w means that water can more easily penetrate into the polymer matrix. Larger values also result in a thicker hydrogel layer and slower release. The highest n value for the Peppas equation was obtained with $p_w = 0.005$, for which n was 0.84. Considering the Swelling number defined in Eq. (4), higher values of p_w mean that the velocity of the swelling front is higher. This in turn implies a larger value for Sw. As deviations from Fickian response were seen in these cases, the parameter set used had a Sw < 1 and the system moved towards anomalous behavior when p_w was increased (Colombo et al., 2000).

The results presented here were for a 2D grid. 3D simulations would of course be more realistic ones, but require considerably longer calculation times, 100 times longer in this case. The effect of going from 2D to 3D is further considered in the supporting information together with further estimations of the Sw and De parameters for the cellular automata simulations. While it may seem that the model has a lot of unknown parameters, they are all based on material properties. Therefore they are not unknown

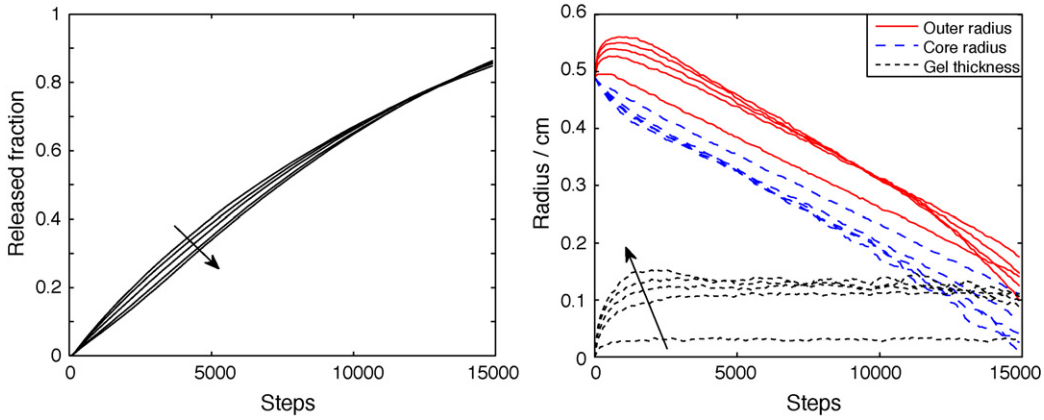

Fig. 7. (Left) Release curves for a simulated swelling-controlled drug release system. Parameters were as follows: $\gamma = 6$, $\theta = 4$, $p_p = 0.10$, $p_w = 0.10n$ and $p_e = 0.005n$ for n flanking W cells. Volume fraction of D cells was 45%. Parameter p_s was varied from 0.10 to 0.90 with 0.20 increments. (Right) Locations of erosion and diffusion fronts and the thickness of the hydrogel layer during the same simulations. (Both) Arrows indicate the effect of increasing p_s on the release curve and hydrogel thickness. Each curve is an average of 10 simulation runs.

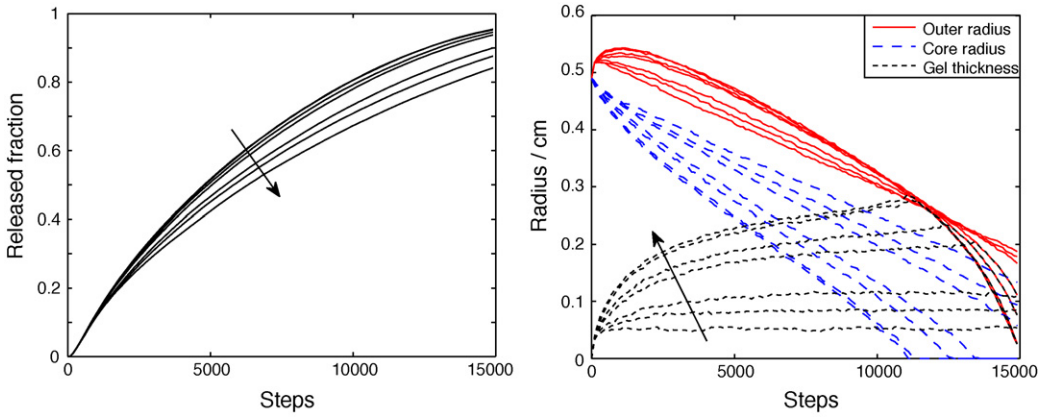

Fig. 8. (Left) Release curves for a simulated swelling-controlled drug release system. Parameters were as follows: $\gamma = 6$, $\theta = 4$, $p_p = 0.30$, $p_s = 0.30$, and $p_e = 0.005n$ for n flanking W cells. Volume fraction of D cells was 45%. Parameter p_w was varied from 0.0001 to 0.10. (Right) Locations of erosion and diffusion fronts and the thickness of the hydrogel layer during the same simulations. (Both) Arrows indicate the effect of increasing p_w on the release curve and hydrogel thickness. Each curve is an average of 10 simulation runs.

if the materials themselves are well characterized. As can be seen from Table 2, most of the parameters can be derived from simple known constants such as diffusion coefficients and solubility data. The most difficult parameters to estimate deal with the swelling kinetics. In order to estimate them, control experiments with only pure polymer should be conducted.

To test the model with real data, experimental data were extracted from two previously published cases (Narasimhan and Peppas, 1997; Conte et al., 1988; Ju et al., 1995). In the first case (Narasimhan and Peppas, 1997; Conte et al., 1988), there is a lot of background information about the diffusion coefficients and volume ratios. These can be used to obtain the simulation parameters as per the instructions in Table 2. Time scale is locked to 100 min and the "yardstick" of the simulations time scale is obtained from Eq. (1). Initial diffusion probabilities are then related to that by Eq. (2). For example, p_p would be 0.13 and $p_w = 0.46$ (diffusion coefficients of the drug, diprophylline, and water were 1.1×10^{-6} cm^2/s and 1.5×10^{-5} cm^2/s, respectively). Erosion probability is obtained from the indicated disentanglement rate (2.0×10^{-5} cm/s) and is estimated to be either 8×10^{-4} or 4×10^{-3}, depending on the perspective whether the tablet is viewed along the long or short axis. The lattice size a in Eq. (3) is different depending on the physical size of the release system, as here the number of cells was always kept the same. All values were then slightly adjusted to find out the best fit. For example, a better fit in the simulations was obtained with $p_e = 4 \times 10^{-3}$ and $p_p = 0.05$. The result is shown in Fig. 9. The fit seems to be relatively good, although the early release is slightly underestimated. Some of the error is naturally due to the different geometry used in the simulation, as the calculations were done on a 2D model. A 3D run with the right geometry was also performed (Fig. 9). The shape of the release curve from the 3D simulation did fit the experimental data slightly better, although early release was overestimated by 5–10%. This is most likely due to the grid size, i.e. the grid points were unnaturally large compared to real particle sizes. Now 5% of the drug cells were on the surface and caused the 5% increase seen in the release profile. Increasing the grid density would reduce the effect of the surface layer on the overall shape of the curve. In these simulations $p_e = 8 \times 10^{-4}$, as the grid size was set by the long axis and the grid spacing was of different length than in the 2D simulations. Overall, the release curve seems to fit the experimental data better in 3D. But as 2D simulations are much faster to perform, it is proposed that these can be used to find the right range of parameters and 3D simulations can then be done with the right parameter set to get a better fit. Finding the right parameters with 3D simulations alone can take a lot of time.

The second case (release of adinazolam mesylate from HPMC matrices, Ju et al., 1995) is a little more demanding to model, as there is less information available about the diffusion coefficients of each species. However, there is information available about the relative diffusion and erosion rates of the different HMPC grades used. Here the first fit is made only to model the release from the

Table 2
List of the model parameters and guidelines for their estimations.

Parameter	Estimation obtained from
Drug fraction, geometry	Experimental details and composition of the drug release device.
θ_0	Solubility of the drug ($\theta_0 = \rho/MS$)[a].
γ_0	Maximum swelling of the drug. Has to be determined from control experiments.
p_p	The diffusion coefficient of the drug inside the polymer (Eq. (2)).
p_e	Eq. (3) or from control experiments.
p_s	Swelling rate of the drug. Has to be determined from control experiments.
p_w	The diffusion coefficient of water inside the polymer (Eq. (2)).

[a] ρ is density of the drug, M is molecular weight of the drug and S is the saturated solubility of the drug.

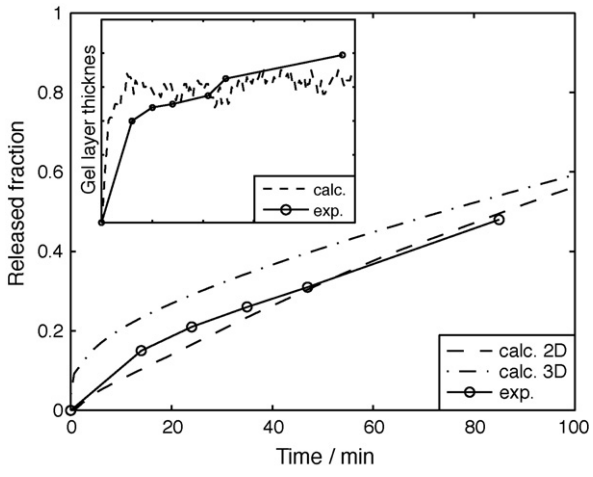

Fig. 9. Release curves fitted to an experimental data set obtained from Narasimhan and Peppas (1997). Parameters were as follows: $\gamma = 9$, $\theta = 8$, $p_p = 0.05$, $p_w = 0.15n^{2/3}$ and $p_s = 0.05$. Volume fraction of D cells was 50%. Erosion probability $p_e = 0.004n^{2/3}$ for n flanking W cells for 2D simulations and $8 \times 10^{-4}n^{2/3}$ for 3D simulations. Normalized gel layer thickness is shown as an inset. Symbols indicate experimental values and dashed lines the simulated release curves.

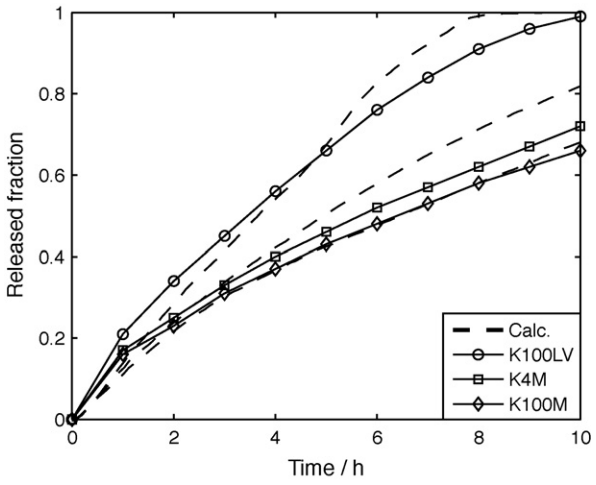

Fig. 10. Release curves fitted to an experimental data set obtained from Ju et al. (1995). Parameters for the K100M curve were as follows: $\gamma = 4$, $\theta = 6$, $p_p = 0.30$, $p_w = 0.20n$, $p_s = 0.30$, and $p_e = 0.005n$ for n flanking W cells. For K4M parameters were changed as follows: $p_s = 0.40$, and $p_e = 0.008n$. For K100LV parameters were as follows: $p_s = 0.55$, and $p_e = 0.013n$. Volume fraction of D cells was 5%. Symbols indicate experimental values and dashed lines the simulated release curves.

heaviest HPMC grade and other fits are then adjusted only by changing the polymer diffusion coefficient D_p (related to p_s) and p_e of the simulation as per Eqs. (1) and (2) and the relations in Ju et al. (1995). The different HPMC grades are assumed to have different diffusion coefficients and erosion rates. For example, the relation of the diffusion coefficients of the polymer from Eq. (26) in Ju et al. (1995) states that the three HPMC grades have diffusion coefficients in ratio of 3.2:1.7:1. Swelling probabilities are therefore in ratios 1.8:1.3:1 as per Eq. (2). D_p was estimated to be 6.7×10^{-7} for the heaviest grade and 2.3×10^{-6} for the lightest grade, not unreasonable numbers. Here the time scale was 10 h, so the diffusion in water phase would be unrealistically slow in just 15,000 steps. But as this is not going to be the rate determining step, it was accommodated by reducing the size of the diffusion layer, i.e. the thickness of the water cell layer. The diffusion layer was further diminished as the device itself shrunk during the simulation. This reduced the dependence of the release curve on the water layer diffusion. Fits are shown in Fig. 10. The lowest curve fits well, as it was separately fitted. The other two curves show relatively good fits, especially as they were not separately adjusted, but only made by changing the p_e and p_s as per literary values. Again, one source of error comes from performing the simulations in 2D. Nevertheless, the fits to both of the presented cases seem to be surprisingly good, especially as the simulations were done by adjusting the parameters according to real-life values and not just to get the best possible fit to data.

In conclusion, a cellular, probabilistic model for swelling-controlled drug release simulations was presented. The effect of selected simulation parameters on the drug release profiles and the locations of erosion and diffusion fronts were considered. The model took into account swelling and erosion of the polymer, drug and water permeations and solubility of the drug. The results obtained corresponded well to real-life performance of swelling-controlled systems. The hydrogel layer thickness could be simulated along with the release profile. The model was simple to implement and gave realistic results with limited calculation power required. It would be simple to extend the model to swelling coated or reservoir type systems with multiple release rate controlling features, as has been previously suggested for erodible devices (Laaksonen et al., 2009). It is therefore envisioned that it could prove to be useful for the design of swelling drug formulations and other controlled release systems.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2009.06.023.

References

Barat, A., Ruskin, H.J., Crane, M., 2006a. Probabilistic methods for drug dissolution. Part 2. Modelling a soluble binary drug delivery system dissolving in vitro. Simul. Model. Pract. Theory 14, 857–873.
Barat, A., Ruskin, H.J., Crane, M., 2006b. Probabilistic models for drug dissolution. Part 1. Review of Monte Carlo and stochastic cellular automata approaches. Simul. Model. Pract. Theory 14, 843–856.
Bernik, D.L., Zubiri, D., Monge, M.E., Negri, R.M., 2006. New kinetic model of drug release from swollen gels under non-sink conditions. Colloids Surf. A 273, 165–173.
Colombo, P., 1993. Swelling-controlled release in hydrogel matrices for oral route. Adv. Drug Deliv. Rev. 11, 37–57.
Colombo, P., Santi, P., Bettini, R., Brazel, C.S., Peppas, N.A., 2000. Drug release from swelling-controlled systems. In: Wise, D.L. (Ed.), Handbook of Pharmaceutical Controlled Release Technology. Marcel Dekker, New York, pp. 183–209.
Conte, U., Colombo, P., Gazziniga, A., Sangalli, M.E., La Manna, A., 1988. Swelling-activated drug delivery systems. Biomaterials 9, 489–493.
Göpferich, A., Langer, R., 1995. Modeling monomer release from bioerodible polymers. J. Control. Release 33, 55–69.
Gupta, P., Vermani, K., Garg, S., 2002. Hydrogels: from controlled release to pH-responsive drug delivery. Drug Discov. Today 7, 569–579.
Ju, R.T.C., Nixon, P.R., Patel, M.V., Tong, D.M., 1995. Drug release from hydrophilic matrices. 2. A Mathematical model based on the polymer disentanglement concentration and the diffusion layer. J. Pharm. Sci. 84, 1464–1477.
Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25–35.
Laaksonen, T., Laaksonen, H., Hirvonen, J., Murtomäki, L., 2009. Cellular automata model for drug release from binary matrix and reservoir polymeric devices. Biomaterials 30, 1978–1987.
Lafage, M., Russier, V., Badiali, J.P., 1998. Simulation of growth and corrosion during the formation of a passive layer. J. Electroanal. Chem. 450, 203–212.
Lin, J., Peng, Y., 2005. Swelling controlled release of drug in spherical polymer–penetrant systems. Int. J. Heat Mass Transfer 48, 1186–1194.
Narasimhan, B., Peppas, N.A., 1997. Molecular analysis of drug delivery systems controlled by dissolution of the polymer carrier. J. Pharm. Sci. 86, 297–304.
Narasimhan, B., 2000. Accurate models in controlled drug delivery systems. In: Wise, D.L. (Ed.), Handbook of Pharmaceutical Controlled Release Technology. Marcel Dekker, New York, pp. 155–181.
Peppas, N., Franson, N.M., 1983. The Swelling interface number as a criterion for prediction of diffusional solute release mechanisms in swellable polymers. J. Polym. Sci. Part B: Polym. Phys. 21, 983–997.
Peppas, N., Gurny, R., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.
Peppas, N.A., Bures, P., Leobandung, W., Ichikawa, H., 2000. Hydrogels in pharmaceutical formulations. Eur. J. Pharm. Biopharm. 50, 27–46.
Peppas, N.A., Khare, A.R., 1993. Preparation, structure and diffusional behavior of hydrogels in controlled release. Adv. Drug Deliv. Rev. 11, 1–35.
Saunier, J., Chaussé, A., Stafiej, J., Badiali, J.P., 2004. Simulations of diffusion limited corrosion at the metal/environment interface. J. Electroanal. Chem. 563, 239–247.
Siepmann, F., Hoffmann, A., Leclercq, B., Carlin, B., Siepmann, J., 2007. How to adjust desired drug release patterns from ethylcellulose-coated dosage forms. J. Control. Release 119, 182–189.
Siepmann, J., Peppas, N.A., 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv. Drug Deliv. Rev. 48, 139–157.
Vrentas, J., Jarzebski, C.M., Duda, J.L., 1975. Deborah number for diffusion in polymer–solvent systems. AIChE J. 21, 894–901.
Zygourakis, K., 1990. Development and temporal evolution of erosion fronts in bioerodible controlled release devices. Chem. Eng. Sci. 45, 2359–2366.
Zygourakis, K., Markenscoff, P.A., 1996. Computer-aided design of bioerodible devices with optimal release characteristics: a cellular automata approach. Biomaterials 17, 125–135.