Research Paper

Parametric simulation of drug release from hydrogel-based matrices

Gaetano Lamberti

Dipartimento di Ingegneria Industriale, Università degli Studi di Salerno, Fisciano (SA), Italy

Abstract

Objectives In this work a model recently proposed to describe the drug release from hydrogel-based matrices was applied to describe the fractional drug release from matrices based on hydroxypropylmethylcellulose (HPMC) and diclofenac.

Methods The model, firstly proposed to describe the behaviour of systems based on HPMC and theophylline and a single set of preparation variables, is based on mass balances and transport phenomena evaluation and it was solved by an FEM-based numerical code. The experimental data on the HPMC–diclofenac matrices, taken from literature, have been obtained by varying the drug loading ratio, the compression force, the powder size of both the drug and the polymer.

Key findings A good agreement between experimental data and model predictions, as calculated in the present work, was obtained without the use of any adjustable parameters.

Conclusions The predictive nature of the model has been confirmed, even changing the drug molecule and other preparative parameters.

Introduction

The drug release from solid matrices is an interesting issue in pharmacology. The kinetics of drug release should be tailored to the therapeutic needs of the body (e.g. to get a constant plasma concentration of a drug, the matrices should give a constant rate of release (the so-called 'zero order' kinetics)).

The process of formulation and testing of novel matrices systems is usually based on a large set of experiments, with the single guide of the formulator experience. By changing each preparative parameter, it is easy to reach a very high number of experimental tests.[1] This is cumbersome and any shortcut would be greatly advantageous.

The mathematical modelling of the phenomena, once the code is fully predictive, could be a tremendous aid in formulation, since it could save resources by substituting experiments with calculations.[2–7] Recently, excellent reviews of the work done have been published.[2,5]

Even though a large amount work has been done in this field, a model able to describe all the phenomena involved in the drug release from matrices based on hydrogels, including the swelling phenomena, which causes a non-affine volume increase (i.e. a deformation in matrix's shape), has been proposed only very recently.[3] This model, however, has been validated by comparison only with the experimental behaviour of a hydroxypropylmethylcellulose (HPMC)–

theophylline system. Its ability to predict the behaviour of different systems (different drugs, different preparative conditions) should be tested. A success in this kind of test would confirm the model's usefulness and would constitute a precious and novel piece of information.

The aim of this work is thus to test a model, previously described and found to be able to capture all the phenomena observed during the release of a drug from a hydrogel-based matrix, by comparison with a large set of experimental data taken from literature, to check the model's ability to predict observed drug release kinetics.

Materials and Methods

Modelling

The transport of water and drug in the matrix can be viewed as two pseudo-diffusion phenomena, which can be described by two transient mass balances ($k = 1$ for the water and 2 for the drug). The balances should to take into account the mass accumulation and the transport phenomena that takes place.

$$\rho \frac{\partial \omega_k}{\partial t} = \vec{\nabla} \cdot \left(\rho D_k \vec{\nabla} \omega_k \right) \qquad (1)$$

In Equation 1, the matrix density is ρ, ω_k is the water and drug mass fraction, D_k is the pseudo-diffusion coefficient.

The initial conditions for integration are given by Equation 2, in which Ω is the integration domain (i.e. the matrix) and $\omega_{k,0}$ is the initial homogeneous mass fraction of water ($k = 1$) and drug ($k = 2$).

$$@t = 0 \quad \forall \vec{x} \in \Omega \quad \omega_k(t = 0, \vec{x}) = \omega_{k,0} \qquad (2)$$

The boundary conditions are defined on the moving boundary $\Gamma(t)$, and they are given by Equation 3.

$$@\vec{x} \in \Gamma(t) \quad \forall t > 0 \quad \omega_k(t > 0, \vec{x} \in \Gamma(t)) = \omega_{k,eq} \quad (3)$$

In Equation 3, $\omega_{k,eq}$ is the equilibrium values for water ($k = 1$) and drug ($k = 2$) mass fraction. The moving boundary, $\Gamma(t)$, is represented by the erosion front (the interface between the matrix and the dissolution medium) both for the water and the drug.

To solve Equation 1, the pseudo-diffusion coefficients, D_k (for $k = 1, 2$), have to be evaluated, accounting for the increase in diffusivity due to the hydration[8]:

$$D_k(\omega_1) = D_k^\star \cdot \exp\left[-\beta_k \cdot \left(1 - \frac{\omega_1}{\omega_{1,eq}}\right)\right] \qquad (4)$$

where $D_k^\star / \exp(\beta_k)$ is the value (for $k = 1$, 2) of the pseudo-diffusion coefficients in the dry matrix ($\omega_1 = 0$), and $D_k^\star$ is the value of the pseudo-diffusion coefficients in the fully swollen matrix ($\omega_1 = \omega_{1,eq}$).

The density of the partially hydrated matrix can be calculated by the simplest mixing rule, which can be written for the specific volume:

$$\frac{1}{\rho} = \frac{\omega_1}{\rho_1} + \frac{\omega_2}{\rho_2} + \frac{1 - \omega_1 - \omega_2}{\rho_3} \qquad (5)$$

where ρ_1, ρ_2 and ρ_3 are the water, the drug and the polymer densities, respectively.

The water uptake causes matrix swelling, and the polymer disentanglement at the matrix surface causes the matrix erosion. Thus, these two phenomena, swelling and erosion, cause the matrix surface to be a moving boundary. Therefore, there is the need for modelling the two phenomena, with the aim of obtaining the function $\Gamma(t)$. Thus, the movement of a surface element is due to the swelling phenomenon (which causes the increase of the matrix size) and to the erosion phenomenon (which causes the decrease of the matrix size). In terms of element velocity, v, the governing equation is:

$$v = v_{swe} + v_{eros} \qquad (6)$$

in which v_{swe} is the size-increase velocity due to the swelling (a positive value) and v_{eros} is the size-decrease velocity due to the erosion (a negative value). The swelling phenomenon has been modelled by:

$$v_{swe} = \frac{d\delta}{dt} = -\frac{j_{1,swe}}{\rho} = -\frac{k_{swe} j_{1,diff}}{\rho} \qquad (7)$$

In Equation 7, $j_{1,diff}$ is the flux of water due to pure diffusive transport (i.e. due to the concentration gradient), and $j_{1,swe}$ is the flux of water that is required by the swelling phenomenon (i.e. the water that remains in the gel networks after the swelling). The basic idea of the modelling is that the swelling contribution is taken as proportional to the diffusion contribution, by the model parameter k_{swe}.

The boundary movement velocity due to the erosion phenomenon is accounted for as a constant velocity, since the erosion is a phenomenon dictated by chemical and physical features of the interface between the matrices and the outer medium, and these features are constant along all the process:

$$v_{eros} = -k_{eros} \qquad (8)$$

In Equation 8, k_{eros} is a proper constant, and the minus sign accounts for the inward nature of the erosion. More details on the model can be found in Lamberti et al.[3] Both k_{swe} and k_{eros} have been optimized by comparison with experimental data in the original work. The equations code were solved by COMSOL Multiphysics 3.4 (Copyright © 1994–2007 by COMSOL AB, Tegnérgatan 23, Stockholm), using the parameter values summarized in Table 1.

Experimental procedure

The experimental data were taken from literature.[1] Authors mixed HPMC K15M (the same polymer used by Lamberti et al.[3]), with diclofenac sodium. Tablets were prepared by direct compression of the drug and the polymer, thoroughly

Table 1 The values of the model parameters used for model simulations (no one of these values was optimized in this work)

Variable and units of measurement		Value	Variable and units of measurement		Value
β_1	Diffusive coefficient, 1	3	β_2	Diffusive coefficient, 2	9
$\omega_{1,eq}$	Equilibrium water fraction	0.97	$\omega_{2,eq}$	Equilibrium drug fraction	0
$D_1^\star$	Critical water diffusivity (cm^2 s^{-1})	$1.6 \cdot 10^{-6}$	$D_2^\star$	Critical drug diffusivity (cm^2 s^{-1})	$1.5 \cdot 10^{-6}$
k_{swe}	Swelling constant	5.32	k_{eros}	Erosion constant (cm·s^{-1})	$1.97 \cdot 10^{-7}$

mixed with low amounts of magnesium stearate and Aerosil 200. The process parameters changed were the drug : polymer ratio (1 : 1 and 1 : 2), the compression force (3, 6, 9 and 12 kN), the drug size fraction (75–180, 180–250 or 250–355 µm) and the polymer size fraction (45–75, 75–150 or 150–250 µm). The total number of runs was therefore $2 \times 3 \times 3 \times 4 = 72$. For each test, the dissolution of the drug was carried out in triplicate in 1000 ml of distilled water at 37°C in a USP Apparatus I (basket), rotating at 50 rpm, following the drug release by an UV spectrometer working at $\lambda = 276$ nm. The fractional release of the drug was fitted by several equations. The drug release from the different tests is reported in terms of the parameters of such equations (the real experimental data were not present in Velasco et al.[1]). It is worth noting that only the early stage of the drug release, up to 80% of the total amount, was correctly reproduced. The geometry of the matrices was of a cylinder, with a radius of 3 mm and a thickness differing for each run, which was reported in the original paper. Therefore, the simulation of each one of the runs carried out by Velasco et al.,[1] and comparison of the code calculations with the release kinetics, could be carried out, since all the data needed are presented in the original paper.[1]

Results and Discussion

Fractional drug release obtained during some of the test runs carried out by Velasco et al.[1] are reported in Figure 1. The drug size and the polymer size were unchanged among them

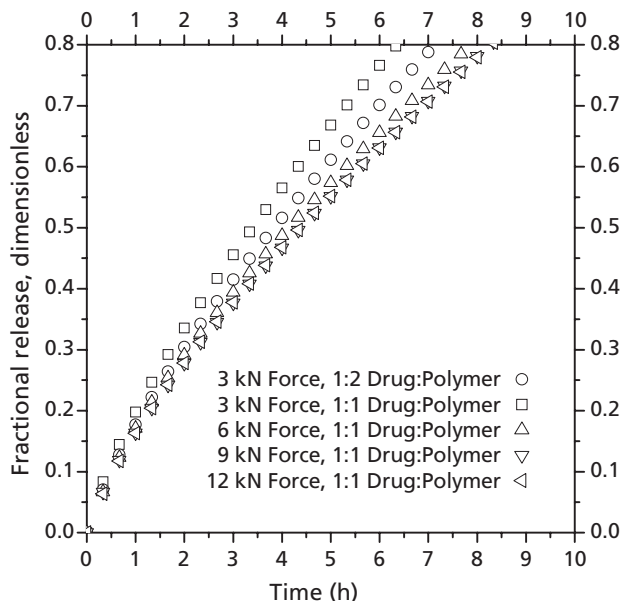(respectively, 75–150 µm and 45–75 µm). The parameters that were changed are thus the drug : polymer ratio and the compression force. It is evident that the increase in polymer content (from 1 : 1 to 1 : 2) causes the fractional drug release to be lower. An increase in the compression force does not cause important effect – as the compression force increases, the kinetics decrease, but it is a very small effect.

The model proposed by Lamberti et al.[3] was applied as is (i.e. without any further optimization procedure for model parameters). In Figure 2 it is evident that the model was able to capture the behaviour of the systems varying the drug : polymer ratio (the parameter which was found to be the most important in changing drug release kinetics). The good correlations between the experimental data and the model predictions were statistically confirmed by the values of the Pearson's coefficient R^2 (the closer R^2 to 1, better the correlation). For the drug : polymer = 1 : 1 system, $R^2 = 0.9995$ and for the drug : polymer = 1 : 2 system, $R^2 = 0.9973$. The small effect that arises by increasing the compression force was not reproduced. The data obtained during a test carried out under completely different conditions (i.e. compression force of 12 kN, a drug size range of 250–355 µm and a polymer size range of 150–250 µm) are reported in Figure 3 along with the model predictions. In this case the agreement is a little worse, even though the Pearson's coefficient was good, $R^2 = 0.9976$. The model prediction capabilities were thus confirmed under very different conditions.

Therefore the model, which was tuned by comparison of a large set of experimental data as reported in Lamberti et al.[3] working with matrices based on HPMC : theophylline = 1 : 1
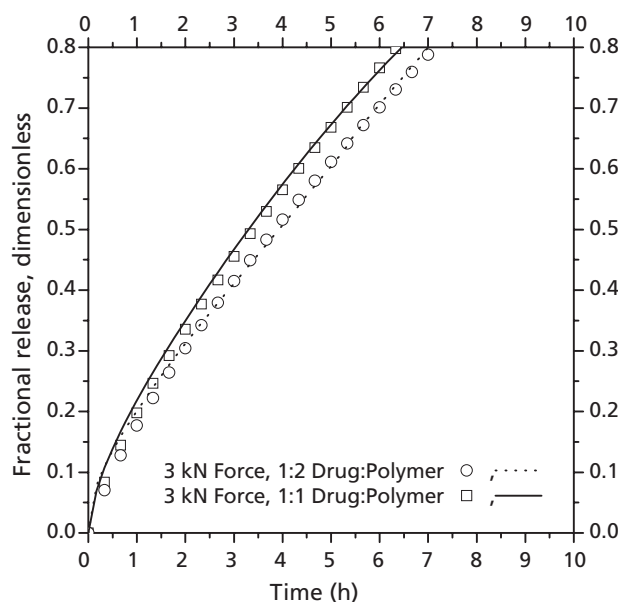

Figure 1 Experimental fractional drug release for some of the runs carried out by Velasco et al.[1] For all of these runs, the drug size was 75–150 µm and the polymer size was 45–75 µm.

Figure 2 Fractional drug release evolutions for two of the experimental tests (symbols) along with the model calculations (lines).
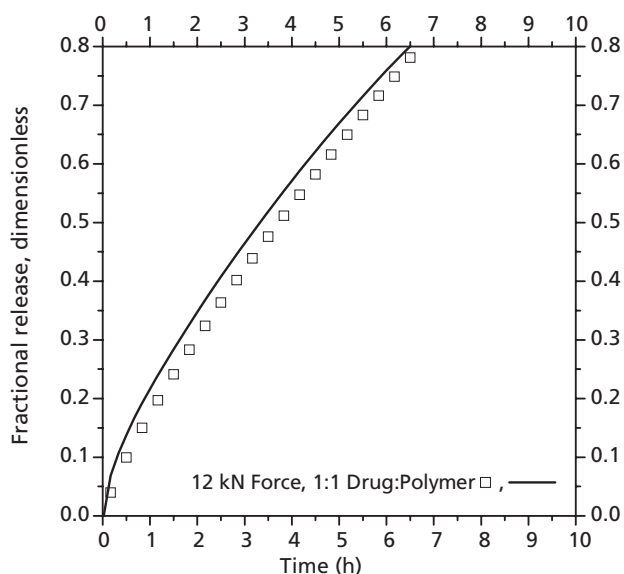
Figure 3 Fractional drug release evolutions for one of the experimental tests (symbols) along with the model calculations (lines). For this run, the drug size was 250–355 μm and the polymer size was 150–250 μm.

(one value of compression force, the original size distributions for the polymer and the drug), was found able to predict the behaviour of different systems based on HPMC (several powder sizes) : diclofenac sodium (several powder

sizes) = 1 : 1 or 1 : 2, obtained by several compression forces. This means that a model, found to be *descriptive* of the phenomena that occur during the release from hydrogel-based matrices, was found to be *predictive* of the drug release kinetics for a different system. This could be a result of huge importance in formulation science.

Conclusions

A rich data set taken from literature in terms of the effect of preparative process parameters on drug release kinetics from hydrogel-based solid matrices[1] was used as the basis to test a model, previously used to work with a different system.[3]

The model, which in its first application was found to be fully *descriptive* (i.e. able to capture all the phenomena observed in the real experiments), in this case was proved to be fully *predictive*, since it was able to describe the observed drug release kinetics, even when varying the preparative process parameters, without the need for adjustable parameters. It is worth noting that, so far, the model has been successfully applied only to HPMC-based systems. Further validation is still needed for different hydrogels, even if the expected behaviour should be the same.

Therefore, the model could be used in industrial practice, as an aid in predicting drug release kinetics, avoiding cumbersome experimental tests, at least for testing HPMC-based systems.

References

1. Velasco M *et al*. Influence of drug: hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. *J Control Release* 1999; 57: 75–85.
2. Grassi M, Grassi G. Mathematical modelling and controlled drug delivery: matrix systems. *Curr Drug Deliv* 2005; 2: 97–116.

3. Lamberti G *et al*. Controlled release from hydrogel-based solid matrices. A model accounting for water up-take, swelling and erosion. *Int J Pharm* 2011; 407: 78–86.
4. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Deliv Rev* 2001; 48: 139–157.
5. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. *Int J Pharm* 2008; 364: 328–343.

6. Grassi M *et al*. Modeling of drug release from a swellable matrix. *Chem Eng Commun* 1998; 169: 79–109.
7. Wu L, Brazel CS. Mathematical model to predict drug release, including the early-time burst effect, from swellable homogeneous hydrogels. *Ind Eng Chem Res* 2008; 47: 1518–1526.
8. Siepmann J *et al*. A new model describing the swelling and drug release kinetics from hydroxypropyl methylcellulose tablets. *J Pharm Sci* 1999; 88: 65–72.