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Research Paper

Modelling of diclofenac sodium diffusion from swellable and water-soluble polyethylene oxide matrices

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Abstract

Objectives The main objective of this study was to develop a mathematical model for the characterization of diclofenac sodium diffusion from polyethylene oxide (PEO) matrices. A model was developed on the basis of the diffusion theory accounting for the characteristics of the polymer: swelling with subsequent dissolution in water. The concentration-dependent diffusion of drug and water was taken into account. Experimental data were analysed using a computer software program as an aid for solving partial differential equations.

Methods Six formulations of matrix tablets with different drug–excipient ratios were prepared using low-molecular-weight PEO as a matrix-forming material. For obtaining drug release data, dissolution studies were performed and water uptake by pure PEO matrices was studied as well.

Key findings A good agreement of the developed model with experimental results was demonstrated. Some anomalies in drug diffusion were observed and their origin was questioned. Changes in the parameters characterizing the process of diffusion are attributed to glassy–rubbery polymer transitions. Additional interpretation of this phenomenon on the basis of percolation theory is also provided.

Conclusions The obtained model has the ability to predict the required characteristics of matrices for desired drug release. The composition of batches with undesirable release properties can be predetermined and avoided in manufacturing.

Keywords controlled release; diffusion; mathematical modelling; polyethylene oxide (PEO) matrix; swelling

Introduction

The characterization of pharmaceutical excipients includes an insight into mechanisms governing drug release. One of the relatively novel polymers in the pharmaceutical industry is polyethylene oxide (PEO) of different grades. PEOs are hydrophilic (i.e. thermodynamically compatible with water), linear and uncrosslinked polymers. After being immersed into water polymeric chains start to swell mainly due to hydrogen bonds formed between water and polymer.[1] The anionic nature of polymers makes it possible to expect that they do not exhibit any interactions with drug substances or the surrounding media. Important PEO features include their unresponsiveness to the pH of the physiological fluids, non-toxicity and ease of production.[2] PEOs have been successfully employed in designing controlled-release swellable matrices[3] as well as hydrogels[4] and mucoadhesive films.[5] Tablets have been made by direct compression or hot-melt granulation.[3] PEO matrices are often referred to as swellable or gel-forming matrices owing to formation of an outer gel layer on the matrix surface once the polymer is fully swollen. This gel layer is responsible for modulation of drug delivery as well as enhanced stability of the inner core of the matrix tablet. PEO is a thermoplastic, bioadhesive material, and is one of the fastest hydrating water-soluble polymers used in pharmaceutical systems.[6] Swelling drives a phase transition from a glassy state wherein polymeric chains are immobile to a rubbery state wherein they rapidly move. Glassy-to-rubbery phase transition occurs at the glass transition temperature, T_g.[7]

Being hydrophilic in nature makes PEO polymeric chains dissolve in media once the swelling process is completed. Hence, there are two processes occurring – swelling and dissolution – providing subsequent formation of three fronts, layers in the cylindrical matrix tablet from the centre of the matrix to its periphery: the swelling front (boundary of

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polymer transition from glassy to rubbery state), the diffusion front (solid drug–drug solution boundary) and the erosion front (swollen matrix–solvent boundary). The erosion front moves outwards, owing to the swelling of the matrix, or inwards when the matrix dissolves whereas the swelling front moves inwards after the penetration of water.[8] Dissolution of polymer from the surface of the matrix is a rather complex process since it involves disentanglement of polymeric chains and a process called reptation. Reptation basically describes the transformation undergone by the polymer from an entangled gel-like phase to a disentangled liquid solution.[9] It owes its name to the snake-like motions of polymeric chains. The dissolution of the polymer requires that the concentration of solvent exceeds a certain critical value and it takes some time for the polymeric chains to become completely disentangled. A detailed description of the mechanisms of polymer dissolution process can be found elsewhere.[10]

The choice of an appropriate PEO for a drug formulation greatly depends on the solubility of the drug and the desired release rate. For example, a freely soluble drug needs a PEO that quickly forms a strong gel layer on the surface of the tablet so as to regulate the release.

Understanding and utilizing the concepts of drug release modelling enables practical and useful drug design. There are examples of drug release being governed solely by dissolution of the drug molecules. But prevailingly one has to consider diffusion of the drug molecules – after being dissolved – from the delivery system into the surrounding media. Release of soluble drugs from PEO matrices is a rather complex process involving diffusion, swelling and dissolution of the polymer. Various modelling approaches have been employed in order to characterize drug release from hydrophilic matrices.[11,12] Recently, a model has been developed to determine apparent drug diffusivity.[13] The finite element method has been applied to solve the diffusion problem in inert matrices of various geometries.[14] Explicit equations for the rate of movement of the swelling, diffusion and erosion fronts for hydroxypropyl methylcellulose matrices have been derived.[15] Extensive literature overview of the mathematical modelling of drug delivery can be found elsewhere.[16,17] Wu *et al.*[2] developed a model for the characterization of drug release from high-molecular-weight PEOs, taking into account the two-dimensional diffusion of the drug together with the polymer swelling and dissolution. The model presented here is expanded to lower-molecular-weight PEOs and is based on the sequential layer model[18] that describes all the phenomena (water diffusion, swelling, drug diffusion, polymer dissolution and erosion), layer by layer, outer to inner part of the matrix.

Mathematical model

The basic definition of diffusion would be that it represents transport phenomena driven by gradients of the chemical potential. In biological systems the concentration gradient is the driving force of diffusion. Simply put, molecules move from regions of higher concentration to those of lower concentration (i.e. the solvent molecules move *vice versa*, diluting the solution until it reaches a state of equilibrium).

The mathematical theory of diffusion is based on the hypothesis that the rate of transfer of diffusing substance through a unit area of a section is proportional to the concentration gradient measured normal to the section:[19]

$$F = -D\ \delta C/\delta x \tag{1}$$

where F is the rate of transfer per unit area of section, C the concentration of diffusing substance, x the space coordinate measured normal to the section and D is the diffusion coefficient. F and C are usually expressed in the same units (e.g. mass per mass). In cases of diffusion taking place in dilute solutions, D can be assumed to be constant whereas in some other cases it can be concentration or time dependent. D is called the diffusivity or diffusion coefficient and has dimensions length^2/time; cm^2/s.

If one considers diffusion of a drug substance from a cylindrical matrix tablet taking place in three dimensions, Equation 1 should be rewritten as:

$$\delta C/\delta t = D(\delta^2 C/\delta x^2 + \delta^2 C/\delta y^2 + \delta^2 C/\delta z^2) \tag{2}$$

with x, y and z being space coordinates and t being time.

Usually, however, diffusion is assumed to occur in one dimension, transforming Equation 2 into Equation 3 which is, together with Equation 1, also known as Fick's first and second laws of diffusion.

$$\delta C/\delta t = D\,\delta^2 C/\delta x^2 \tag{3}$$

Equations 1 and 3 are most commonly met in the literature; nevertheless they are too simplifying.[19]

In many systems, such as a drug substance diffusing from a polymer matrix, it is necessary to acknowledge that diffusivity, D, changes with the concentration of diffusing species. Thus, one can apply the following equation:

$$\begin{aligned}\delta C/\delta t = {} & (\delta/\delta x)(D\,\delta C/\delta x) + (\delta/\delta y)(D\,\delta C/\delta y) \\ & + (\delta/\delta z)(D\,\delta C/\delta z)\end{aligned} \tag{4}$$

where it is shown how D depends on space coordinates x, y and z, as well as on concentration C. Where the diffusivity coefficient is time dependent, expression is similar to Equation 2 so it will not be shown here. Also, in the model developed here, diffusivities are considered to be time invariant.

Application of Equation 4 to different systems depends greatly on their geometry. For a cylinder-shape matrix tablet with coordinates r, θ and z, Equation 4 becomes:

$$\begin{aligned}\delta C/\delta t = {} & (1/r)[(\delta/\delta r)(rD\,\delta C/\delta r) + (\delta/\delta\theta)(D/r\,\delta C/\delta\theta) \\ & + (\delta/\delta z)(rD\,\delta C/\delta z)]\end{aligned} \tag{5}$$

where r and z denote the radial and axial coordinate of the cylinder, respectively, and θ is the angle perpendicular to both axes. Figure 1 is a schematic plot of the cylindrical matrix tablet described here. As there is no concentration gradient for any component with respect to θ, Equation 5 can be transformed to:

$$\begin{aligned}\delta C_i/\delta t = {} & (\delta/\delta r)(D_i\,\delta C_i/\delta r) + (D_i/r)\,(\delta C_i/\delta r) \\ & + (\delta/\delta z)(D_i\,\delta C_i/\delta z)\end{aligned} \tag{6}$$

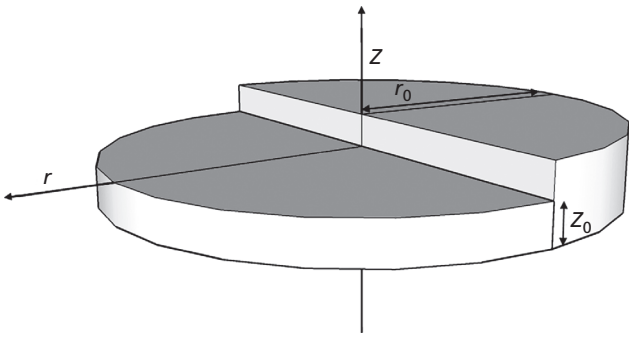

Figure 1 Schematic representation of matrix tablet for mathematical modelling

where i is introduced to distinguish the diffusion of two different species: $i = 1$ for water and $i = 2$ for drug. Ci is therefore the mass concentration of component i within the matrix.

The diffusivities of drug and water are assumed to be concentration-dependent and are represented by a free-volume model proposed by Fujita.[20] The free-volume theory was developed by Cohen and Turnbull to describe liquids and was adapted to polymers by Fujita with later developments by Vrentas and Duda.[21] In the free-volume theory the volume of the polymer is assumed to be apportioned between the occupied volume of the polymer molecules themselves and free volume through which the molecules of the solvent and drug substance move. When the polymer is swollen the solvent also contributes both to the free and occupied volume. For a drug molecule, the diffusion coefficient depends on its size relative to the amount of room it has to move. In the model developed here, Fujita's theory is implied in the terms that the volume of the system is at every time moment equal to the sum of volumes of polymer, water and drug substance. This is particularly important when mass balance calculations are performed, which will be shown later.

Equation 7 shows the concentration-dependent diffusivities of drug and water based on Fujita's theory:

$$D_i = D_{i,e} \exp[-\beta_i(1-C_1/C_{1,e})] \tag{7}$$

where D_i,e is the diffusivity of the water or drug in the fully swollen polymer matrix system – equilibrium state, β is a constant describing concentration dependence of diffusivities and C_1,e is the equilibrium water concentration in the fully swollen matrix.[2] It should be clearly noted that the concentration dependency of diffusivities is based solely on the equilibrium concentration of water as shown in Equation 7. Taking into account the dependency on a drug's concentration as well would be more complex and is not considered in the model developed here.

To obtain D_1,e and β_1 values, experimental data from pure polymer swelling and dissolution studies will be used whereas determination of D_2,e and β_2 values involves fitting the data from drug release studies.

Taking a look at Figure 1 again, one can see that the diffusion of the drug and water molecule will take place in a radial, r, direction and axial, z, direction. A cylindrical matrix has two identical halves with an initial radius of r_0 and initial half-height of z_0. After being immersed into water, a matrix tablet will start to swell in both the axial and radial directions, changing its volume, which gives rise to changed concentration of all of the system components. The increase in volume in the radial direction is only dependent on the amount of water occluding from the radial direction and the same applies to the axial direction. Together with swelling, the polymer also starts to dissolve leading to changed volume again. The swelling and dissolution fronts of the polymer are basically the same and are denominated as a and b for radial and axial directions, respectively. The rate of the advancement of fronts is determined by the amount of water diffusing in the cylindrical matrix, drug diffusing out of it and polymer dissolving from the matrix.

With the above knowledge and taking into account some other points which will be highlighted, the mathematical model can be applied as follows. At the beginning of the process the matrix is dry and the drug substance is uniformly distributed throughout it. The drug concentration is equal to the initial drug concentration, C_0, and the water concentration is equal to zero. This statement is valid for any position within the matrix giving rise to the initial conditions:

$$t = 0 \quad C_1 = 0 \qquad 0 \le r \le r_0 \quad 0 \le z \le z_0 \tag{8}$$

$$t = 0 \quad C_2 = C_0 \qquad 0 \le r \le r_0 \quad 0 \le z \le z_0 \tag{9}$$

where r_0 stands for initial radius of the cylinder and z_0 for the initial half height.

The boundary conditions are:

$$t > 0 \quad C_1 = C_1,e \qquad 0 \le r \le r_t \quad z = z_t \tag{10}$$

$$t > 0 \quad C_1 = C_1,e \qquad 0 \le zz_t \quad r = r_t \tag{11}$$

$$t > 0 \quad C_2 = 0 \qquad 0 \le r \le r_t \quad z = z_t \tag{12}$$

$$t > 0 \quad C_2 = 0 \qquad 0 \le z \le z_t \quad r = r_t \tag{13}$$

$$t > 0 \quad \delta C_1/\delta z = 0 \qquad 0 \le r \le r_t \quad z = 0 \tag{14}$$

$$t > 0 \quad \delta C_1/\delta r = 0 \qquad 0 \le z \le z_t \quad r = 0 \tag{15}$$

$$t > 0 \quad \delta C_2/\delta z = 0 \qquad 0 \le r \le r_t \quad z = 0 \tag{16}$$

$$t > 0 \quad \delta C_2/\delta r = 0 \qquad 0 \le z \le z_t \quad r = 0 \tag{17}$$

where r_t and z_t are time-dependent radius and half height of the matrix cylinder, respectively.

Several points are made with the boundary conditions: water concentration at the water surface of the polymer is constant and equal to the equilibrium concentration C_1,e, stated in Equations 10 and 11. On the other hand, the concentration of the drug at the surface of the matrix after its immersion in the water is always zero, i.e. perfect sink conditions are supposed, shown in Equations 12 and 13.

Swelling fronts a and b in radial and axial directions, respectively, also need boundary conditions. These conditions

can be derived from the previously mentioned volume and mass balance. It is assumed that the whole volume and mass of the system remain the same and are comprised of polymer, water and drug substance. The following equation shows this coherency:

$$2\pi a^2 b = 2\frac{1}{\rho_1}\int_0^b\int_0^a C_1(r,z,t)2\pi r\mathrm{d}r\mathrm{d}z + 2\frac{1}{\rho_2}\int_0^b\int_0^a C_2(r,z,t)2\pi r\mathrm{d}r\mathrm{d}z + \frac{1}{\rho_p}[m_{p,0} - \int_0^t K_p A_s \mathrm{d}t] \quad (18)$$

where ρ_i is the density ($i = 1$ for water, $i = 2$ for drug substance and $i = p$ for polymer); $m_{p,0}$ is the initial mass of the polymer, A_s is the total surface area of polymer matrix in contact with the release medium and K_p is the polymer's dissolution rate constant. We can also put:

$$1/A_s\ \mathrm{d}m_p/\mathrm{d}t = -K_p \quad (19)$$

The dissolution rate constant K_p is used to characterize surface dissolution of the polymer. Equations 18 and 19 are very important for calculation of the changed dimensions of the matrix during the swelling and dissolution processes.

Differentiating Equation 18 and substituting Equation 6 in it, one can get description of the rate of swelling front advancement in r and z directions, respectively:

$$b(1-f_1)\frac{\mathrm{d}a}{\mathrm{d}t} = \frac{1}{\rho_1}\int_0^b D_1\frac{\partial C_1}{\partial r}|_{r=\mathrm{a}}\mathrm{d}z + \frac{1}{\rho_2}\int_0^b D_2\frac{\partial C_2}{\partial r}|_{r=\mathrm{a}}\mathrm{d}z - b\frac{K_p}{\rho_p} \quad (20)$$

$$a^2(1-f_1)\frac{\mathrm{d}b}{\mathrm{d}t} = \frac{1}{\rho_1}\int_0^a D_1\frac{\partial C_1}{\partial z}|_{z=\mathrm{b}}2r\mathrm{d}r + \frac{1}{\rho_2}\int_0^a D_2\frac{\partial C_2}{\partial z}|_{z=\mathrm{b}}2r\mathrm{d}r - a^2\frac{K_p}{\rho_p} \quad (21)$$

where f_1 is the equilibrium volume fraction of water in the fully swollen matrix.[2] The model developed here calculates at the same time the amount of water uptake and dissolution of polymer versus the time during drug release, which is difficult to evaluate experimentally.

Materials and Methods

Materials

The following chemicals were obtained from commercial suppliers: diclofenac sodium (Galenika, Belgrade, Serbia), Sentry Polyox WSR 1105 – LEO NF Grade (Dow Chemical Company, Charleston, USA). Molecular weight of Polyox WSR 1105 is approximately 900 000 (i.e. 0.9×10^6). It is one of the lower molecular weight PEOs. Drug-containing PEO matrices were prepared by compressing a homogeneous mixture of the drug and polymer powders with an excenter tablet press (Ek0 Korsch, Germany). Before compression, polymer and drug were thoroughly manually mixed and the tablet weight was kept constant at 450 mg. Six different batches (F1–F6) were made with different loadings of diclofenac sodium (90%, 80%, 75%, 70%, 60% and 55%, respectively). The composition of tablets is given in Table 1.

Table 1 Composition of the matrices prepared with diclofenac sodium/Polyox WSR 1105

Batch	F1	F2	F3	F4	F5	F6
Diclofenac sodium (% w/w)	90	80	75	70	60	55
Polyox WSR 1105 (% w/w)	10	20	25	30	40	45

Drug release studies

Drug release was studied in a dissolution apparatus (Erweka DT6; Hausenstamm, Germany) using the rotating paddle method (50 rev/min). Phosphate buffer (USP 28), pH 6.8, 900 ml, was used as dissolution medium. Dissolution tests were conducted for 8 h. The amount of diclofenac sodium was determined using a UV spectrophotometer ($\lambda = 275$ nm).

Swelling and dissolution of polymer

Tablets of pure polymer were made using the same method previously described and the weight of wet and dry PEO tablet was monitored as a function of time. Studies of polymer swelling and dissolution were conducted by placing the tablets in a Petri plate containing a previously measured amount of medium. At specific time points tablets were taken out of the plate (for each time point there was one plate with a tablet) and their wet mass was measured. They were then dried until a constant weight was reached. The weight loss was the difference between the original weight of tablet and the weight of dry tablet and the amount of water uptake was the weight difference between the wet tablet and weight of the dry tablet.

Mathematical analysis

The purpose of the mathematical analysis was to calculate the concentration profiles of water and drug within the tablet at certain time points and, by fitting the results to experimental data, to obtain unknown parameters D_1,e and β_i (i = 1 water, i = 2 drug). Because of the concentration dependence of diffusion coefficients, the problem was reduced to evaluation of a set of partial differential equations (Equations 6 and 7) with boundary conditions (Equations 8–17). This was done by applying an explicit finite-difference scheme,[18] in four steps:

Step 1: The time-dependent radius (r_t) and half-height (z_t) of the cylindrical matrix tablet are divided into K and L space intervals, $< r$ and $< z$, respectively, generating a grid of (K + 1) (L + 1) points, or KL segments of the matrix (Figure 2). The time is divided into h short time intervals, $< t$. For most simulations, run in MATLAB program for PC, we had K = L = 50, h = 57 600.

Step 2: Concentration profiles of both diffusing species at the beginning of the process ($t = 0$), at each segment of the matrix, are given by initial conditions (Equations 8 and 9).

Step 3: Knowing concentration profiles at previous time step ($t = t_0$), concentration profiles at the next time step ($t = t_0 + < t$) are calculated, using finite-difference

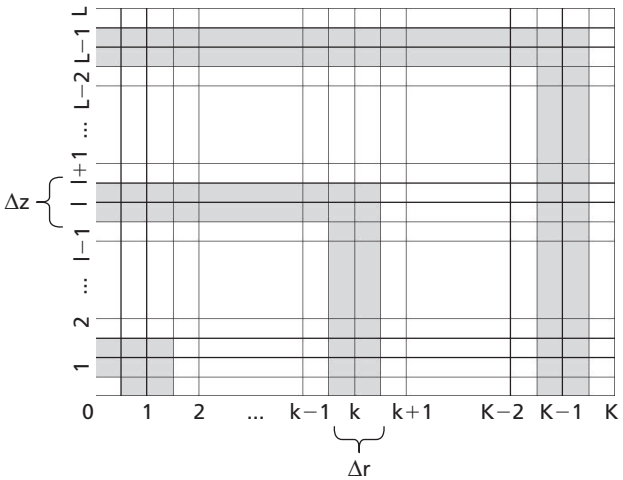

Figure 2 Schematic representation of matrix division into space intervals Δr and Δz

transformation of Equations 6 and 7 and boundary conditions (Equations 10–17). This is done for each segment of the matrix.

Step 4: New dimensions of the tablet are calculated, using Equations 20 and 21, assuming the volume and mass balance of the system, homogeneous swelling, and that volume increase in each direction (both radial and axial) is proportional to the surface area in that direction.

Steps 3 and 4 are repeated over and over, until the concentration profile is known at all time points.

The optimization of unknown parameters D_1,e and β_i (Equation 7) was based on the Nelder–Mead simplex method.[18] D_1,e and β_1 were obtained by fitting the model to experimental data of pure polymer swelling and dissolution studies, and, knowing these values, D_2,e and β_2 were obtained by fitting the model to experimental data from drug release studies.

Both fitting procedures were based on the least squares method. As a measure of the goodness of fit, the coefficient of determination R^2 was calculated:

$$R^2 = 1 - \frac{\sum_{i=1}^{n} \left(y(x)_{i,\exp} - y(x)_{i,theo} \right)^2}{\sum_{i=1}^{n} \left(y(x)_{i,\exp} - y(x)_{arithm} \right)^2} \qquad (22)$$

where $y(x)_{i,\exp}$ and $y(x)_{i,theo}$ are the experimental and theoretical y co-ordinates of a series of n data points, and $y(x)_{arithm}$ is the arithmetic mean of the experimental y co-ordinates of the series.

Results

Swelling and dissolution of pure polyethylene oxide matrices

Water uptake studies of pure PEO tablets were first conducted to determine the diffusion coefficient of water within the fully swollen PEO tablet, D_1,e and constant β_1 describing concentration dependence of diffusivity. The results obtained in the experiments were fitted to the proposed model (Figure 3). The coefficient of determination ($R^2 = 0.9$) indicated a very good fit of the model to the experiments.

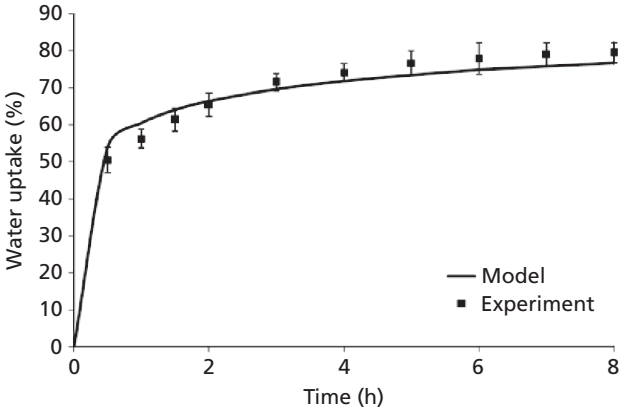

Figure 3 Theoretical and experimental profiles of relative water uptake of pure polyethylene oxide tablets. Uptake is expressed as a function of time after immersion in the medium ($R^2 = 0.9$).

It was found that the diffusivity of water within fully swollen PEO matrices was 3.4×10^{-5} cm^2/s. Studies of water uptake were conducted for 8 h. During this period it was observed that the swelling of the polymer prevailed, and the dissolution started at a later point, with the dissolution rate constant being 1.8×10^{-6} mg/cm^2 s.

Drug release from polyethylene oxide matrices

Diclofenac sodium release from PEO matrices of different drug loadings into phosphate buffer is shown in Figures 4 and 5. The developed model was fitted to the experimentally determined amount of drug released versus time. Figures 4 and 5 demonstrate good agreement of the model to the experimental results.

Drug release was relatively fast and complete from batches F1–F3 with high amounts of diclofenac sodium released, whereas increase in the amount of polymer in batches F4–F6 slowed the release, which was even incomplete for batch F6 (less than 50% of drug released after 8 h).

An interesting finding is shown in Figure 6, demonstrating changes in polymer dissolution rate constant K_p with different drug loadings. It can be seen that for almost all batches, the polymer dissolution rate is approximately 1.5×10^{-6} mg/cm^2 s, which is close to the K_p observed for pure PEO matrices (1.8×10^{-6} mg/cm^2 s). However, batch F3 (75% initial diclofenac sodium loading) showed five times lower K_p, at 0.3×10^{-6} mg/cm^2 s. Similarly, it was observed that there is a change in the equilibrium diffusivity of diclofenac sodium D_2,e, with different initial drug loading. For almost all batches there was an anticipated increase of drug diffusivity with increased initial loading of drug – increase of drug loading implicates decrease of polymer loading and subsequent decrease of amount of gel layer formed on the surface. The release of the soluble molecule diclofenac sodium has to be slowed down by increase of initial loading of polyethylene oxide in matrices. Figure 7

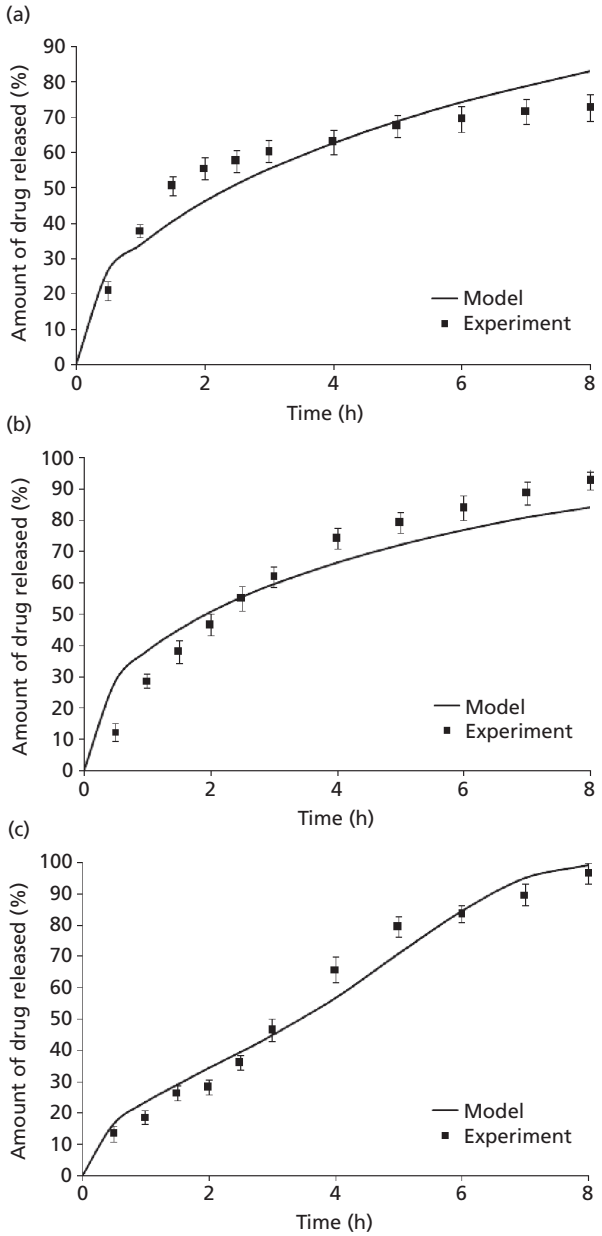

Figure 4 Fit of the model to the experimentally determined amount of diclofenac sodium released from batches with different initial drug loadings. (a) Batch F1 (R^2 = 0.82); (b) batch F2 (R^2 = 0.84); (c) batch F3 (R^2 = 0.93).

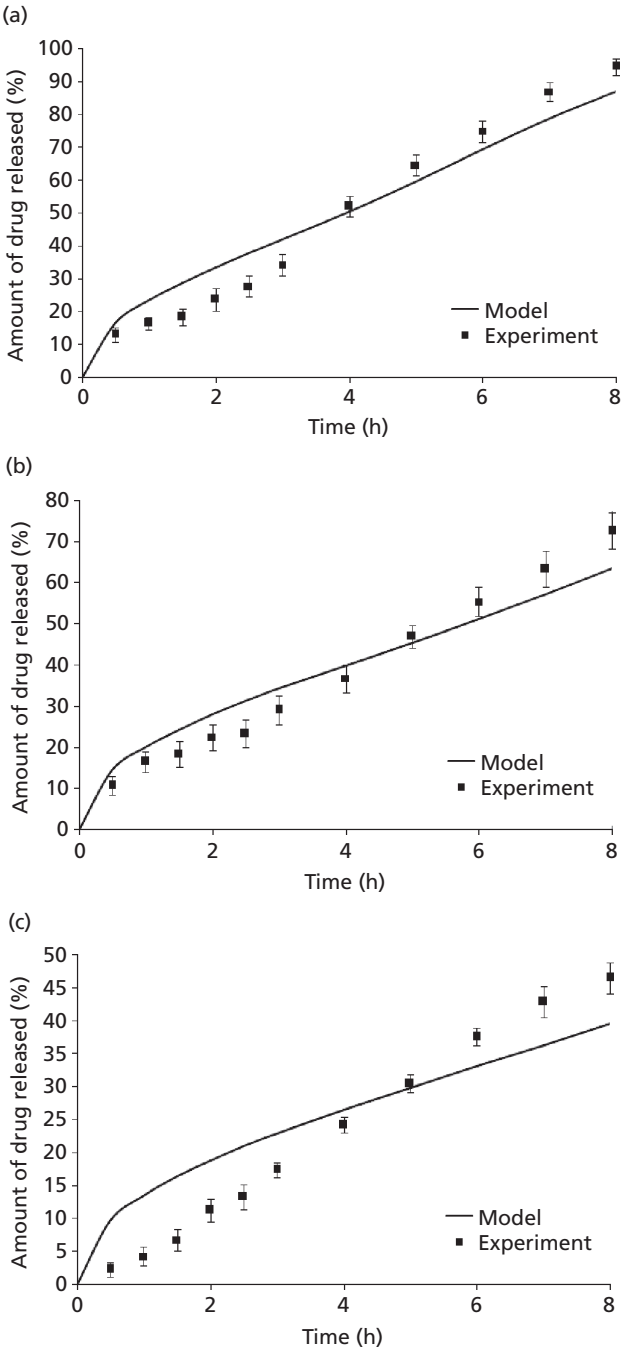

Figure 5 Fit of the model to the experimentally determined amount of diclofenac sodium released from batches with different initial drug loadings. (a) Batch F4 (R^2 = 0.88); (b) batch F5 (R^2 = 0.84); (c) batch F6 (R^2 = 0.80).

demonstrates the observed increase of diffusivity with increased drug loading, with an abrupt decrease of D_2,e for batch F3.

Discussion

Swelling and dissolution of pure polyethylene oxide matrices

For polymer with molecular weight ten times lower we observed diffusivity to be ten times higher compared with the experiments of Wu *et al.*,[2] indicating that PEOs of lower molecular weight have higher values for water diffusivity. Values for water diffusivity coefficients from hydrogels have been reported to vary from 5.0×10^{-6} cm^2/s to 2.0×10^{-5} cm^2/s.[22] The obtained value for water diffusivity in low-molecular-weight PEO suggests that polymeric chains are of appreciable mobility, allowing water to diffuse rather fast. It is important to emphasize that in polymeric systems

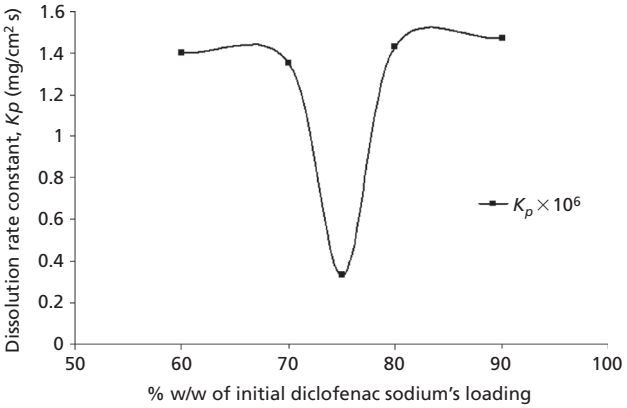

Figure 6 The effect of initial loading of diclofenac sodium on the dissolution rate constant of the polymer

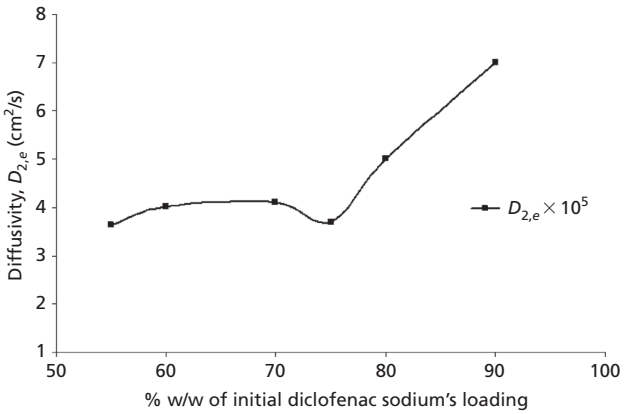

Figure 7 The effect of initial drug loading on it's equilibrium solubility, $D_{2,e}$

subjected to swelling, the diffusion coefficient is not constant, being low in the dry polymer and increasing as the water content increases.[23] The reported water diffusivity coefficient refers to the rate of diffusion of water on the outer surface of the tablet.

Drug release from polyethylene oxide matrices

It is clear that diclofenac sodium release is governed both by swelling and dissolution of PEO, the former being marked in the first stages of the drug release and the latter subsequently. One could expect a zero-order release rate in the case of synchronization of swelling and dissolution,[2] which was not observed in our study.

Results obtained for drug release profiles were expected and the model enables us to calculate the polymer–drug ratio for a satisfactory regime of drug release. For orally administered controlled-release dosage forms it is usually expected that the drug is released within 8 h. In the case of high-molecular-weight PEOs, the sustained release of drug is achieved for a longer period of time, even up to 36 h.[2] In comparison with high-molecular-weight PEOs, lower-molecular-weight PEOs (such as PEO WSR 1105 studied here) provide complete and sustained release of drug for a satisfactory time period.

The observed polymer dissolution rate constant, K_p, and diclofenac sodium equilibrium diffusivity, D_2,e, are in accordance. Sudden decrease in solubility of the polymer led to a decrease in diffusivity of diclofenac sodium. To pass the diffusion front (from solid to dissolved state) drug molecules also have to pass through polymeric chains. When these chains are entangled molecules pass through them slowly. Enhancement of the mobility of polymeric chains and their disentanglement is accomplished by rapid dissolution of polymer. Diffusion anomalies are intimately associated with a glassy–rubbery transition of the polymer.[9] It is possible that there is a critical concentration of polymer in matrices that is responsible for sudden glassy–rubbery transition (i.e. at this concentration of the polymer glass transition temperature T_g is adjacent to experimental temperature and glass transition readily occurs). This critical concentration of the polymer, or threshold, can be described by means of percolation theory[24] as a specific point when polymeric chains have formed a connected network spreading through whole matrix. It is this connected network that rapidly transforms from glassy to rubbery state. Water itself decreases the glass transition temperature of polymers to the experimental temperature.[25] Enhanced mobility of the network of polymeric chains favours the transport of water, further facilitating glassy to rubbery transition. Reaching percolation threshold implies anomalies in diffusivity of the drug and release rate as well as changes in some other characteristics of the tablet (mechanical properties, disintegration time, etc.).[26] Therefore, batch F3 represents a possible percolative matrix system with anomalous drug diffusivity and polymer dissolution rate. It has been shown elsewhere by the authors that usage of empirical models for drug release characterization is also useful for determination of percolation threshold.[27] We demonstrated[27] that using Peppas–Sahlin's equation, as the most adequate empirical model for description of drug release from hydrophilic matrices, it is possible to estimate percolation threshold for PEO. Changes in the relaxational rate constant and dissolution rate constant Kd and Kr were studied and similar change in the release behaviour was shown in that study as in the one presented here. The percolation threshold was found to be at lower percentage weight-for-weight of PEO, which can be attributed to the fact that in the study based on empirical models results greatly depend on experimental setup.

Therefore, in the case of low-weight PEO–diclofenac sodium matrices the optimal polymer ratio for achieving sustained release of diclofenac sodium is in the range of 20–40% w/w, with careful avoidance of formulations close to percolation threshold (batch F3).

Conclusions

It has been shown that it is possible to develop a mathematical model for accurate description of the diffusion of diclofenac sodium from low-molecular-weight PEO matrices. The model is based on simulation of axial and radial diffusion of drug from swelling matrices taking into

account dissolution and disentanglement of the polymer. This model enabled deeper insight into changes in drug diffusion properties from matrices with different initial loadings. It was possible to observe sudden changes in the diffusivity of the drug coupled with changes in solubility of the polymer. Our proposed explanation for this phenomenon is based on percolation theory. The benefit of the developed model lies in the fact that it facilitates selection of the appropriate ratio of PEO in matrices for oral drug delivery. Identification of potentially ambiguous formulations with unexpected values for drug diffusivity is possible. The composition of batches with undesirable release properties can be predetermined and avoided in manufacturing.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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