Journal of Membrane Science 350 (2010) 10–18

Contents lists available at ScienceDirect

Journal of Membrane Science

journal homepage: www.elsevier.com/locate/memsci

Modeling of drug delivery from erodible and non-erodible laminated planar devices into a finite external medium

Ignacio M. Helbling*, Juan C.D. Ibarra, Julio A. Luna, María I. Cabrera, Ricardo J.A. Grau

Laboratorio de Química Fina, Instituto de Desarrollo Tecnológico para la Industria Química (INTEC), Universidad Nacional del Litoral and Consejo Nacional de Investigaciones Científicas y Técnicas (UNL-CONICET), Centro Científico Tecnológico, Ruta Nacional 168, Paraje El Pozo 3000, Santa Fe, Argentina

ARTICLE INFO

Article history:
Received 2 October 2009
Received in revised form 2 December 2009
Accepted 4 December 2009
Available online 30 December 2009

Keywords:
Mathematical modeling
Dispersed drug
Moving front
Finite external medium
Erodible device

ABSTRACT

Analytical solutions based on the pseudo-steady state approximation (PSSA) were derived for the case of controlled dispersed-drug release from erodible and non-erodible planar matrices, through a membrane, and taking into account the existence of a diffusion boundary layer and a finite release medium. The solutions can be applied to a broad range of situations from drug release into finite or infinite medium, from erodible or non-erodible matrices, in the presence or absence of a membrane, and in the presence or absence of a stagnant liquid layer. The prediction is accurate for the cases in which the initial drug load is higher than the drug solubility in the polymer (e.g. $A/Cs \geq 3$) till the entire dispersed drug is dissolved. The dependence on the release kinetics with different parameters was simulated and provides a theoretical platform for the design of dispersed-drug release devices.

1. Introduction

In the last few decades, transdermal therapeutic systems (TTS) have been designed and employed to provide a controlled release of drugs through the skin to the systemic bloodstream. The first transdermal patch released scopolamine and was manufactured in 1981 [1]. The TTS may consist of matrix or reservoir systems. In matrix systems, the initial drug loading (A) is generally uniform and can be lower [2–7] or higher [6–11] than the maximum solubility in the polymer (Cs).

In the cases in which $A > Cs$, the drug is homogeneously dispersed as discrete crystals or solid particles in a matrix environment formed by the cross-linking of linear polymer chains. The dispersed drug crystals (particles) cannot delocalize their positions in the polymeric matrix. It is assumed that the drug molecules can elute outside the matrix only by dissolution in and then by diffusion through the polymeric structure. Microscopically, the solid drug particles in the layer closer to the device surface are the first to elute. When this layer becomes "exhausted", the solid drugs in the next layer begin to be depleted. There exists a drug depletion zone with a thickness S. This thickness increases with time and as more solid drugs elute out of the device, thus leading to the inward advancement of the interface of the dispersed drug zone/depleted drug zone, phenomenon commonly referred to as "dissolution–diffusion moving front" [9].

In the last five decades, there have been numerous attempts to model the kinetics of the dispersed-drug release from planar matrices. Higuchi was the first to propose a pseudo-steady state approximation (PSSA) to derive an analytical solution for the slab under "sink condition" [12]. Later, Paul and McSpadden achieved an exact solution for slabs under "sink condition" [13]. Lee developed an approximate explicit analytical solution [14], which is simpler than McSpadden's but more accurate than Higuchi's for small A/Cs ratio. The modeling for a device with a membrane was developed by Paul [15]. The effect of the presence of a diffusion boundary layer on the release kinetics was taken into account in the models developed by Roseman and Higuchi [16] and Tojo [17] for dispersed-drug release in slabs under "sink condition" assuming PSSA. The same analysis but incorporating a finite external medium was carried out by Zhou and Wu, who derived an explicit analytical solution assuming PSSA [18].

Another area of interest is the development of degradable controlled-release devices. Lee analyzed the diffusive drug release from a device strictly assuming surface erosion by formulating two moving fronts, one dissolution–diffusion front and an erosion front [14]. Baker and Lonsdale incorporated bulk erosion in the analysis [19]. Thombre and Himmelstein analyzed the case of a matrix with surface erosion, laminated with a membrane [20]. A similar analysis was performed by Fischel-Ghodsian and Newton [21].

Because of the difficulties in the mathematical modeling when certain phenomena are incorporated such as the presence of diffusion boundary layer, finite external medium and the presence of membrane, to date there is no exact solution for dispersed-drug release from planar matrices taking into account these phenomena.

* Corresponding author. Tel.: +54 342 4511597; fax: +54 342 4511597.
E-mail address: ihelbling@santafe-conicet.gov.ar (I.M. Helbling).

0376-7388/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.memsci.2009.12.007

Even though these complex systems can be solved by numerical methods, such as the finite element method [22–24], their application is limited because it is a sophisticated method that requires special knowledge and training. Therefore, from a practical viewpoint, useful mathematical solutions can be obtained with reasonable precision assuming certain approximations.

The pseudo-steady state approximation yields satisfactory results for the cases in which $A/Cs \geq 3$, and approximates the exact solution for $A \gg Cs$ [8,13,23,25]. The purpose of the present work was to derive an explicit analytical solution for the case of dispersed-drug controlled release from erodible and non-erodible planar matrices, through a membrane, and taking into account the existence of a diffusion boundary layer and finite release medium.

2. Model development

2.1. Non-erodible matrix

The mathematical model is developed for a rectangular matrix containing solid drug particles. The device is schematically illustrated in Fig. 1.

The assumptions of the model to be mathematically formulated are the following: (i) the mass transport of drug is assumed to be effectively one-dimensional; (ii) the drug diffusion process is described according to Fick's laws; (iii) the dissolution of the solid drug particles in the matrix occurs at a high rate and does not constitute a controlling step of the general release process; (iv) the initial drug loading in the matrix is homogeneous; (v) the initial drug loading in the matrix is higher than the maximum drug solubility in the polymer; (vi) all the drug particles have the same size; (vii) at $r = 0$ there is an impermeable coating; there is no drug release through that surface; (viii) the matrix is inert, unswellable and non-erodible; (ix) the initial drug loading in the membrane is zero; (x) the drug diffusion coefficient in the membrane is assumed to be smaller than in the matrix; (xi) the membrane is inert, unswellable and non-erodible; (xii) resistance to external mass transfer is not negligible; (xiii) the volume of the release medium is finite; (xiv) the drug diffusion coefficients are constant; (xv) The pseudo-steady state approximation (PSSA) is assumed during the whole modeling process; the dissolved drug profiles in the matrix, membrane and stagnant liquid layer are considered linear; (xvi) modeling time goes from t_m to t_f, t_f being the time in which the dissolution–diffusion moving front reaches $r = 0$; (xvii) when there is no lag time, $t_m = 0$.

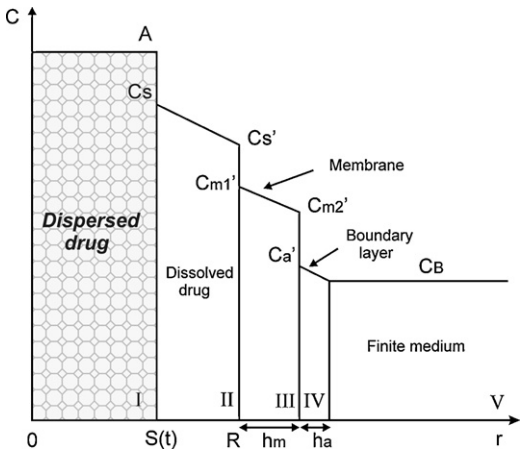

Fig. 1. Schematic illustration of drug concentration profiles in a non-erodible polymeric device. I. Dispersed drug zone; II. dissolved drug zone; III. membrane; IV. diffusion boundary layer; V. finite release medium.

According to Fick's laws and with the PSSA simplification, the mass balances in the matrix, membrane and diffusion boundary layer are given by

$$\frac{\partial Q}{\partial t} = -D_i \left(\frac{\partial C}{\partial r} \right)_i \tag{1}$$

where Q is the cumulative amount of drug released per unit area, t is the time, D is the drug diffusion coefficient, C is the dissolved-drug concentration and r is the coordinate along the matrix thickness. The subscript i indicates the different diffusion zones: $i = p, m, a$ for matrix, membrane and diffusion boundary layer, respectively. In the following analysis, all the variables (except time) were transformed to dimensionless variables in order to generalize the analysis. Even though other authors have considered dimensionless time, the present work has excluded the dimensionless time variable since it is considered that otherwise the notion of real-scale applicability of the devices would be lost. With reduced dimensionless variables defined as:

$$x = \frac{r}{R} \quad \delta(t) = \frac{S(t)}{R} \quad \theta = \frac{C}{Cs}$$

a more general set of equations is obtained:

$$\frac{\partial Q}{\partial t} = D_p \frac{Cs}{R} \frac{(1 - \theta_s^*)}{(1 - \delta)} \tag{2}$$

$$\frac{\partial Q}{\partial t} = D_m \frac{Cs}{R} \frac{(K_1 \theta_s^* - (\theta_a^*/K_2))}{L} \tag{3}$$

$$\frac{\partial Q}{\partial t} = D_a \frac{Cs}{R} \frac{(\theta_a^* - \theta_B)}{f} \tag{4}$$

where x is the dimensionless coordinate along the matrix thickness, R is the matrix thickness, $S(t)$ and $\delta(t)$ are the positions of the dimensional and dimensionless dissolution–diffusion moving fronts, respectively, θ is the dimensionless drug concentration in the matrix, θ_s^* is the dimensionless drug concentration in the matrix, at the matrix–membrane interface, θ_a^* is the dimensionless drug concentration in the boundary layer, at the membrane–boundary layer interface, L is the dimensionless thickness of the membrane, θ_B is the dimensionless drug concentration in the release medium and f is the dimensionless thickness of the diffusion boundary layer. K_1 and K_2 are the drug partition coefficients at the membrane–matrix and boundary layer–membrane interfaces, respectively, which are defined by

$$K_1 = \frac{\theta_{m1}^*}{\theta_s^*} \quad K_2 = \frac{\theta_a^*}{\theta_{m2}^*} \tag{5}$$

where θ_{m1}^* and θ_{m2}^* are the dimensionless drug concentrations in the membrane, at the matrix–membrane and membrane–boundary layer interfaces, respectively. The drug concentration in the release medium can be expressed as follows:

$$\theta_B = \frac{\left[(A/Cs) - (1/2)(1 + \theta_s{}^*) \right] R \,\text{area}(1 - \delta)}{V} \tag{6}$$

where V is the volume of the release medium and area is the release area of the matrix.

2.1.1. General solutions

Taking into account the amount of dissolved drug present in the matrix ($C \leq Cs$), the cumulative amount of drug released per unit area of the device is [18]:

$$Q = \left[A - \frac{Cs}{2}(1 + \theta_s^*) \right] R(1 - \delta) \tag{7}$$

Note that the difference with Zhou and Wu [18] is due to the edge definition and the dimensionless passage. Differentiating Eq. (7)

with respect to time, the drug release rate can be obtained:

$$\frac{\partial Q}{\partial t} = -\left[A - \frac{Cs}{2}(1+\theta_s^*)\right] R\frac{\partial \delta}{\partial t} - \frac{R\,Cs(1-\delta)}{2}\frac{\partial \theta_s^*}{\partial \delta}\frac{\partial \delta}{\partial t} \tag{8}$$

Zhou and Wu [18] reported that the second term of Eq. (8) poses a slight contribution to the release rate in a broad range of experimental situations, and can be omitted. Thus, equating Eq. (2) with the first term of Eq. (8), it yields:

$$\frac{D_p Cs}{R}\frac{(1-\theta_s^*)}{(1-\delta)} = -\left[A - \frac{Cs}{2}(1+\theta_s^*)\right] R\frac{\partial \delta}{\partial t} \tag{9}$$

The dimensionless drug concentration in the matrix at the matrix–membrane interface, θ_s^* can be obtained from Eqs. (2)–(6). Substituting Eq. (6) into Eq. (4) and equating Eqs. (3) and (4), the expression for θ_a^* can be obtained. Introducing expression θ_a^* into Eq. (3) and equating Eqs. (2) and (3), one can solve for θ_s^*:

$$\theta_s^* = \frac{((A/Cs)-(1/2))R\,\text{area}(1-\delta)^2 + ((f/D_a)+(K_2L/D_m))D_pV}{K_1K_2V(1-\delta) + \frac{R}{2}\,\text{area}(1-\delta)^2 + ((f/D_a)+(K_2L/D_m))D_pV} \tag{10}$$

Introducing the expression for θ_s^* into Eq. (9), rearranging the said expression, and integrating within the time lapse corresponding to the moving front between [1, δ], it yields:

$$t - t_m = F_1(1-\delta) - F_2\ \ln\left[1 - \frac{(A-Cs)\,\text{area}\,R}{CsK_1K_2V}(1-\delta)\right] \tag{11}$$

where

$$F_1 = -\frac{K_1K_2V(2A-Cs)R}{2D_p\ \text{area}\,(A-Cs)} \tag{12}$$

$$F_2 = \frac{VfR}{D_a\,\text{area}} + \frac{K_2VLR}{D_m\,\text{area}} + \frac{CsV^2K_1^2K_2^2(2A-Cs)}{2D_p\,\text{area}^2\,(A-Cs)^2} \tag{13}$$

From Eq. (7) we can obtain the cumulative amount of drug released per unit area, in a time t, as a function of δ, which can be obtained from Eq. (11). This analysis is valid till all drug dispersed in the device is dissolved ($\delta = 0$).

The fraction of drug released (F_R) is defined as:

$$F_R = \frac{Q}{AR} \tag{14}$$

2.2. Erodible matrix

The mathematical model is developed for the case of a rectangular, erodible, polymeric matrix containing dispersed drug. The device is schematically illustrated in Fig. 2.

The assumptions of the model to be developed are the same as those of the first case, except for item (viii) and adding the following ones: (xviii) the matrix is inert, unswellable but erodible; (xix) the erosion is superficial, characterized by an erosion constant rate; (xx) the membrane remains stuck to the matrix during the entire process; (xxi) at time $t = 0$, $e(t) = R$.

The erosion process is characterized by an erosion constant rate. The erosion moving front is expressed as:

$$e(t) = R - Bt \tag{15}$$

where $e(t)$ is the position of the erosion front and B is the erosion constant rate. In the analysis, the variables are transformed into dimensionless variables in the same way as in the case of the non-erodible matrix, incorporating:

$$E(t) = \frac{e(t)}{R}$$

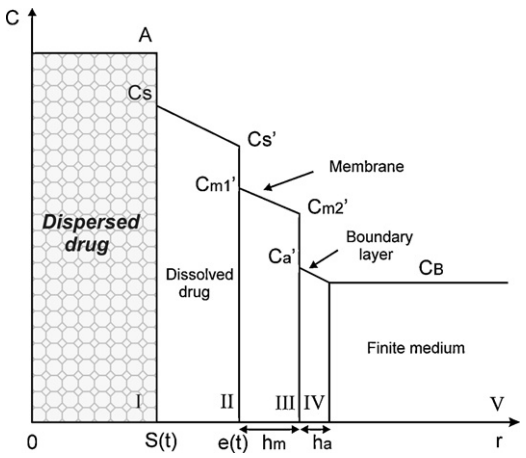

Fig. 2. Schematic illustration of drug concentration profiles in an erodible polymeric device. I. Dispersed drug zone; II. dissolved drug zone; III. membrane; IV. diffusion boundary layer; V. finite release medium.

where $E(t)$ is the dimensionless position of the erosion front. According to Fick's laws and with the PSSA simplification, the mass balance in dimensionless form in the matrix is given by

$$\frac{\partial Q}{\partial t} = D_p\frac{Cs}{R}\frac{(1-\theta_s^*)}{(E-\delta)} \tag{16}$$

The mass balances in the membrane and in the diffusion boundary layer are given again by Eqs. (3) and (4) respectively. The drug concentration in the release medium is given by Eq. (6).

2.2.1. General solutions

The cumulative amount of drug released per unit area is given by Eq. (7). Similarly to the case of the non-erodible matrix, from Eq. (7) one can obtain the drug release rate given by Eq. (8). Dropping the second term as previously done and equating Eq. (16) with the first term of Eq. (8) it yields:

$$\frac{D_pCs}{R}\frac{(1-\theta_s^*)}{(E-\delta)} = -\left[A - \frac{Cs}{2}(1+\theta_s^*)\right] R\,\frac{\partial \delta}{\partial t} \tag{17}$$

The dimensionless drug concentration in the matrix at the matrix–membrane interface, θ_s^* can be obtained as previously done:

$$\theta_s^* = \frac{((A/Cs)-(1/2))R\,\text{area}\,(1-\delta)(E-\delta) + ((f/D_a)+(K_2\,L/D_m))D_pV}{K_1K_2V(E-\delta) + (R/2)\,\text{area}\,(1-\delta)(E-\delta) + ((f/D_a)+(K_2L/D_m))D_pV} \tag{18}$$

Introducing the expression for θ_s^* into Eq. (17), substituting $E(t)$ by its expression and multiplying by an integrating factor, an expression is obtained that can be solved as an exact differential equation. By solving this equation, and finding the potential function, one obtains the expression of the dissolution–diffusion moving front as a function of time:

$$t - t_m = G_1\left[\frac{(a\delta+b)^{(c+2)} - (a+b)^{(c+2)}}{(a\delta+b)^{(c+1)}}\right] + G_2\left[1 - \left(\frac{a+b}{a\delta+b}\right)^{(c+1)}\right] \tag{19}$$

where

$$a = \frac{D_pD_mD_a\ \text{area}}{R}\left(\frac{A}{Cs} - 1\right) \tag{20}$$

$$b = \frac{D_pD_mD_a}{R^2}\left[K_1K_2V - R\,\text{area}\left(\frac{A}{Cs} - 1\right)\right] \tag{21}$$

$$c = -\frac{K_1K_2VB((A/Cs)-(1/2))}{D_p\,\text{area}\,((A/Cs)-1)} - 1 \tag{22}$$

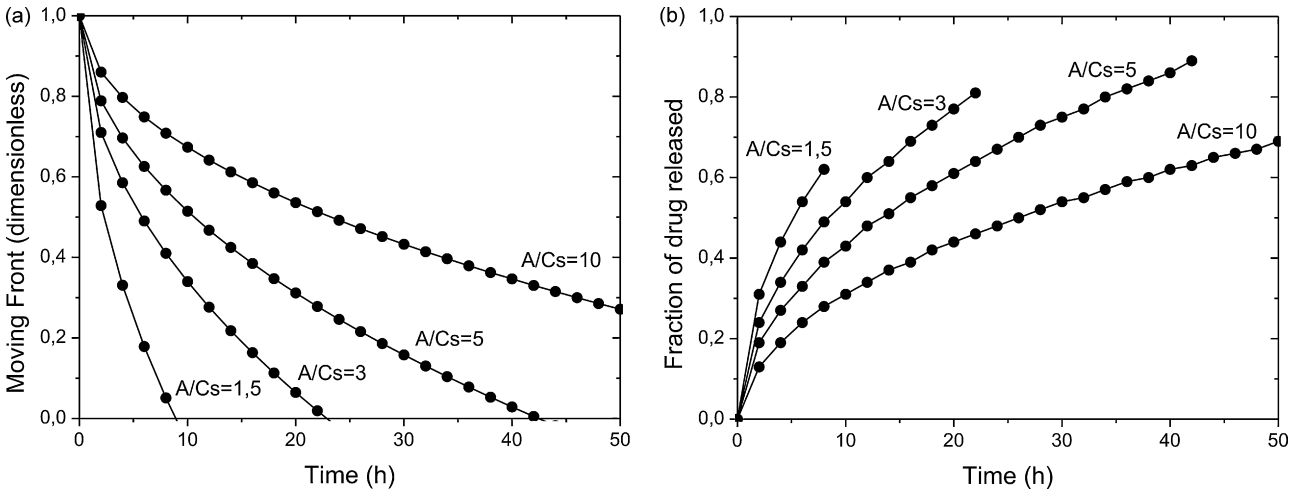

Fig. 3. Comparison of the position of the dissolution–diffusion moving front (a) and the fraction of drug released (b) calculated according to Eqs. (11) and (14) (—) with the model prediction reported by Zhou and Wu (●) [18]. The parameters used are: $R = 0.25$ cm; area = 1 cm^2; $h_m = 0$ cm; $h_a = 0.01$ cm; $D_p = 1 \times 10^{-6}$ cm^2/s; $D_a = 5 \times 10^{-6}$ cm^2/s; $K_1 = 0.8333$; $K_2 = 0.6$; $V/Vs = 100$, where Vs is the matrix volume.

$$G_1 = \frac{K_1 K_2 VR((A/Cs) - (1/2))}{D_p \,\text{area}\,((A/Cs) - 1)a(c + 2)} \tag{23}$$

$$G_2 = \frac{K_1 K_2 V}{B\,\text{area}\,((A/Cs) - 1)} + \frac{D_p R((A/Cs) - 1)(D_m f + D_a K_2 L)}{D_m D_a K_1 K_2 B((A/Cs) - (1/2))} \tag{24}$$

From Eq. (7), it can be obtained the cumulative amount of drug released per unit area in a time t, as a function of δ, which is determined by Eq. (19). Again, this analysis is valid only till the entire drug dispersed in the matrix is dissolved ($\delta = 0$). The fraction of drug released is defined as above in Eq. (14).

3. Results and discussion

3.1. Non-erodible matrix

In the case of a non-erodible matrix, the results obtained through Eqs. (11) and (14) with the use of a computational software (MATLAB®) were first compared with the analytical solutions available in the literature, i.e. the solutions reported by Zhou and Wu [18]. In Eq. (11) let $L = 0$, the position of the dissolution–diffusion moving front, and then the fraction of drug released were calculated in the device without a membrane, as a function of time. These results were plotted in Fig. 3 as a function of time t for different initial drug loadings. It shows that the prediction of the model fits perfectly well with the solution reported by Zhou and Wu. This result was expected due to the fact that in the derivation of both models, one starts from the same assumptions.

In order to illustrate the usefulness of the model in the analysis of controlled drug release from polymeric matrix systems, several examples of profiles are presented and compared with experimental data reported in the literature for finite and infinite release medium. Zhou and Wu reported that $V/Vs = 5000$ approximate $V \to \infty$ [18]. With the purpose of ascertain that the equations can be used not only for finite medium, in Fig. 4 is presented the release of estradiol from a polymeric patch with initial drug loading higher than solubility into infinite medium. The experimental data were reported by Kurnik and Potts [26]. Except for the diffusion coefficient in matrix, all the other parameters employed in the model were taken from this work. The diffusion coefficient calculated from the model is slightly smaller than the one reported by Kurnik and Potts. These authors reported a $D_p = 5.4 \times 10^{-10}$ cm^2/s, which was determined by independent studies with dissolved estradiol (without dispersed drug). It shows that the model fitting is in agreement with the experimental data within the experimental error range.

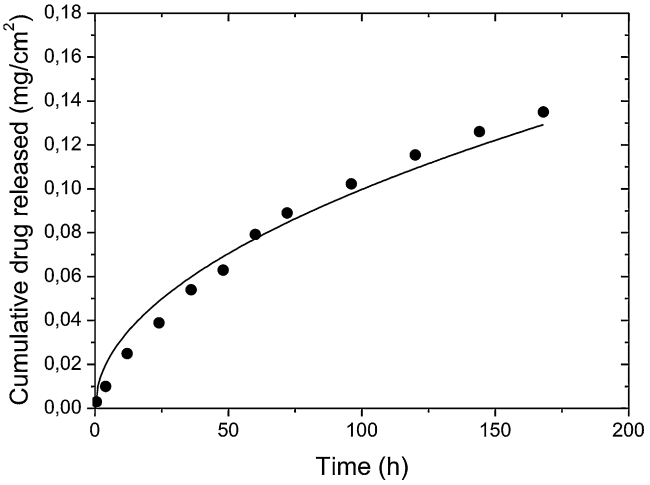

Fig. 4. Comparison of release profile calculated according to Eq. (7) (—) and the experimental data reported by Kurnik and Potts (●) [26], for estradiol release from a polymeric matrix into water. The parameters used are: $R = 0.0195$ cm; area = 30 cm^2; $V/Vs = 5000$; $h_m = 0$ cm; $D_p = 1.6 \times 10^{-10}$ cm^2/s.

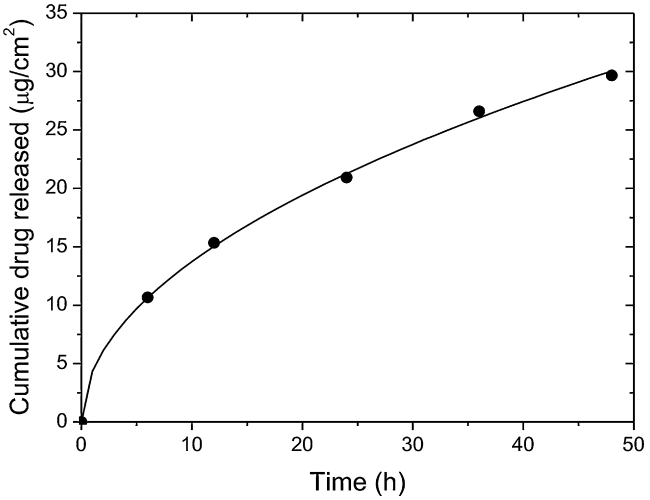

Fig. 5. Comparison of release profile calculated according to Eq. (7) (—) and the experimental data reported by Park et al. (●) [27], for estradiol release from a matrix of EVA 18% into PBS pH 7.4. The parameters used are: $R = 0.0130$ cm; area = 1.77 cm^2; $V/Vs = 1303.78$; $h_m = 0$ cm; $D_p = 1.1 \times 10^{-9}$ cm^2/s.

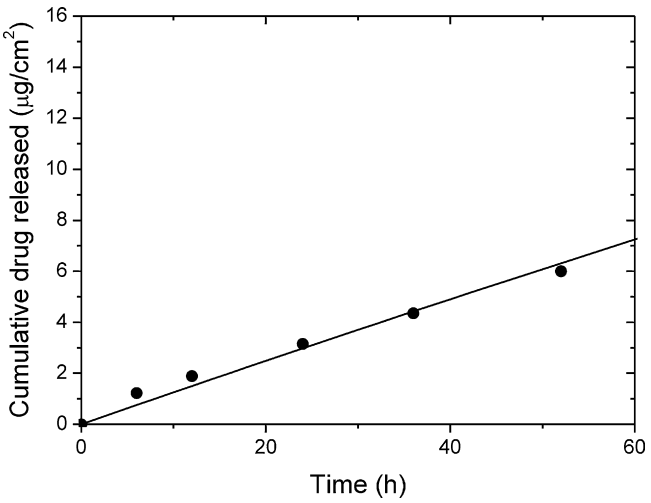

Fig. 6. Comparison of release profile calculated according to Eq. (7) (—) and the experimental data reported by Park et al. (●) [27], for estradiol release from a matrix of EVA 18% through mouse epidermis into 20% PEG400 saline buffer. The parameters used are: $R = 0.0130$ cm; area = 5 cm^2; $V/Vs = 1303.78$; $h_m = 0.001$ cm; $D_p = 1.1 \times 10^{-9}$ cm^2/s; $D_m = 4 \times 10^{-11}$ cm^2/s.

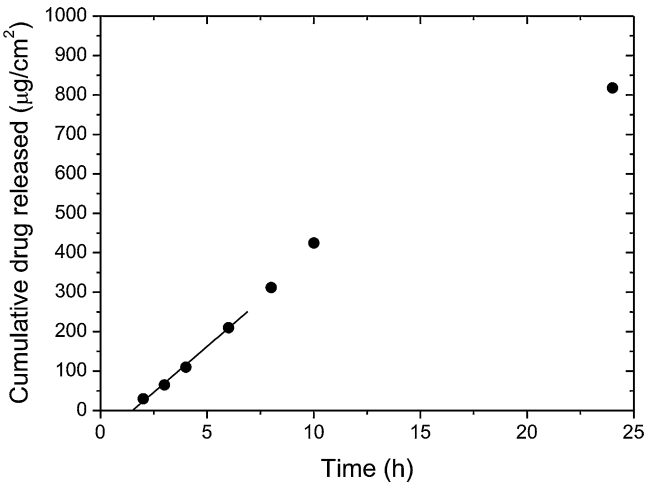

Fig. 7. Comparison of release profile calculated according to Eq. (7) (—) and the experimental data reported by Sato et al. (●) [30], for 5-ISMN release from an acrylic matrix through rat epidermis into water. The parameters used are: $R = 0.004$ cm; area = 0.95 cm^2; $V/Vs = 658$; $h_m = 0.00154$ cm; $D_p = 2.69 \times 10^{-7}$ cm^2/s; $D_m = 2.52 \times 10^{-10}$ cm^2/s.

Fig. 5 shows experimental data reported by Park et al. [27] and the release profile calculated for estradiol release from a polymeric matrix of EVA 18% with initial loading higher than solubility into finite medium. The parameters employed were taken from Park et al. [27], except for the diffusion coefficient in matrix which was found to be $D_p = 1.1 \times 10^{-9}$ cm^2/s from the fitting. The estradiol diffusion coefficient in EVA copolymer was reported to be in the order of 10^{-9} cm^2/s [28]. The agreement between experimental data and theory is good.

Fig. 6 presents experimental data reported by Park et al. [27] and the release profile calculated for estradiol release from a polymeric matrix of EVA 18% with initial loading higher than solubility through abdominal mouse skin into finite medium. The thickness of the abdominal mouse skin was 10 μm [26,29]. $D_p = 1.1 \times 10^{-9}$ cm^2/s was determinated previously. Setting this, $D_m = 4 \times 10^{-11}$ cm^2/s was calculated from the model adjustment. A close match between the model and the experimental data was observed.

Fig. 7 presents experimental data reported by Sato et al. [30] and the release profile calculated for the release of 5-ISMN from an acrylic matrix with initial loading higher than solubility through abdominal rat skin into finite medium. All the parameters employed were taken from Sato et al. [30,31]. The thickness of the abdominal rat skin was 15.4 μm [31]. The model predicts the experimental profile perfectly well. It can be observed that the straight line covers approximately the first 7 h of release. From that moment on, only dissolved drug remains in the device; therefore, the model is not applicable. The release percentage that can be modelled depends primarily on the A/Cs ratio. This modeling percentage is defined as the quotient between the amount of drug released from the device at the moment in which the dissolution–diffusion moving front reached the other extreme of the slab ($\delta = 0$), and the initial drug loading.

For the case of a matrix without membrane exemplified in Figs. 4 and 5, $A/Cs \geq 3$ and the modelled percentage is above 83%. Besides, the presence of the membrane decreases the modelled percentage because part of the drug previously released is now retained in the membrane. Thus, in Fig. 6, the ratio is still $A/Cs \geq 3$; however, the modelled percentage drops to 76.63%. In the final example of Fig. 7, where the membrane is still present and $A/Cs = 1.33$, it can be seen that only 25.08% of the release can be modelled. It shows that the model becomes truly useful when $A/Cs \geq 3$.

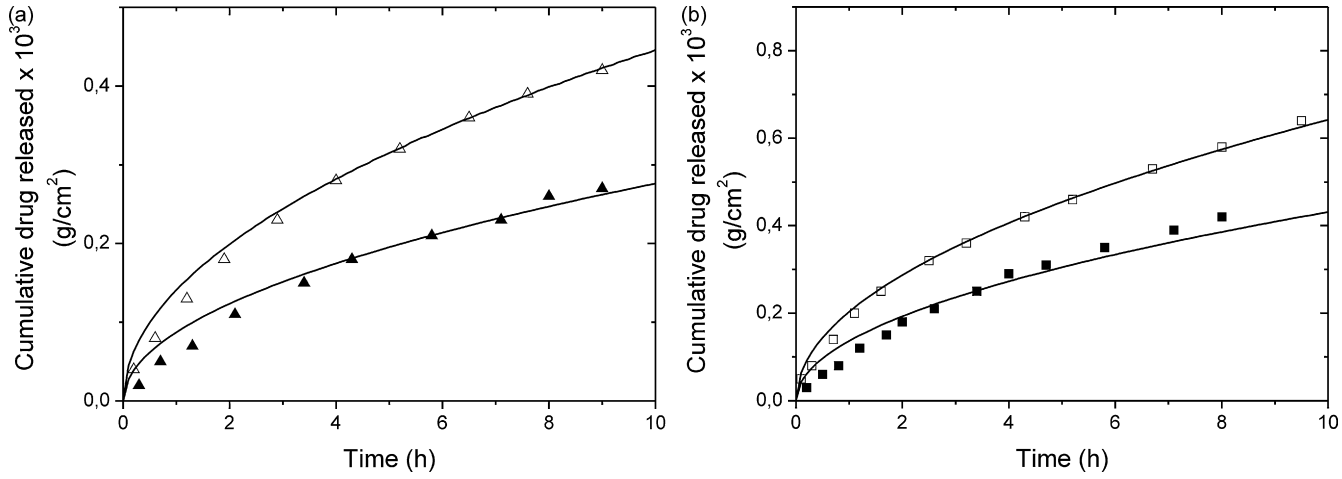

Fig. 8. Comparison of release profile calculated according to Eq. (7) (—) and the experimental data reported by Papadokostaki and Petropoulos (symbols) [32], for 4-aminoazobenzene release from a matrix of cellulose acetate into water: (a) $A/Cs = 3.7$, (△) 300 rpm (▲) 45 rpm. (b) $A/Cs = 8.3$, (□) 300 rpm (■) 45 rpm.

Fig. 8 shows experimental data reported by Papadokostaki and Petropoulos [32] and the theoretical profiles calculated for the release of 4-aminoazobenzene from an acetate cellulose matrix with initial loading higher than solubility into finite medium considering the existence of diffusion boundary layer. The model parameters were taken from Papadokostaki's work [32]. For 45 and 300 rpm stirring rate, the thickness of the boundary layer was $h_a = 0.0022$ and $h_a = 0.0003$ cm, respectively. These values were obtained from the model adjustment. It can be observed that as the stirring rate increases, the thickness of stagnant layer decreases. This is consistent with that reported by Chien about the dependency of stagnant layer with the viscosity, drug diffusion coefficient and agitation speed of the release medium [9].

A simulation was carried out in order to illustrate the effect of the external medium volume on release. To do so, a matrix augmented with a second membrane was used as device. The simulation was performed with real data of progesterone considering a silicon matrix and human skin as second membrane. The maximum solubility of progesterone in silicone was reported to be 0.5947 mg/cm^3 [9]. The diffusion coefficients of this drug in silicone and human skin were previously reported [9,33]. For the simulation, the initial drug loading was set according to the maximum

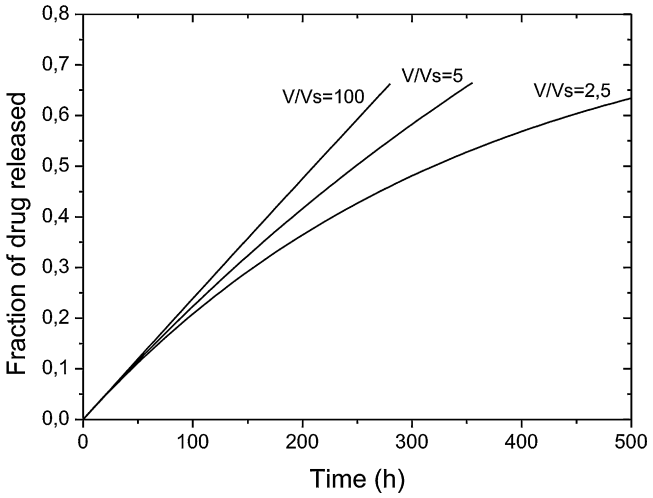

Fig. 9. Fraction of progesterone released calculated according to Eq. (14) from a silicone matrix through human skin into different release medium volume. The parameters used are: $R = 0.010$ cm; area = 30 cm^2; $h_m = 0.001$ cm; $D_p = 2.15 \times 10^{-8}$ cm^2/s; $D_m = 2 \times 10^{-11}$ cm^2/s.

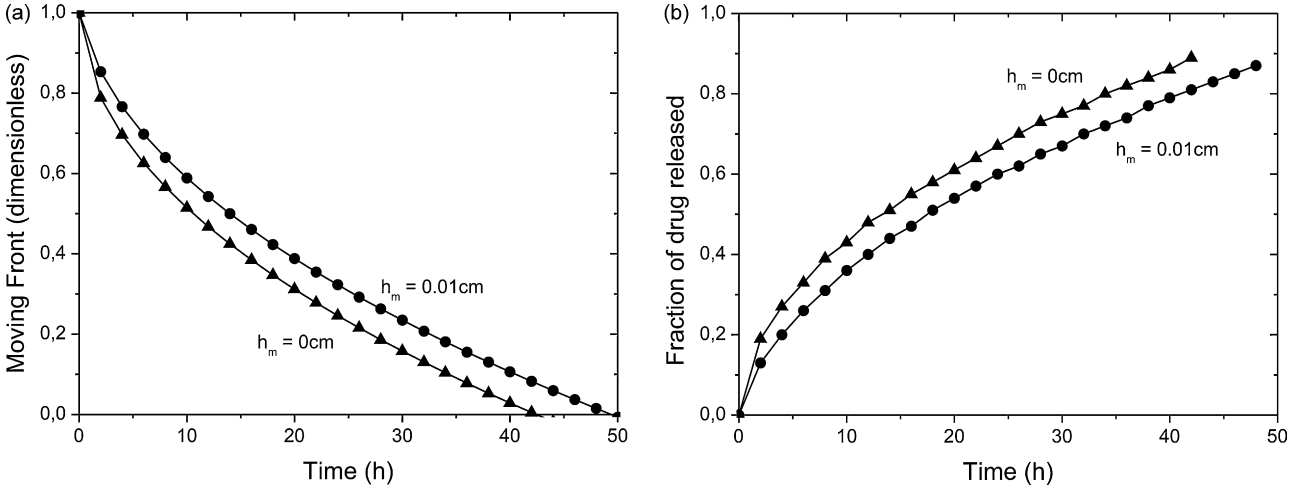

Fig. 10. Comparison of the position of the dissolution–diffusion moving front (a) and the fraction of drug released (b) calculated according to Eqs. (19) and (14) (—), according to Eqs. (11) and (14) (●) and according to the model reported by Zhou and Wu (▲) [18]. The parameters used are: $R = 0.25$ cm; area = 1 cm^2; $V/Vs = 100$; $h_a = 0.01$ cm; $A = 0.5$ g/cm^3; $Cs = 0.1$ g/cm^3; $D_p = 1 \times 10^{-6}$ cm^2/s; $D_m = 5 \times 10^{-7}$ cm^2/s; $D_a = 5 \times 10^{-6}$ cm^2/s; $K_1 = 0.8333$; $K_2 = 0.6$.

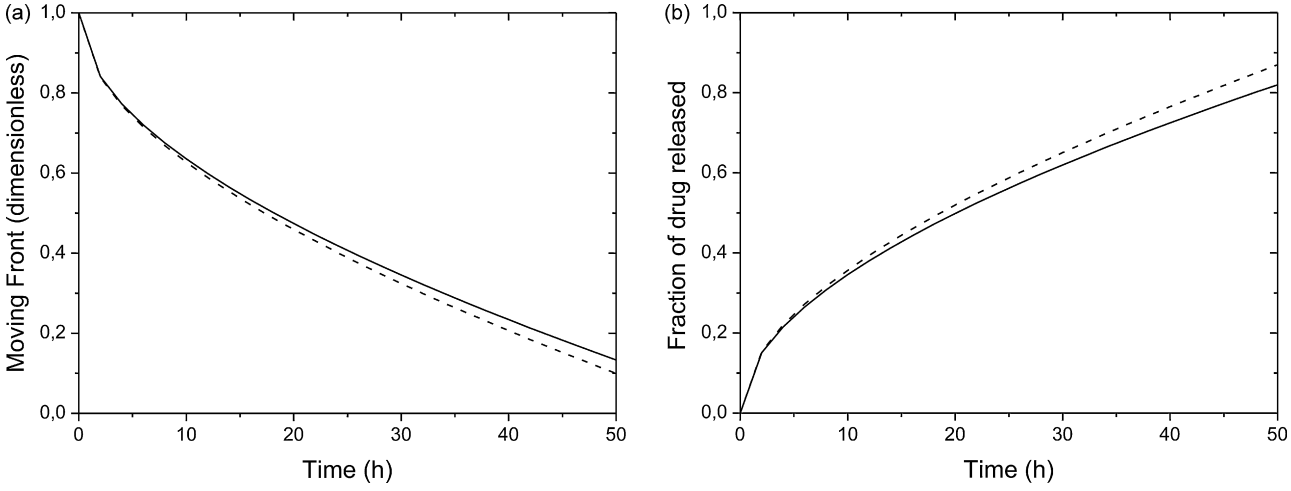

Fig. 11. Comparison of the position of the dissolution–diffusion moving front (a) and the fraction of drug released (b) calculated according to Eqs. (19) and (14) (—) with the analytical solution reported by Lee (—) [14]. The parameters used are: $R = 0.25$ cm; area = 1 cm^2; $V/Vs = 100$; $h_a = 0$ cm; $h_m = 0$ cm; $A = 1$ g/cm^3; $Cs = 0.1$ g/cm^3; $D_p = 1 \times 10^{-6}$ cm^2/s; $B = 4 \times 10^{-7}$ cm^2/s.

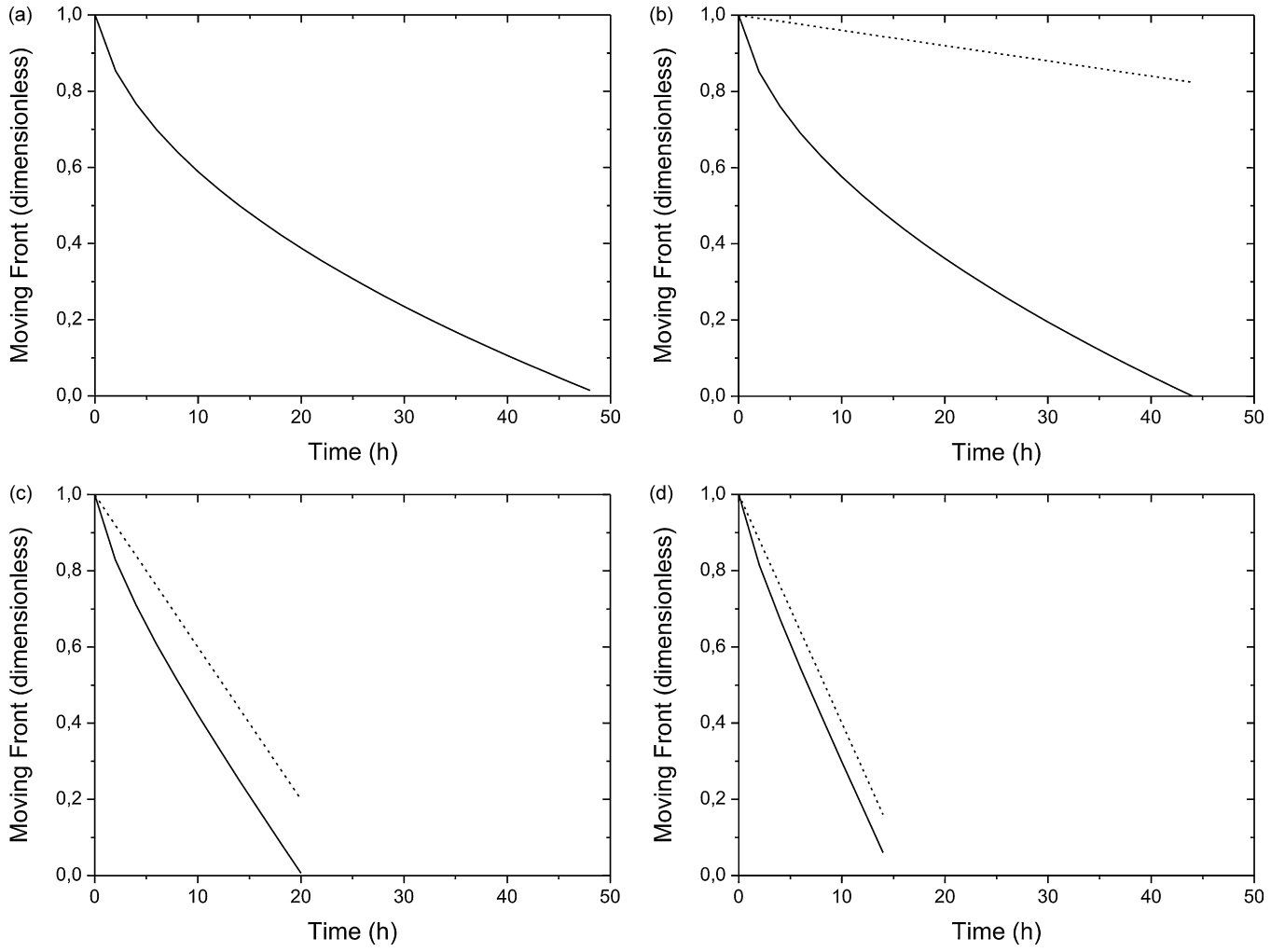

Fig. 12. Comparison of the positions of the dissolution–diffusion moving front (—) and the erosion moving front (—) calculated according to Eqs. (19) and (15) respectively for different erosion constant rates: (a) $B = 1 \times 10^{-6}$ cm/h; (b) $B = 1 \times 10^{-3}$ cm/h; (c) $B = 1 \times 10^{-2}$ cm/h; (d) $B = 1.5 \times 10^{-2}$ cm/h. The parameters used are: $R = 0.25$ cm; area = 1 cm^2; $V/Vs = 100$; $h_a = 0.01$ cm; $h_m = 0.01$ cm; $A = 0.5$ g/cm^3; $Cs = 0.1$ g/cm^3; $D_p = 1 \times 10^{-6}$ cm^2/s; $D_m = 5 \times 10^{-7}$ cm^2/s; $D_a = 5 \times 10^{-6}$ cm^2/s; $K_1 = 0.8333$; $K_2 = 0.6$.

solubility of this hormone in silicone. The A/Cs ratio was adjusted to 3 in order to minimize the error derived from the PSSA assumption. The predictions obtained are depicted in Fig. 9. It shows that a decrease in the V/Vs ratio leads to a lower amount of drug released. It can be explained by a fast increment of the drug concentration in a smaller receptor volume, which decreases the concentration gradient between the release medium and the device.

3.2. Erodible matrix

In the case of an erodible matrix, the results obtained through Eqs. (14) and (19) were first compared to those obtained through Eqs. (11) and (14) and with the analytical solution reported by Zhou and Wu [18]. In Eq. (19), let $B = 0$, the position of the dissolution–diffusion moving front and then the fraction of drug released as a function of time were calculated. For comparison with Eqs. (11) and (14), a membrane thickness of 0.01 cm was considered while for the comparison with Zhou and Wu $h_m = 0$ was set. The position of the $\delta(t)$ front and the fraction of drug released are illustrated in Fig. 10 as a function of time t. It can be observed that the prediction of the model fits well in both cases. This is an expected result because the same assumptions are used to derive both models.

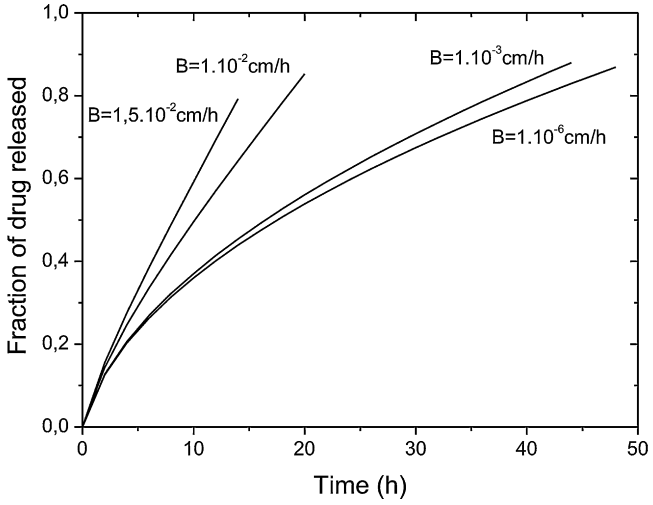

Fig. 13. Comparison of the fraction of drug released calculated according to Eq. (14) for different erosion constant rates. The parameters used are: $R = 0.25$ cm; area = 1 cm^2; $V/Vs = 100$; $h_a = 0.01$ cm; $h_m = 0.01$ cm; $A = 0.5$ g/cm^3; $Cs = 0.1$ g/cm^3; $D_p = 1 \times 10^{-6}$ cm^2/s; $D_m = 5 \times 10^{-7}$ cm^2/s; $D_a = 5 \times 10^{-6}$ cm^2/s; $K_1 = 0.8333$; $K_2 = 0.6$.

In addition, the results obtained through Eqs. (14) and (19) were compared with the approximate analytical solution derived by Lee [14]. The results are presented in Fig. 11. It shows that Eqs. (14) and (19) approach Lee's solution within a certain error range. As expected, there is a little difference between both originated in the fact that PSSA was applied for the model derivation, instead of applying the refined integral method used by the author.

A few examples of simulations are presented below in order to illustrate the usefulness of the model in the analysis of controlled drug release from an erodible polymeric matrix. The effect of the surface erosion rate of the polymeric matrix on the drug release can be seen in Figs. 12 and 13. Fig. 12 presents the positions of the dimensionless dissolution–diffusion and erosion moving fronts taking into account different erosion constant rates. Fig. 13 shows the fractions of drug released corresponding to those erosion rates. It can be observed that as the erosion constant rates increase, the lifetime of the devices decreases and the drug release becomes faster.

4. Conclusions

Analytical solutions were derived for the case of controlled dispersed-drug release from erodible and non-erodible planar matrices, through a membrane, considering the existence of a diffusion boundary layer and a finite release medium, based on PSSA. These solutions are of practical usefulness and relatively simple to use with the help of an adequate computational software. They can be applied to a broad range of situations, namely drug release in a finite or infinite medium, erodible or non-erodible matrices, in the presence or absence of a membrane, or in the presence or absence of a stagnant liquid layer. These solutions offer an accurate prediction of the release kinetics in the cases of $A/Cs \geq 3$, till all dispersed drug is dissolved. This was corroborated by comparison with experimental profiles reported in the literature. In the case of erodible matrices, good agreement was verified with the approximate analytical solution reported by Lee [14]. The dependence of the release kinetics on parameters such as initial drug loading, external medium volume, and surface erosion constant rate was also analyzed. Similar analyses can be carried out for the other parameters included in the solutions presented. The greatest utility of these models lies in their prediction capacity of *in vitro* release profiles from transdermal patches through the skin.

Acknowledgments

The authors wish to express their gratitude to Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), and to Universidad Nacional del Litoral (UNL) of Argentina, for the financial support granted to this contribution.

Nomenclature

area	release area of matrix (cm^2)
A	initial drug loading in matrix (g/cm^3)
B	erosion constant rate (cm/h)
C	drug concentration in matrix (g/cm^3)
C'_a	drug concentration in diffusion boundary layer at the membrane–boundary layer interface (g/cm^3)
C_B	drug concentration in external medium (g/cm^3)
C'_{m1}	drug concentration in membrane at the matrix–membrane interface (g/cm^3)
C'_{m2}	drug concentration in membrane at the membrane–boundary layer interface (g/cm^3)
Cs	maximum drug solubility in matrix (g/cm^3)
Cs'	drug concentration in matrix at the matrix–membrane interface (g/cm^3)
D_a	drug diffusion coefficient in diffusion boundary layer (cm^2/s)
D_m	drug diffusion coefficient in membrane (cm^2/s)
D_p	drug diffusion coefficient in matrix (cm^2/s)
$e(t)$	position of erosion moving front (cm)
$E(t)$	$e(t)/R$, position of erosion moving front (dimensionless)
f	h_a/R, diffusion boundary layer thickness (dimensionless)
F_R	Q/AR, fraction of drug released (dimensionless)
h_a	diffusion boundary layer thickness (cm)
h_m	membrane thickness (cm)
K_1	drug partition coefficient at the membrane–matrix interface (dimensionless)
K_2	drug partition coefficient at the boundary layer–membrane interface (dimensionless)
L	h_m/R, membrane thickness (dimensionless)
Mt	cumulative amount of drug released (g)
Q	cumulative amount of drug released per unit area (g/cm^2)
r	coordinate along the matrix thickness (cm)
R	matrix thickness (cm)
$S(t)$	position of dissolution–diffusion moving front (cm)
t	time (s)
t_f	final time of modeling (s)
t_m	lag time (s)
V	release medium volume (cm^3)
Vs	matrix volume (cm^3)
x	r/R, coordinate along the matrix thickness (dimensionless)

Greek letters

$\delta(t)$	$S(t)/R$, position of the dissolution–diffusion moving front (dimensionless)
θ	C/Cs, drug concentration in matrix (dimensionless)
θ^*_a	C'_a/Cs, drug concentration in diffusion boundary layer at the membrane–boundary layer interface (dimensionless)
θ_B	C_B/Cs, drug concentration in external medium (dimensionless)
θ^*_{m1}	C'_{m1}/Cs, drug concentration in membrane at the matrix–membrane interface (dimensionless)
θ^*_{m2}	C'_{m2}/Cs, drug concentration in membrane at the membrane–boundary layer interface (dimensionless)
θ^*_s	Cs'/Cs, drug concentration in matrix at the matrix–membrane interface (dimensionless)

References

[1] P. Costa, J.M. Sousa Lobo, Evaluation of mathematical models describing drug release from estradiol transdermal systems, Drug Dev. Ind. Pharm. 29 (2003) 89–97.
[2] R. Guy, J. Hadgraft, A theoretical description relating skin permeation to the thickness of the applied medicament, Int. J. Pharm. 6 (1980) 321–332.
[3] W.J. Addicks, G. Flynn, N. Weiner, R. Curl, A mathematical model to describe drug release from thin topical applications, Int. J. Pharm. 56 (1989) 243–248.
[4] M. Fernandes, L. Simon, N.W. Loney, Mathematical modeling of transdermal drug-delivery systems: analysis and applications, J. Membr. Sci. 256 (2005) 184–192.
[5] A. Sagiv, Theoretical formulation of the diffusion through a slab-theory validation, J. Membr. Sci. 199 (2002) 125–134.

[6] R. Langer, Polymeric delivery systems for controlled drug release, Chem. Eng. Commun. 6 (1980) 1–48.
[7] J. Siepmann, F. Siepmann, Mathematical modelling of drug delivery, Int. J. Pharm. 364 (2008) 328–343.
[8] T. Higuchi, Mechanism of sustained-action medication, J. Pharm. Sci. 52 (1963) 1145–1149.
[9] Y.W. Chien, Fundamentals of controlled-release drug administration, in: J. Swarbrick (Ed.), Novel Drug Delivery Systems, Marcel Dekker Inc., New York and Basel, 1982, pp. 465–574.
[10] D.R. Paul, Modeling of solute release from laminated matrices, J. Membr. Sci. 23 (1985) 221–235.
[11] G.C. Charalambopoulou, E.S. Kikkinides, K.G. Papadokostaki, A.K. Stubos, A.T. Papaioannou, Numerical and experimental investigation of the diffusional release of a dispersed solute from polymeric multilaminate matrices, J. Control. Release 70 (2001) 309–319.
[12] T. Higuchi, Rate of release of medicaments from ointment bases containing drug in suspension, J. Pharm. Sci. 50 (1961) 874–875.
[13] D.R. Paul, S.K. McSpadden, Diffusional release of a solute from a polymeric matrix, J. Membr. Sci. 1 (1976) 33–48.
[14] P.I. Lee, Diffusional release of a solute from a polymeric matrix—approximate analytical solutions, J. Membr. Sci. 7 (1980) 255–275.
[15] D.R. Paul, Solute release from membrane–matrix composites, J. Membr. Sci. 21 (1984) 203–207.
[16] T.J. Roseman, W.I. Higuchi, Release of medroxyprogesterone acetate from a silicone polymer, J. Pharm. Sci. 59 (1970) 353–357.
[17] K. Tojo, Intrinsic release rate from matrix-type drug delivery systems, J. Pharm. Sci. 74 (1985) 685–687.
[18] Y. Zhou, X.Y. Wu, Theoretical analyses of dispersed-drug release from planar matrices with a boundary layer in a finite medium, J. Control. Release 84 (2002) 1–13.
[19] R.W. Baker, H.K. Lonsdale, Principles of controlled release, in: F.W. Harris (Ed.), Proceedings of the International Controlled Release Pesticide Symposium, Wright State University, OH, 1975, pp. 9–39.
[20] A.G. Thombre, K.J. Himmelstein, Modelling of drug release kinetics from a laminated device having and erodible drug reservoir, Biomaterials 5 (1984) 250–254.
[21] F. Fischel-Ghodsian, J.M. Newton, Analysis of drug release kinetics from degradable polymeric devices, J. Drug Target. 1 (1993) 51–57.
[22] Y. Zhou, X.Y. Wu, Finite element analysis of diffusional drug release from complex matrix systems. I. Complex geometries and composite structures, J. Control. Release 49 (1997) 277–288.
[23] X.Y. Wu, Y. Zhou, Study of diffusional release of a dispersed solute from polymeric matrices by finite element method, J. Pharm. Sci. 88 (1999) 1050–1057.
[24] J. Huang, H.L. Wong, Y. Zhou, X.Y. Wu, H. Grad, R. Komorowski, S. Friedman, In vitro studies an modeling of a controlled-release device for root canal therapy, J. Control. Release 67 (2000) 293–307.
[25] R.A. Siegel, Theoretical analysis of inward hemispheric release above and below drug solubility, J. Control. Release 69 (2000) 109–126.
[26] R.T. Kurnik, R.O. Potts, Modeling of diffusion and crystal dissolution in controlled release systems, J. Control. Release 45 (1997) 257–264.
[27] S.J. Park, Y.J. Park, H.W. Kang, C.K. Kim, Solvent effects on physicochemical behavior of estradiols recrystallized transdermal delivery, Arch. Pharm. Res. 31 (2008) 111–116.
[28] R. Altenburger, U.D. Rohr, T. Kissel, Rate control in transdermal β-estradiol reservoir membrane systems: the role of membrane and adhesive layer, Pharm. Res. 15 (1998) 1238–1243.
[29] L.S. Hansen, J.E. Coggle, J. Wells, M.W. Charles, The influence of the hair cycle on the thickness of mouse skin, Anat. Rec. 210 (1984) 569–573.
[30] K. Sato, N. Mitsui, T. Hasegawa, K. Sugibayashi, Y. Morimoto, Potential usefulness of solubility index for prediction of the skin permeation rate of 5-ISMN from pressure sensitive adhesive tape, J. Control. Release 73 (2001) 269–277.
[31] K. Sato, K. Sugibayashi, Y. Morimoto, Species differences in percutaneous absorption of nicorandil, J. Pharm. Sci. 80 (1991) 104–107.
[32] K.G. Papadokostaki, J.H. Petropoulos, Kinetics of release of a model disperse dye from supersaturated cellulose acetate matrices, J. Control. Release 54 (1998) 251–264.
[33] B.W. Barry, Dermatological formulations percutaneous absorption, in: J. Swarbrick (Ed.), Drugs and the Pharmaceutical Sciences, Marcel Dekker Inc., New York, 1983, pp. 1–480.