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Drug release modeled by dissolution, diffusion, and immobilization

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Abstract

This article presents a novel drug release model that combines drug dissolution, diffusion, and immobilization caused by adsorption of the drug to the tablet constituents. Drug dissolution is described by the well-known Noyes–Whitney equation and drug adsorption by a Langmuir–Freundlich adsorption isotherm, and these two processes are included as source and sink terms in the diffusion equation. The model is applicable to tablets that disintegrate into a number of approximately spherical fragments. In order to simplify the analysis it is assumed that liquid absorption, matrix swelling, and tablet disintegration are much faster than drug dissolution and subsequent drug release. The resulting model is shown to yield release characteristics in good agreement with those observed experimentally.

Keywords: Drug release; Diffusion; Modelling; Tablets

1. Introduction

The most well-known mathematical model of drug release from matrix systems is perhaps the Higuchi equation, first published in 1961 for planar systems (Higuchi, 1961) and later extended to other geometries (Higuchi, 1963). After Higuchi's pioneering work, much effort has been devoted to the mathematical description of the drug release process (see, e.g. Siepmann and Peppas, 2001 and references therein). Recently Siepmann and Peppas, among others, have published a series of papers dealing with the mathematical modelling of drug release from delivery systems based on hydroxypropyl methylcellulose (Siepmann et al., 1999a,b, 2000; Siepmann and Peppas, 2000; Siepmann et al., 2002). These authors have developed a detailed model combining matrix swelling, diffusion, and polymer dissolution.

However, although the effect of drug dissolution has been included to some extent in an improved 'sequential layer' model (Siepmann and Peppas, 2000; Siepmann et al., 2002), we think that this phenomenon is modeled in a simplistic way only. Furthermore, to the best of our knowledge, perfect sink conditions have almost universally been

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assumed in all drug release modeling. Hence the existing models may not be predictive when drug absorption is permeability limited or when liquid is in shortage, especially if the drug is rather insoluble. Recently, the release of sodium chloride (NaCl) from disintegrating tablets made of agglomerated micronized cellulose (AMC) has been shown to exhibit a delay, and the delay time was found to increase in shortage of liquid (Frenning et al., 2002). Since the delay time was larger than the liquid absorption, matrix swelling, and tablet disintegration times, it cannot be explained by existing drug release models.

In this article we present a new model combining drug dissolution, diffusion, and immobilization caused by adsorption of the drug to the tablet constituents, under the assumption that liquid absorption, matrix swelling, and tablet disintegration are much faster than drug dissolution and subsequent drug release. This model is offered as one possible explanation for the observed delay in the NaCl release from AMC tablets, and is shown to yield release characteristics in good agreement with those observed experimentally.

2. Experimental

2.1. Tablet preparation and characterization

Microcrystalline cellulose (Avicel PH 101, Lot 6536, FMC, USA) was ground with a mortar grinder (Retsch KMI, Retsch AG, Germany) until the thread shaped cellulose disappeared as observed by light microscopy. The micronized cellulose was suspended in water, in which NaCl (crystalline, puriss, Rectapur F80G, KEBO, Sweden) was dissolved, and was then spray dried (Minor, Niro Atomiser, A/S, Denmark) to yield NaCl containing AMC powder. The NaCl content was 30 wt.%. Tablets were compressed in a single punch tablet machine (Korch EKO, Germany) equipped with 11.3 mm punches. The powder was carefully weighed and manually poured into the die for each tablet. The motor was started (30 rev/min) with the upper punch in its highest position and the motor was stopped and the flywheel manually arrested immediately after each compression. During compression, the upper punch pressure was recorded. No lubrication was used. The maximal compression pressure was 101.6 ± 4.5 MPa (mean values $\pm$ standard deviation), and the tablet weight and height were 325 ± 2 mg and 2.72 ± 0.02 mm, respectively. Environmental scanning electron microscopy showed that the tablets consisted of ~ 20 μm AMC granules, in which smaller (~ 2 μm) NaCl crystals were dispersed.

2.2. Alternating ionic current measurements

Drug release experiments were performed by using the alternating ionic current method (Frenning et al., 2002). The experimental set-up consisted of a liquid container $3 \times 3 \times 3$ cm^3 in a propylene carbonate unit, with silver electrodes mounted on two of its sides. The liquid container was filled with 10 ml distilled water. The tablet to be studied was put in the liquid and the drug release was monitored by measuring the conductance of the liquid as a function of time. During the whole measurement, the liquid was mixed by a 5 mm magnet located in the corner of the liquid container, by using a Metrohm 728 Stirrer (Metrohm Ltd, Herisau, Switzerland) set at rotation speed 3.

The conductance of the liquid was determined by using voltage division. The measuring cell was connected in series with a 100 Ω resistor to the voltage source (HP3325A, Hewlett-Packard, Palo Alto, USA), which gave a sinusoidal voltage of frequency 10.0 kHz and nominal amplitude 1.0 V. Since the output voltage decreased somewhat with increasing current conducted through the circuit, both the output voltage and the voltage across the 100 Ω resistor was measured by using digital multimeters (HP34401A, Hewlett-Packard), and from the readings the conductance of the liquid was calculated. The instruments were remotely controlled by a PC by using HPVEE and a GPIB interface.

3. Theory

In this section we derive general equations describing drug dissolution and subsequent drug

release from a tablet under the following assumptions: (i) The tablet contains a large number of drug crystals, of approximately the same size and shape, dispersed into an insoluble matrix. (ii) In contact with water the tablet breaks up into a number of approximately spherical tablet fragments. (iii) Liquid absorption and tablet disintegration are much faster than drug dissolution. Accordingly, the initial state is characterized by virtually complete liquid absorption, matrix swelling, and disintegration but negligible drug dissolution. (iv) The surrounding liquid is well mixed, so that its concentration is independent of the space coordinates.

3.1. Fundamental equations

Since all tablet fragments are assumed to have approximately the same size and shape, it suffices to consider the release from one fragment only. Our starting point is the equation of continuity (Landau and Lifshitz, 1987), which relates the concentration of dissolved and mobile drug $c(t, \mathbf{x})$ within the tablet fragment (expressed as mass per unit volume) to the drug flux $\mathbf{j}(t, \mathbf{x})$ and the average source density $R(t, \mathbf{x})$, i.e.

$$\frac{\partial c}{\partial t} + \nabla \cdot \mathbf{j} = R. \tag{1}$$

As usual, t and $\mathbf{x}$ denote the time and space coordinates, respectively. In order to simplify the description of the release process, the source density R represents an average over a volume much smaller than the tablet fragment but large enough to accommodate many drug crystals. Consequently, the particulate nature of the drug crystals is not considered explicitly, and the drug is instead assumed to be evenly distributed within the tablet fragment.

Assuming the drug flux within each fragment to be caused by diffusion we can use Fick's law (Bard and Faulkner, 2001), with a possibly concentration-dependent chemical diffusion coefficient $D(c)$, to describe the flux, i.e.,

$$\mathbf{j} = -D\nabla c. \tag{2}$$

For drug diffusion in polymers it has been found that the diffusion coefficient, at least in a limited concentration range, decreases exponentially with increasing drug concentration (Masaro and Zhu, 1999). We use this observation as starting point and assume that the diffusion coefficient for high concentrations approaches a nonzero constant value. Accordingly, we express the diffusion coefficient as

$$D = D_0[(1-\varepsilon)\exp(-bc) + \varepsilon], \tag{3}$$

where D_0, b, and ε are positive constants. The constant D_0 represents the value of the diffusion coefficient at infinite dilution (i.e., $D \to D_0$ when $c \to 0$), ε characterizes its limiting value for high concentrations (i.e., $D \to \varepsilon D_0$ when $c \to \infty$), and b characterizes the concentration dependence.

There are, in principle, two possible contributions to the average source density. When drug initially present in solid crystal form dissolves, the concentration of dissolved and mobile drug within the tablet fragment obviously increases. Drug dissolution, therefore, gives a positive contribution $R_\mathrm{d}(t, \mathbf{x})$ to the average source density R. Furthermore, some of the dissolved drug may be adsorbed to the tablet constituents and, hence, become immobilized. The adsorption process, thus, gives a negative contribution $-R_\mathrm{b}(t, \mathbf{x})$ to the source density R. Taking both contributions into account, the total source density is written as

$$R = R_\mathrm{d} - R_\mathrm{b}. \tag{4}$$

The dissolution process is described by the well-known Noyes–Whitney equation (Noyes and Whitney, 1897), averaged over a small volume,

$$R_\mathrm{d} = k_\mathrm{d}\overline{A}(c_\mathrm{s} - c). \tag{5}$$

In Eq. (5), k_d is a dissolution rate constant, c_s is the solubility of the drug, and $\overline{A}(t, \mathbf{x})$ denotes the average surface area of undissolved drug per unit volume (we use the convention that a bar drawn above a quantity designates the value of that quantity per unit volume, i.e., a density).

In order to describe the adsorption process, let us first note that the adsorption rate can be written as the time derivative of the amount adsorbed drug per unit volume, denoted by $s(t, \mathbf{x})$, i.e.,

$$R_b = \frac{\partial s}{\partial t}. \tag{6}$$

If the adsorption by which the drug becomes immobilized proceeds very rapidly in comparison with the diffusion process, local equilibrium can be assumed to exist between the mobile and immobilized components of the diffusing substance (Crank, 1979). This equilibrium may be described by an adsorption isotherm, that gives the functional relationship between the adsorbed and mobile drug concentrations. Assuming that a certain amount c_b can be adsorbed per volume tablet, and using a Langmuir–Freundlich adsorption isotherm (Sips, 1948; Koble and Corrigan, 1952; Rudziński et al., 1996) to describe the adsorption, we obtain that the ratio between the amount of adsorbed drug per unit volume to the maximum amount that is physically possible to adsorb is given by

$$\frac{s}{c_b} = \frac{(k_b c)^\delta}{1 + (k_b c)^\delta}. \tag{7}$$

Here k_b is the adsorption constant. The heterogeneity parameter δ appearing in Eq. (7) is a measure of the width of the distribution of adsorption energies, and assumes a value between zero (wide distribution) and unity (narrow distribution) (Sips, 1948). Inserting Eq. (7) into Eq. (6) we find that the adsorption rate can be expressed as

$$R_b = k_b c_b \delta \frac{(k_b c)^{\delta-1}}{[1 + (k_b c)^\delta]^2} \frac{\partial c}{\partial t}. \tag{8}$$

Collecting our results, we find by combining Eqs. (1)–(5) and Eq. (8) that the mobile drug concentration obeys the nonlinear inhomogeneous diffusion equation

$$\left(1 + k_b c_b \delta \frac{(k_b c)^{\delta-1}}{[1 + (k_b c)^\delta]^2}\right) \frac{\partial c}{\partial t} = D_0 \nabla \cdot \{[(1-\varepsilon)\exp(-bc) + \varepsilon]\nabla c\} + k_d \overline{A}(c_s - c). \tag{9}$$

We next want to relate the average surface area of undissolved drug $\overline{A}(t, \mathbf{x})$ to the mobile drug concentration $c(t, \mathbf{x})$. Since all drug crystals are assumed to have approximately the same size and shape, we obtain from purely geometrical considerations that the area is proportional to the volume, and hence the mass, to the power of 2/3, i.e.

$$\frac{\overline{A}}{\overline{A_0}} = \left(\frac{\bar{m}}{\bar{m}_0}\right)^{2/3}, \tag{10}$$

where $\bar{m}(t, \mathbf{x})$ denotes the average mass of undissolved drug per unit volume, and the indexed quantities denote the initial values. Similar assumptions have been made previously in order to calculate the dissolution rate of dispersed materials (Hixson and Crowell, 1931; Edwards, 1951). Since the source density R_d is a measure of the magnitude of the decrease of undissolved mass per unit volume per unit time, we obtain from Eq. (5) that

$$\frac{\partial \bar{m}}{\partial t} = -R_d = -k_d \overline{A}(c_s - c). \tag{11}$$

By combining Eqs. (10) and (11) we then obtain an equation for the average surface area of undissolved drug as

$$\frac{1}{\overline{A_0}} \frac{\partial \overline{A}}{\partial t} = -\frac{2}{3} \frac{k_d \overline{A_0}}{\bar{m}_0} \left(\frac{\overline{A}}{\overline{A_0}}\right)^{1/2} (c_s - c). \tag{12}$$

When supplemented with appropriate initial and boundary conditions, Eqs. (9) and (12) provide the mathematical description of the drug release process.

3.2. Spherical symmetry

As already mentioned, we assume that the tablet after swelling disintegrates into a number N of approximately spherical tablet fragments, each with a radius a. It is convenient to use spherical coordinates (r, θ, φ), with the origin at the center of the tablet fragment, to describe the release process. The volume of the tablet fragment is V_{sph}, and the volume of liquid surrounding all tablet fragments is V_{sol}. Since each tablet fragment has a spherical symmetry, the mobile drug concentration is a function of time and the radial coordinate only, i.e., $c = c(t, r)$. Writing Eq. (9) in spherical coordinates then results in

$$\left(1+k_b c_b \delta \frac{(k_b c)^{\delta-1}}{[1+(k_b c)^{\delta}]^2}\right)\frac{\partial c}{\partial t} = \frac{D_0}{r^2}\frac{\partial}{\partial r}\left(r^2[(1-\varepsilon)\exp(-bc)+\varepsilon]\frac{\partial c}{\partial r}\right) + k_d \overline{A}(c_s - c). \quad (13)$$

From the fact that the concentration is finite everywhere, with finite derivatives, we immediately obtain one boundary condition as

$$\left.\frac{\partial c}{\partial r}\right|_{r=0} = 0, \quad t > 0. \quad (14)$$

We assume that a partition coefficient γ exists between the mobile drug inside the tablet fragment and in the solution, i.e., that the mobile drug concentration in the tablet fragment in equilibrium is γ times that of the solution. If $c_{sol}(t)$ denotes the drug concentration in the surrounding solution at time t the second boundary condition then becomes

$$c(t,\ a) = \gamma c_{sol}(t). \quad (15)$$

The boundary condition Eq. (15) may be expressed without reference to the external concentration $c_{sol}(t)$. Let us to this end first note that $c_{sol}(t)$ can be written as

$$c_{sol}(t) = \frac{m_{sol}(t)}{V_{sol}}, \quad (16)$$

where $m_{sol}(t)$ is the mass of drug present in the surrounding liquid at time t. The rate of change of $m_{sol}(t)$ is computed from the total flux out from all N tablet fragments, i.e.,

$$\frac{dm_{sol}}{dt} = N\int_{r=a} \mathbf{j}\cdot d\mathbf{s} = -4\pi a^2 N D \left.\frac{\partial c}{\partial r}\right|_{r=a}, \quad (17)$$

where the second equality follows from Fick's law Eq. (2). By using Eqs. (16) and (17) the boundary condition Eq. (15) can be rewritten as

$$\frac{dc(t,\ a)}{dt} = -3\frac{\gamma\rho}{a} D \left.\frac{\partial c}{\partial r}\right|_{r=a}. \quad (18)$$

In Eq. (18) we have introduced the dimensionless parameter

$$\rho = \frac{N V_{sph}}{V_{sol}}, \quad (19)$$

which is the ratio between the total volume occupied by the tablet fragments and the volume of the surrounding solution.

3.3. Dimensionless form

In order to more clearly bring out the structure of the problem to be solved, and to reduce the number of independent parameters, it is instructive to write the equations in a dimensionless form. Let us to this end introduce the dimensionless dependent variables

$$\psi = \frac{c}{\bar{m}_0} \quad \text{and} \quad \alpha = \frac{\overline{A}}{\overline{A}_0}, \quad (20)$$

which are normalized measures of the mobile drug concentration and the surface area of the undissolved drug per unit volume, respectively. To scale the problem it is convenient to introduce the dimensionless independent variables

$$\tau = \frac{D_0 t}{a^2} \quad \text{and} \quad \xi = \frac{r}{a}, \quad (21)$$

together with the dimensionless parameters

$$\beta = \bar{m}_0 b, \quad \psi_b = \frac{c_b}{\bar{m}_0}, \quad \kappa_b = \bar{m}_0 k_b, \quad \kappa_d = \frac{k_d a^2 \overline{A}_0}{D_0}, \quad \text{and} \quad \psi_s = \frac{c_s}{\bar{m}_0}. \quad (22)$$

Let us, furthermore, introduce the auxiliary function

$$g(\psi) = 1 + \kappa_b \psi_b \delta \frac{(\kappa_b \psi)^{\delta-1}}{[1+(\kappa_b\psi)^{\delta}]^2} \quad (23)$$

and the auxiliary variable

$$\Psi(\psi) = \int^{\psi}[(1-\varepsilon)\exp(-\beta\psi') + \varepsilon]d\psi' = -\frac{(1-\varepsilon)}{\beta}\exp(-\beta\psi) + \varepsilon\psi, \quad (24)$$

where the constant of integration has been omitted since only the derivative of $\Psi(\psi)$ will be used in the

following derivation. Expressed in these dimensionless variables Eq. (13) and Eq. (12) take the form

$$g(\psi)\frac{\partial\psi}{\partial\tau}=\frac{1}{\xi^2}\frac{\partial}{\partial\xi}\left(\xi^2\frac{\partial\Psi}{\partial\xi}\right)+\kappa_{\mathrm{d}}\alpha(\psi_{\mathrm{s}}-\psi), \tag{25a}$$

$$\frac{\partial\alpha}{\partial\tau}=-\frac{2}{3}\kappa_{\mathrm{d}}\alpha^{1/2}(\psi_{\mathrm{s}}-\psi), \tag{25b}$$

while the boundary conditions Eq. (14) and Eq. (18) become

$$\left.\frac{\partial\psi}{\partial\xi}\right|_{\xi=0}=0, \tag{26a}$$

$$\frac{\partial\psi(\tau,\ 1)}{\partial\tau}=-3\gamma\rho\left.\frac{\partial\Psi}{\partial\xi}\right|_{\xi=1}. \tag{26b}$$

The initial conditions, obtained from the assumption that all drug is undissolved in the initial state, can be stated as

$$\psi(0,\ \xi)=0, \tag{27a}$$

$$\alpha(0,\ \xi)=1. \tag{27b}$$

We finally note that the drug concentration in the solution surrounding the tablet fragments can be expressed in dimensionless form as

$$\psi_{\mathrm{sol}}(\tau)\equiv\frac{c_{\mathrm{sol}}}{\bar{m}_0}=\frac{\psi(\tau,1)}{\gamma}, \tag{28}$$

according to Eq. (15).

3.4. Numerical solution

Since Eqs. (25a) and (25b) are highly nonlinear, there exists no analytical solution. Therefore, these equations were solved numerically, by using finite differences (Golub and Ortega, 1992). The interval $0<\tau<\tau_{\max}$ (where $\tau_{\max}$ is the maximal value of τ considered in the calculation) was divided into K subintervals each of length $\Delta\tau$, and the interval $0<\xi<1$ was divided into L subintervals each of length $\Delta\xi$. In this way a grid of points $(\tau_k,\ \xi_l)$ was generated, where $\tau_k=k\Delta\tau$ $(k=0,\ldots,\ K)$ and $\xi=l\Delta\xi$ $(l=0,\ldots,\ L)$. The approximate solutions to Eqs. (25a) and (25b) at each grid point $(\tau_k,\ \xi_l)$, denoted by ψ_l^k and α_l^k, respectively, was then calculated in sequence. Eq. (25b) was solved by using a second order forward difference scheme, i.e., the value of α at the next time step (α_l^{k+1}) was calculated from the values of α at the previous two time steps (α_l^{k-1} and α_l^k). Eq. (25a) was solved by using the Crank–Nicholson difference scheme (Crank, 1979; Golub and Ortega, 1992), with appropriate modifications to handle the nonlinearity introduced by the function $\Psi(\psi)$, as described in Press et al. (1992). The values of ψ at the next time step (ψ_l^{k+1}) was, thus, calculated from the knowledge of ψ at the previous time step (ψ_l^k), and the values of α at the next and previous time steps (α_l^{k+1} and α_l^k). This was accomplished by solving a linear tridiagonal system of equations for ψ_l^{k+1}, $l=0,\ldots,\ L$, which included the boundary conditions Eqs. (26a) and (26b), since these translate into equations involving ψ_0^{k+1} and ψ_L^{k+1}, respectively. In order to obtain a linear set of equations, the function $g(\psi)$ was evaluated at the previous time step, i.e., by using ψ_l^k. The tridiagonal system was solved by using the standard FORTRAN LAPACK package [see, e.g., Anderson (1995)]. The step-sizes used in the calculations were $\Delta\tau=1\times10^{-3}$ and $\Delta\xi=5\times10^{-3}$.

4. Results and discussion

In contact with water, the experimentally studied AMC tablets very rapidly (in a few seconds) disintegrated into a large number of tablet fragments. The total volume occupied by these fragments was estimated to be 0.80 ml and the volume of liquid surrounding the fragments was 9.35 ml; hence the ratio ρ between these volumes was 0.086. Since each tablet weighed 325 mg and contained 30 wt.% NaCl, the initial drug concentration within each fragment was determined to be $\bar{m}_0=122$ mg/ml.

The drug concentration in the liquid surrounding the tablet fragments was extracted from the experimentally determined conductance according to the procedure described in Frenning et al. (2002). The cumulative amount released drug is shown as a function of time in Fig. 1. The values shown are the averages of 5 repeated measurements, while the error bars indicate ±1 standard

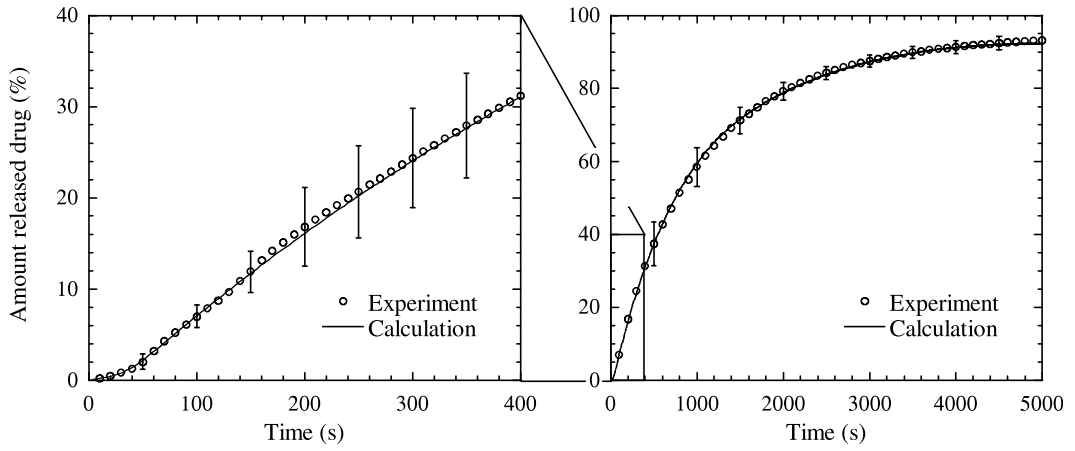

Fig. 1. Comparison between experimental (circles) and calculated (solid lines) cumulative amounts of released drug.

deviation. As is seen in the figure, the release is delayed, and the maximal release rate occurs ~ 60 s after the tablet was put in the liquid (at time zero). The solid lines in Fig. 1 is a fit of the calculated amount released drug to the experimental result. It is evident from the figure that the agreement between the theoretically calculated and experimentally determined amount is good, and it can also be seen that the initial delay is accurately described.

Starting with drug dissolution, the optimal value for the dimensionless dissolution rate constant κ_d was determined to be 0.40. If the initial surface area of undissolved salt was known, it would from this κ_d value be possible to determine the value of the dimensional dissolution rate constant k_d. It should be remembered, however, that the dissolution rate is strongly dependent on the hydrodynamic conditions around each dissolving salt grain (Grijseels et al., 1981). Moreover, the local mobile drug concentration may in the very vicinity of each salt grain be larger than the value $c(t, r)$ which, in fact, is an average over a small volume.

From the fit the solubility of NaCl inside the tablet fragments was found to be 90 mg/ml, which is 25% of the value for pure water (Weast, 1974). The partition coefficient γ was also determined to have the value 0.25. Taken together, these findings clearly show that the pores in the AMC in which the mobile NaCl was present constituted 25% of the total volume of the tablet fragment.

From the fit it was found that 8.9% of the initial amount of NaCl present in the tablet fragment could be adsorbed to the AMC, i.e., $c_b = 11$ mg/ml. Furthermore, the adsorption constant κ_b was determined to be 2.0×10^3. As a consequence of this large value, initially almost all of the dissolved NaCl was adsorbed, which accounts for the initial delay observed in Fig. 1. The heterogeneity parameter δ was found to take a value very close to unity, indicating a narrow distribution of adsorption energies. Therefore, one single process most likely dominates the adsorption. Several mechanisms contributing equally to the adsorption process would have resulted in a wider distribution (smaller δ). One possible way to look more deeply into the adsorption process would be to perform a temperature dependent analysis of the drug release process and thus extract an activation energy.

The diffusion coefficient was found to decrease very fast initially, the optimal β value being 120, and approached for high concentrations a value that was 1.0% of its value at infinite dissolution. The magnitude of D_0 was obtained as 2.6×10^{-8} cm^2/s, which is ~ 600 times smaller than that in aqueous solutions (Weast, 1974).

By using the optimal parameter values given above, the amounts of undissolved drug, dissolved and mobile drug, and dissolved but immobilized drug within each tablet fragment was calculated. The result obtained is displayed in Fig. 2.

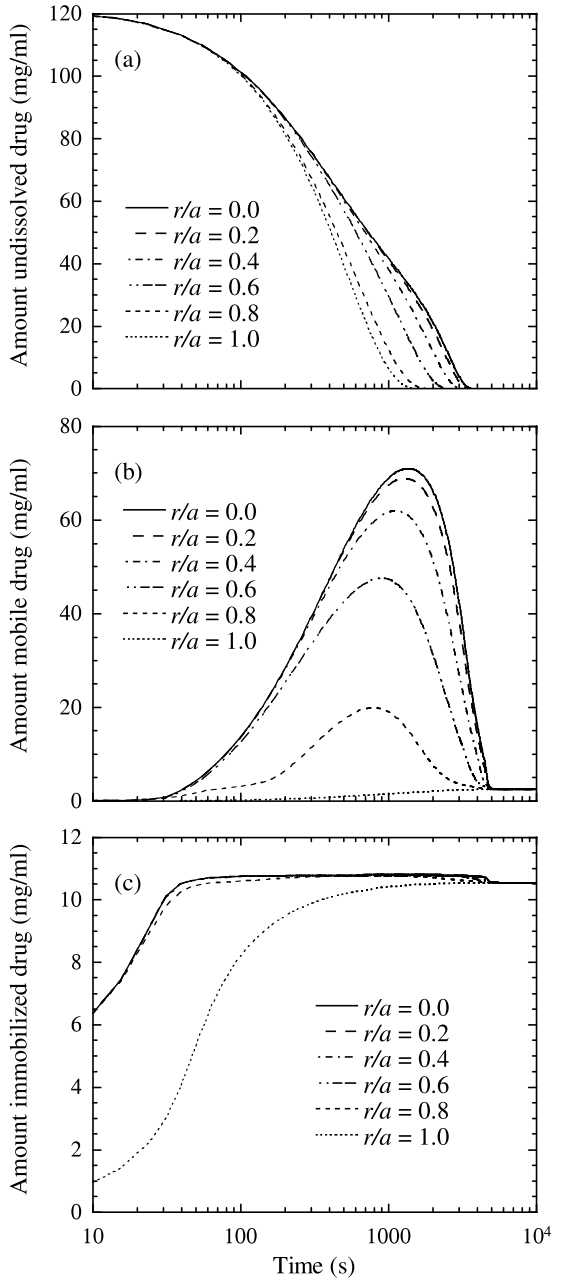

Fig. 2. Calculated amounts of (a) undissolved drug, (b) dissolved and mobile drug, and (c) dissolved but immobilized drug inside each tablet fragment. The curves are shown for various distances r from the center of the tablet fragment. Note that logarithmic time-scale have been used.

Fig. 2a shows the calculated amount of undissolved drug as a function of time. The amount is plotted for various distances from the center of the tablet fragment. Initially, when there is no dissolved and mobile NaCl present, the dissolution rate is the same everywhere in the tablet fragment. When a gradient in the mobile NaCl concentration starts to develop the dissolution rate is lower at the center of the fragment, where the concentration is higher, than at the surface.

Fig. 2b shows the calculated amount of dissolved and mobile drug. As seen in the figure, this concentration is very low initially, as a consequence of the finding that most of the dissolved drug is adsorbed by the AMC. When the immobilized drug concentration, Fig. 2c, reaches its maximal value the mobile drug concentration starts to increase more rapidly. The mobile drug concentration is seen to reach its maximum value at ~ 1000 s, and then starts to decrease as the drug diffuses out from the fragment. Finally, the mobile drug concentration within the fragment reaches a value that is 25% of that in the surrounding solution.

Fig. 2c shows the calculated amount of dissolved but immobilized drug. As already mentioned, almost all dissolved drug is adsorbed initially, as a consequence of the large κ_b value. Except at the surface of the tablet fragment, the amount immobilized drug is seen to reach its maximal value quite rapidly (after ~ 30 s) and then stays more or less constant. In the final stage of the release process, when the concentration mobile drug within each tablet fragment decreases, some of the adsorbed drug is released.

We finally mention that the proposed model may be modified in three ways without changing its principal physical content. Firstly, other concentration-dependencies of the diffusion coefficient than the exponential one introduced by Eq. (3) are possible. Secondly, other partitions between mobile and immobilized drug than that given by Eq. (7) may be used, provided, of course, there is a mechanism that guarantees that only a certain amount of drug becomes immobilized per volume unit tablet. Thirdly, one may solve the problem using cylindrical coordinates, instead of the spherical ones used here, to be able to describe non-disintegration matrix systems.

5. Summary and conclusion

A new drug release model has been developed, that combines drug dissolution, diffusion and immobilization caused by adsorption to the tablet constituents. The model is formulated in terms of a pair of coupled nonlinear partial differential equations, which are solved numerically, by using finite differences. This model is offered as a possible explanation for the observed delay in the NaCl release from AMC tablets, and is shown to yield release characteristics in good agreement with those observed experimentally.

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References

Anderson, E., 1995. LAPACK User's Guide, second ed.. Society for Industrial and Applied Mathematics, Philadelphia.

Bard, A.J., Faulkner, L.R., 2001. Electrochemical Methods: Fundamentals and Applications, second ed.. Wiley, New York.

Crank, J. The Mathematics of Diffusion. Paperback Edition, 1979. Oxford science publications, Clarendon Press, Oxford, pp. 144–146, 326–329, Ch. 8, 14

Edwards, L.J., 1951. The dissolution of aspirin in aqueous media. Trans. Faraday Soc. 47, 1191–1210.

Frenning, G., Ek, R., Strømme, M., 2002. A new method for characterizing the release of drugs from tablets in low liquid surroundings. J. Pharm. Sci. 91, 776–784.

Golub, G.H., Ortega, J.M., 1992. Scientific Computing and Differential Equations: an Introduction to Numerical Methods, second ed.. Academic Press, Boston.

Grijseels, H., Crommelin, D.J.A., Blaey, C.J.D., 1981. Hydrodynamic approach to dissolution rate. Pharmaceutisch Weekblad Scientific Edition 3, 1005–1020.

Higuchi, T., 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci. 50, 874–875.

Higuchi, T., 1963. Mechanisms of sustained-action medication: theoretical analysis of the rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.

Hixson, A.W., Crowell, J.H., 1931. Dependence of reaction velocity upon surface and agitation. Ind. Eng. Chem. 23, 923–931.

Koble, R.A., Corrigan, T.E., 1952. Adsorption isotherms for pure hydrocarbons. Ind. Eng. Chem. 44, 383–387.

Landau, L.D., Lifshitz, E.M., 1987. Fluid mechanics. In: Course Of Theoretical Physics, vol. 6, second ed. (translated from the Russian by J.B. Sykes and W.H. Reid). Pergamon Press, Oxford.

Masaro, L., Zhu, X.X., 1999. Physical models of diffusion for polymer solutions, gels and solids. Prog. Polym. Sci. 24, 731–775.

Noyes, A.A., Whitney, W., 1897. Auflösungsgeschwindigkeit von festen Stoffen in ihren eigenen Lösungen. Z. Physik. Chemie 23, 689.

Press, W.H., Teukolsky, S.A., Vetterling, W.T., Flannery, B.P., 1992. Numerical recipes in FORTRAN 77: the art of scientific computing. In: Fortran Numerical Recipes, vol. 1, second ed. (Ch. 19). Cambridge University Press, Cambridge.

Rudziński, W., Dominko, A., Wojciechowski, B.W., 1996. Mixed-gas adsorption on real solid surfaces: lack of correlations between adsorption energies of various components related to the wide applicability of the generalized Langmuir–Freundlich isotherm equation. Chem. Eng. J. 64, 85–98.

Siepmann, J., Kranz, H., Bodmeier, R., Peppas, N.A., 1999a. HPMC-matrices for controlled drug delivery: a new model combining diffusion, swelling, and dissolution mechanisms and predicting the release kinetics. Pharm. Res. 16, 1748–1756.

Siepmann, J., Kranz, H., Peppas, N.A., Bodmeier, R., 2000. Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles. Int. J. Pharm. 201, 151–164.

Siepmann, J., Peppas, N.A., 2000. Hydrophilic matrices for controlled drug delivery: An improved mathematical model to predict the resulting drug release kinetics (the 'sequential layer' model). Pharm. Res. 17, 1290–1298.

Siepmann, J., Peppas, N.A., 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv. Drug Deliver. Rev. 48, 139–157.

Siepmann, J., Podual, K., Sriwongjanya, M., Peppas, N.A., Bodmeier, R., 1999b. A new model describing the swelling and drug release kinetics from hydroxypropyl methylcellulose tablets. J. Pharm. Sci. 88, 65–72.

Siepmann, J., Streubel, A., Peppas, N.A., 2002. Understanding and predicting drug delivery from hydrophilic matrix tablets using the 'sequential layer' model. Pharm. Res. 3, 306–314.

Sips, R., 1948. On the structure of a catalyst surface. J. Chem. Phys. 16, 490–495.

Weast, R.C. (Ed.), CRC handbook of chemistry and physics: a ready-reference book of chemical and physical data, 55th ed.. CRC Press, Cleveland, Ohio 1974, p. F60.