International Journal of Pharmaceutics 509 (2016) 477–482

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

A three-dimensional semi-analytical solution for predicting drug release through the orifice of a spherical device

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ARTICLE INFO

Article history:
Received 5 February 2016
Received in revised form 10 May 2016
Accepted 7 June 2016
Available online 7 June 2016

Keywords:
Spherical device
Effective time constant
Controlled release
Laplace transform

ABSTRACT

Three-dimensional solute transport was investigated for a spherical device with a release hole. The governing equation was derived using the Fick's second law. A mixed Neumann-Dirichlet condition was imposed at the boundary to represent diffusion through a small region on the surface of the device. The cumulative percentage of drug released was calculated in the Laplace domain and represented by the first term of an infinite series of Legendre and modified Bessel functions of the first kind. Application of the Zakian algorithm yielded the time-domain closed-form expression. The first-order solution closely matched a numerical solution generated by Mathematica®. The proposed method allowed computation of the characteristic time. A larger surface pore resulted in a smaller effective time constant. The agreement between the numerical solution and the semi-analytical method improved noticeably as the size of the orifice increased. It took four time constants for the device to release approximately ninety-eight of its drug content.

1. Introduction

Mathematical modeling of drug-delivery systems is a growing research area within the controlled release community. It is expected that an accurate description of the delivery process would allow manufacturers to build devices able to release precise doses of a therapeutic agent to a target site at specific times. As part of this effort, researchers first try to identify the main mechanisms controlling release of the drug from the product. This step is complex as it involves, based on the device, a fundamental knowledge of mass transport phenomena, chemistry and physics. For example, when building a model for bioerodible polymeric systems, at least fourteen steps have been identified (Siepmann and Gopferich, 2001), that include water influx into the device, polymer degradation, diffusion and convection, Based on the experimental conditions and intended operations of the device, an assessment of the relative importance of each mechanism to the release kinetics is conducted. Response surface methods are useful in identifying some of the key factors, especially in formulation study, responsible for the observed kinetics (Roy et al., 2012). A combination of polymers incorporated in metformin-hydrochloride matrix tablets determines the release profile of the drug (Roy et al., 2012).

Even with a comprehensive model which includes all the relevant mechanisms, it would be difficult to evaluate the device performance if the geometry is not mapped accurately. The effect of the physical characteristics of the release is described in several contributions (Collins et al., 1997; Shefeeq et al., 2012; Simon and Ospina, 2012). For example, liposomal spherical vesicles have important applications in drug delivery. Researchers are interested in estimating the effusion time of an active pharmaceutical ingredient (API) through an open pore of a vesicle (Levin et al., 2005). The orifice diameter of a cylindrical device may also be manipulated to control the transport behavior of the API (Simon and Ospina, 2012). Other problems, such as diffusion-limited reactions within spherical cavities to promote a bimolecular reaction in biological systems (Bug et al., 1992) or drug release from arterial stents (McGinty, 2014), require the use of spherical and cylindrical geometries to represent the transport phenomena accurately.

Simpson et al. studied the fitting size and shape of hydroxypropyl methylcellulose matrices to achieve preset drug-release profiles (Siepmann et al., 2000). They presented a mathematical model that was able to compute drug release kinetics from polymeric matrices showing different shapes and sizes. The aspect ratio and dimensions are easily calculated with the model to help

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http://dx.doi.org/10.1016/j.ijpharm.2016.06.020
0378-5173/

develop new controlled-release devices. Finite differences were chosen to solve a set of partial differential equations because of concentration-dependent diffusion coefficients. A review was prepared to document the increasing role of particle shape in drug delivery (Champion et al., 2007). This tuning parameter is likely to influence the degradation and transport and, eventually, the device performance.

With the increased interest in high-dimension models, efficient computational strategies are being developed to simulate those processes. Most contributions in the drug-delivery area have relied on numerical techniques to reproduce the concentration and flux profiles for 2- and 3-D systems (Ferreira et al., 2014; George, 2005; George et al., 2004). Closed-form solutions of such models are lagging behind. As a result, valuable insight and knowledge, similar to what were gained from analytical solutions of 1-D systems, are greatly lacking for 2- and 3-D systems. For example, the lag-time method, which allows researchers to estimate the diffusion coefficient, is defined to explain drug permeation through a flat membrane (Crank, 1975). It is obvious that the simplicity of a 1-D solution may be lost when dealing with higher-dimension transport models. However, the development of new controlled-release products, with complex geometries, requires exhaustive analytical and suitable tools instead of methods defined for 1-D systems.

2. Theory

2.1. Mathematical Modeling

Initially, a drug of concentration ρ_0 is uniformly distributed within a spherical matrix. The surface of the device is impermeable except in a zone delimited by a spherical triangle with $\theta_0 \le \theta < \pi$ and $\phi_0 \le \phi < 2\pi$(Fig. 1). The drug can only exit through this region, which is in contact with a tissue or an organ where it is instantaneously removed, i.e., perfect sink conditions. Thus, the governing equation is (Crank, 1975)

$$\frac{\partial \rho(r,\theta,\phi,t)}{\partial t} = \frac{D}{r^2}\left[\frac{\partial}{\partial r}\left(r^2\frac{\partial \rho(r,\theta,\phi,t)}{\partial r}\right) + \frac{1}{\sin(\theta)}\frac{\partial}{\partial \theta}\left(\sin(\theta)\frac{\partial \rho(r,\theta,\phi,t)}{\partial \theta}\right) + \frac{1}{\sin^2(\theta)}\frac{\partial^2 \rho(r,\theta,\phi,t)}{\partial \phi^2}\right] \quad (1)$$

where ρ is the drug concentration in the vesicle, r is the radial distance, θ is the zenith angle or latitude, ϕ is the azimuthal angle or longitude, t represents the time and D is the diffusion coefficient within the matrix. As noted above, the initial condition is given by

$$\rho(r,\theta,\phi,0) = \rho_0 \quad (2)$$

and the combined Neumann and Dirichlet boundary conditions are

$$\rho(R,\theta,\phi,t) = 0,\ 0 \le \theta < \theta_0,\ 0 \le \phi < \phi_0 \quad (3)$$

and

$$\frac{\partial \rho(r,\theta,\phi,t)}{\partial r}\Big|_{r=R} = 0,\ \theta_0 \le \theta < \pi,\ \phi_0 \le \phi < 2\pi \quad (4)$$

Note that dimensionless forms of Eqs. (1)–(4) can be obtained by defining the following variables:

$$\overline{\rho} = \frac{\rho}{\rho_0},\ \overline{t} = \frac{tD}{R^2},\ \overline{r} = \frac{r}{R} \quad (5)$$

The model is applicable to a monolithic system where the drug is uniformly dispersed or dissolved in a matrix. The device is covered with an impermeable coating material except for an aperture defined by a spherical triangle with $\theta_0 \le \theta < \pi$ and $\phi_0 \le \phi < 2\pi$(Fig. 1). Diffusion is the main transport mechanism. No mass transfer limitation exists across the orifice. The model can be applied to model drug release from spherical microcapsules with a tiny hole in the surface for controlled delivery (Jerri et al., 2009). Only five percent of the sphere's surface formed an escape area for the medicine. Sheu used a similar 3D spherical model to help explain the escape of a ligand out of a spherical cavity with a hole on the surface (Sheu and Yang, 2000). The model (Eq. (1) – (4)) is relevant for the case of a large gate reaction rate constant. Lastly, this framework can help compare the effectiveness of a spherical device with existing formulations. For example, Tojo and Miyanami investigated the release of benzoic acid through a small aperture centered on cylindrical devices coated with a layer of polymethyl methacrylate (Tojo and Miyanami, 1983). A spherical configuration can be tested without the need to conduct additional experiments.

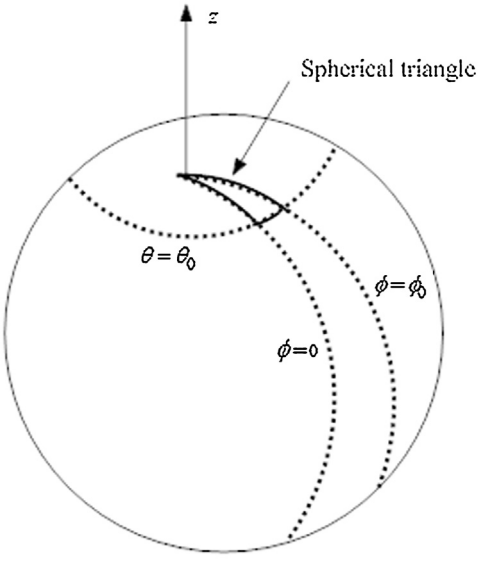

Fig. 1. The surface of the device is impermeable to drug diffusion except through a region delimited by a spherical triangle with $\theta_0 \le \theta < \pi$and $\phi_0 \le \phi < 2\pi$.

2.2. Solution Procedure

The Laplace transformation gives

$$sp(r,\theta,\phi) - \rho_0 = D\left[\frac{2}{r}\frac{\partial p(r,\theta,\phi)}{\partial r} + \frac{\partial^2 p(r,\theta,\phi)}{\partial r^2} + \frac{\cot(\theta)}{r^2}\frac{\partial p(r,\theta,\phi)}{\partial \theta} + \frac{1}{r^2}\frac{\partial^2 p(r,\theta,\phi)}{\partial \theta^2} + \frac{1}{r^2 sin(\theta)^2}\frac{\partial^2 p(r,\theta,\phi)}{\partial \phi^2}\right] \quad (6)$$

where

$$p(r,\theta,\phi) = \int_0^\infty \rho(r,\theta,\phi,t)e^{-st}dt \quad (7)$$

After making the change of variable $x = \cos(\theta)$, Eq. (6) is transformed to

$$sp(r,\theta,\phi) - \rho_0 = D\left[\begin{array}{l}\frac{2}{r}\frac{\partial p(r,x,\phi)}{\partial r} + \frac{\partial^2 p(r,x,\phi)}{\partial r^2} - \frac{x}{r^2}\frac{\partial p(r,x,\phi)}{\partial x} \\ -\frac{\sqrt{1-x^2}}{r^2}\left(\frac{x}{\sqrt{1-x^2}}\frac{\partial p(r,x,\phi)}{\partial x} - \sqrt{1-x^2}\frac{\partial^2 p(r,x,\phi)}{\partial x^2}\right) \\ +\frac{1}{r^2(1-x^2)}\frac{\partial^2 p(r,x,\phi)}{\partial \phi^2}\end{array}\right] \tag{8}$$

We look for a solution to Eq. (8) of the form

$$p(r,x,\phi) = f(r)g(x)h(\phi) + \frac{\rho_0}{s} \tag{9}$$

with

$$\frac{d^2 f(r)}{dr^2} = -\frac{c_1 f(r)}{Dr^2} - \frac{2df(r)}{r\ dr} + \frac{sf(r)}{D} \tag{10}$$

$$\frac{d^2 g(x)}{dx^2} = \frac{c_1 g(x)}{D(x^2-1)} - \frac{c_2 g(x)}{x^4 - 2x^2 + 1} - \frac{2x}{x^2-1}\frac{dg(x)}{dx} \tag{11}$$

and

$$\frac{d^2 h(\phi)}{d\phi^2} = c_2 h(\phi) \tag{12}$$

where c_1 and c_2 are integration constants to be determined by the boundary conditions. The simultaneous equations (10), (11) and (12) are solved to give

$$f(r)g(x)h(\phi) = \frac{e^{-\phi\sqrt{c_2}}}{\sqrt{r}}\left(C_5 e^{2\phi\sqrt{c_2}} + C_6\right)\left(C_1 I_{\frac{1}{2}\sqrt{\frac{D-4c_1}{D}}}\left(r\sqrt{\frac{s}{D}}\right) + C_2 K_{\frac{1}{2}\sqrt{\frac{D-4c_1}{D}}}\left(r\sqrt{\frac{s}{D}}\right)\right)\times \left(C_3 P^{i\sqrt{c_2}}_{-\frac{1}{2}\frac{\sqrt{D}-\sqrt{D-4c_1}}{\sqrt{D}}}(x) + C_4 Q^{i\sqrt{c_2}}_{-\frac{1}{2}\frac{\sqrt{D}-\sqrt{D-4c_1}}{\sqrt{D}}}(x)\right) \tag{13}$$

Given that the associated Legendre function Q is singular at $x = 1$ ($\theta = 0$,north pole) and at $x = -1$ ($\theta = \pi$,south pole), we demand that $C_4 = 0$. Similarly, C_2 is set equal to zero because the modified Bessel function of the second kind K has a singularity at $r = 0$. Note that P and I are the Legendre function and the modified Bessel function of the first kind, respectively. Without loss of generality, we write $C_3 = 1$ and get

$$f(r)g(x)h(\phi) = \frac{e^{-\phi\sqrt{c_2}}}{\sqrt{r}}\left(C_5 e^{2\phi\sqrt{c_2}} + C_6\right)\left(C_1 I_{\frac{1}{2}\sqrt{\frac{D-4c_1}{D}}}\left(r\sqrt{\frac{s}{D}}\right)\right)\left(P^{i\sqrt{c_2}}_{-\frac{1}{2}\frac{\sqrt{D}-\sqrt{D-4c_1}}{\sqrt{D}}}(x)\right) \tag{14}$$

The Legendre function P becomes a polynomial by writing

$$\frac{1}{2}\frac{\sqrt{D-4c_1} - \sqrt{D}}{\sqrt{D}} = n \tag{15}$$

where n is an integer. We derive from Eq. (15):

$$c_1 = -\frac{\left(2n\sqrt{D} + \sqrt{D}\right)^2}{4} + \frac{D}{4} \tag{16}$$

After replacing c_1 in Eq. (14), we have

$$f(r)g(x)h(\phi) = \frac{e^{-\phi\sqrt{c_2}}}{\sqrt{r}}\left(C_5 e^{2\phi\sqrt{c_2}} + C_6\right)\left(C_1 I_{n+\frac{1}{2}}\left(r\sqrt{\frac{s}{D}}\right)P^{i\sqrt{c_2}}_n(x)\right) \tag{17}$$

We then set $c_2 = -m^2$ to obtain a periodic solution in ϕ with a period of2π. Eq. (17) becomes

$$f(r)g(x)h(\phi) = \frac{e^{-m\phi i}}{\sqrt{r}}\left(C_5 e^{2m\phi i} + C_6\right)\left(C_1 I_{n+\frac{1}{2}}\left(r\sqrt{\frac{s}{D}}\right)P^m_n(x)\right) \tag{18}$$

We set $C_6 = 0$ and $C_5 = 1$ without loss of generality:

$$f(r)g(x)h(\phi) = C_1\frac{e^{m\phi i}}{\sqrt{r}} I_{n+\frac{1}{2}}\left(r\sqrt{\frac{s}{D}}\right)P^m_n(x) \tag{19}$$

Given that i) $x = \cos(\theta)$ and ii) there is a solution of the form (19) for every pair (n,m), it is possible to rewrite (19) as

$$f(r)g(\theta)h(\phi) = A_{n,m}\frac{e^{m\phi i}}{\sqrt{r}} I_{n+\frac{1}{2}}\left(r\sqrt{\frac{s}{D}}\right)P^m_n(\cos(\theta)) \tag{20}$$

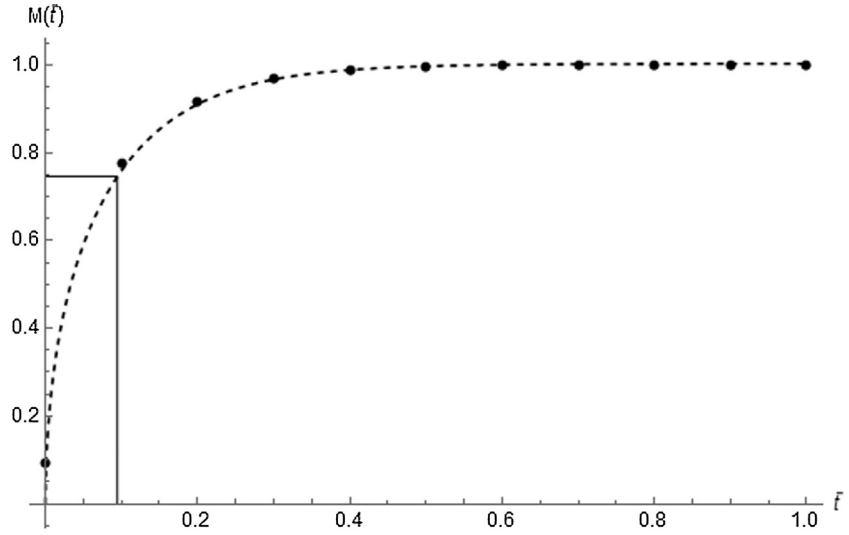

Fig. 2. Fractional drug released $M(\bar{t})$ through the aperture when $\theta_0 = \pi$and $\phi_0 = 2\pi$. The analytical profile (----) was compared to the numerical solution (●). The intersection of the two lines shows the dimensionless effective time constant.

Finally, using Eq. (9) and the superposition principle leads to the general solution:

$$p(r,\theta,\phi)=\sum_{n=0}^{\infty}\left(\sum_{m=-n}^{n}\left(A_{n,m}\frac{e^{m\phi i}}{\sqrt{r}}I_{n+\frac{1}{2}}\left(r\sqrt{\frac{s}{D}}\right)P_n^m(\cos(\theta))\right)\right)+\frac{\rho_0}{s} \tag{21}$$

The following boundary conditions hold for the spherical rectangle (Fig. 1):

$$p(r,\theta,\phi)=0,\ 0\le\theta<\theta_0,\ 0\le\phi<\phi_0 \tag{22}$$

and

$$\frac{\partial p(r,\theta,\phi)}{\partial r}|_{r=R}=0,\ \theta_0\le\theta<\pi,\ \phi_0\le\phi<2\pi \tag{23}$$

in accordance with Eqs. (3) and (4) and can be combined into

$$q_N(\theta,\phi)=\frac{\partial p(r,\theta,\phi)}{\partial r}|_{r=R}[1-(H(\theta)-H(\theta-\theta_0))(H(\phi)-H(\phi-\phi_0))]+$$
$$p(R,\theta,\phi)[(H(\theta)-H(\theta-\theta_0))(1-H(\phi)-H(\phi-\phi_0))]=0 \tag{24}$$

where $H$is the Heaviside function and the index N is a finite upper limit for the outer summation in Eq. (21). In principle, it is possible to solve Eqs. (21) and (24) in terms of an infinite number of coefficients $A_{n,m}$. But such a procedure is difficult to implement in practice. Here, we try to find a first-order approximation. Therefore, we truncate the series with$N=1$. To determine the coefficients, both sides of (24) are first multiplied by $\sin(\theta)$. The resulting expression is then integrated from 0 to π with respect toθ and from 0 to 2π with respect to ϕ:

$$\int_0^{2\pi}\left[\int_0^{\pi}[q_1(\theta,\phi)\sin(\theta)]d\theta\right]d\phi=0 \tag{25}$$

Three additional equations are derived by multiplying the integrand of Eq. (25) by $\cos(\theta)$, $\sin(\theta)e^{\phi i}$ and $\sin(\theta)e^{-\phi i}$ to yield

$$\int_0^{2\pi}\left[\int_0^{\pi}[q_1(\theta,\phi)\sin(\theta)\cos(\theta)]d\theta\right]d\phi=0 \tag{26}$$

$$\int_0^{2\pi}\left[\int_0^{\pi}\left[q_1(\theta,\phi)\sin^2(\theta)e^{\phi i}\right]d\theta\right]d\phi=0 \tag{27}$$

and

$$\int_0^{2\pi}\left[\int_0^{\pi}\left[q_1(\theta,\phi)\sin^2(\theta)e^{-\phi i}\right]d\theta\right]d\phi=0 \tag{28}$$

respectively. Finally, The system defined by Eqs. (25)–(28) is solved for $A_{0,0}$, $A_{1,0}$, $A_{1,-1}$ and $A_{1,1}$after taken advantage of the orthogonality properties.

The cumulative amount of drug released at time t is the difference between the mass initially dissolved and the amount that remains in the matrix. In normalized form, we have

$$M(t)=\frac{\rho_0\frac{4}{3}\pi R^3-\int_0^{2\pi}\int_0^{\pi}\int_0^{R}[\sin(\theta)r^2\rho(r,\theta,\phi,t)]drd\theta d\phi}{\rho_0\frac{4}{3}\pi R^3} \tag{29}$$

or

$$M(t)=1-\frac{\int_0^{2\pi}\int_0^{\pi}\int_0^{R}[\sin(\theta)r^2\rho(r,\theta,\phi,t)]drd\theta d\phi}{\rho_0\frac{4}{3}\pi R^3} \tag{30}$$

which represents the fractional amount of drug released. The Laplace transform of $M(t)$is

$$\overline{M}(s)=\frac{1}{s}-\frac{\int_0^{2\pi}\int_0^{\pi}\int_0^{R}[\sin(\theta)r^2p(r,\theta,\phi)]drd\theta d\phi}{\rho_0\frac{4}{3}\pi R^3} \tag{31}$$

which gives

$$\overline{M}(s)=-\frac{3}{4\rho_0\pi R^3}\frac{4\sqrt{2\pi R}A_{0,0}\left(s\sqrt{D}R\cosh\left(R\sqrt{\frac{s}{D}}\right)-D\sqrt{s}\sinh\left(R\sqrt{\frac{s}{D}}\right)\right)}{s^{\frac{3}{2}}\sqrt{R\sqrt{\frac{s}{D}}}} \tag{32}$$

after further manipulation. Several numerical methods are available to invert Eq. (32) (Rice and Do, 1995). The Zakian algorithm is implemented here:

$$M(t)=\frac{2}{t}\sum_{i=1}^{5}\mathrm{Re}\left(K_iM\left(\frac{a_i}{t}\right)\right) \tag{33}$$

where K_i and a_i are complex numbers.

2.3. Derivation of a Time Constant for Drug Release

The notion of a time constant (Ferreira et al., 2011; Simon and Ospina, 2015) is introduced to measure the time it takes to release the drug from the spherical vehicle. The method proposed by

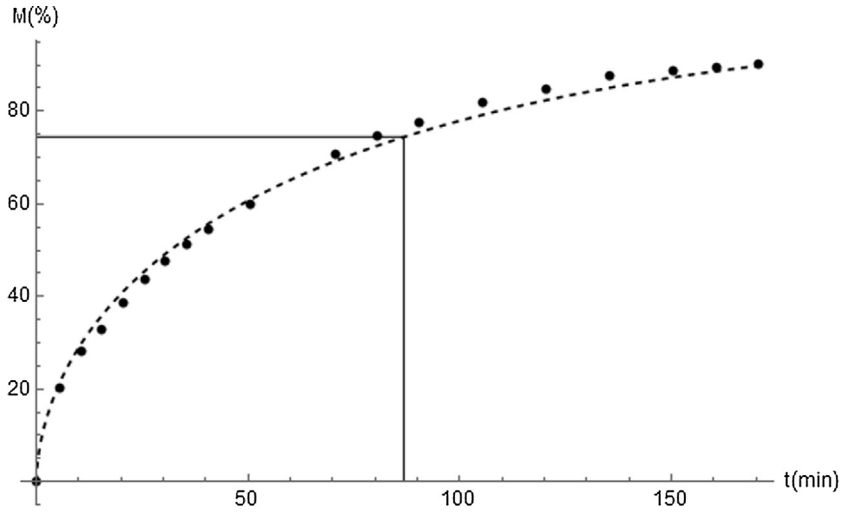

Fig. 3. Fractional drug released from a spherical bead matrix (Kim, 2000). The analytical profile (----) was compared to the data (●). The effective time constant was 87.0 min.

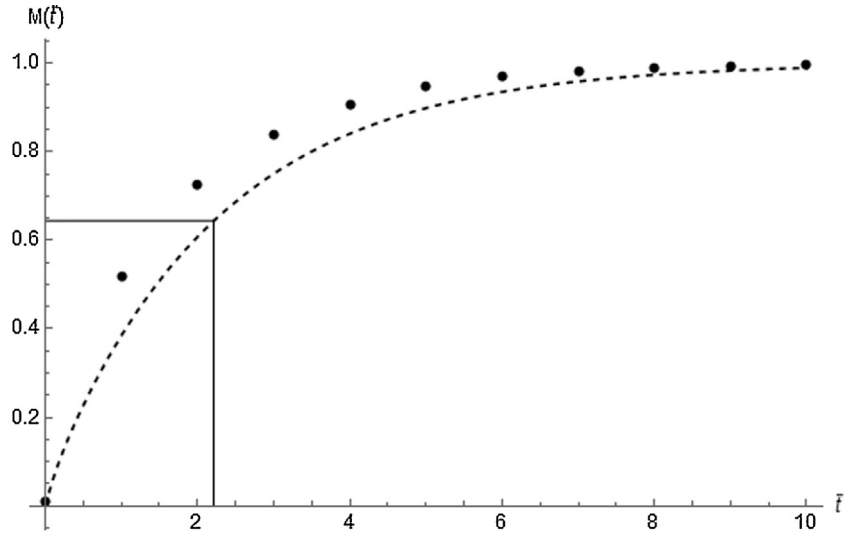

Fig. 4. Fractional drug released $M(\bar{t})$ through the aperture when $\theta_0 = \frac{2\pi}{5}$and $\phi_0 = \frac{4\pi}{5}$. The analytical profile (----) was compared to the numerical solution (●). The intersection of the two lines shows the dimensionless effective time constant.

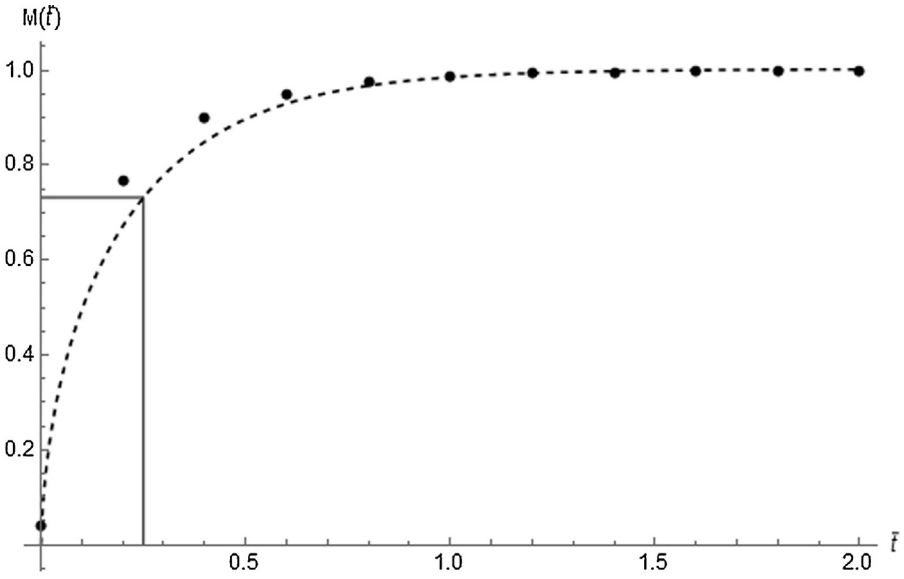

Fig. 5. Fractional drug released $M(\bar{t})$ through the aperture when $\theta_0 = \frac{4\pi}{5}$and $\phi_0 = \frac{8\pi}{5}$. The analytical profile (----) was compared to the numerical solution (●). The intersection of the two lines shows the dimensionless effective time constant.

Collins is adopted (Collins, 1980):

$$\tau_{eff} = \int_0^\infty t\Omega(t)dt \tag{34}$$

where the probability density function $\Omega(t)$ is

$$\Omega(t) = \frac{(M(\infty) - M(t))}{\int_0^\infty (M(\infty) - M(t))dt} \tag{35}$$

After using the Laplace variable, Eq. (34) becomes

$$\tau_{eff} = \lim_{s\to 0}\left(\frac{M(\infty)}{s^2} + \frac{d\overline{M}(s)}{ds}\right)\left[\lim_{s\to 0}\left(\frac{M(\infty)}{s} - \overline{M}(s)\right)\right]^{-1} \tag{36}$$

An expression for $\tau_{eff}$is developed after using Eqs. (31) and (36). Another method to calculate τ_{eff} is to allow a power series expansion of $\overline{M}(s)$ around $s = 0$ of order s such as

$$\overline{M}(s) = \frac{M(\infty)}{s} + B + Cs \tag{37}$$

The time constant is

$$\tau_{eff} = -C/B \tag{38}$$

3. Results and Discussions

Case 1. $\theta_0 = \pi$and $\phi_0 = 2\pi$

When $\theta_0 = \pi$ and $\phi_0 = 2\pi$, the system represents a one-dimensional diffusion through a sphere with a perfect sink boundary condition. The following normalized parameters were selected for the simulation: $\overline{R} = R/R = 1$ and $\bar{t}_{fin} = Dt_{fin}/R^2 = 1$, where t_{fun} stood for the simulation time. The profile was compared

to a solution produced by the function "NDSolveValue", from Mathematica (Wolfram Research, Inc.). The two solutions are indistinguishable (Fig. 2) with a dimensionless time constant of 0.095. This validation step proves the reliability of Eq. (33). The percentage release at $4 \times \overline{\tau}_{eff}$ is 98.5 as predicted by a first-order process (Simon, 2013; Smith and Corripio, 2006). The parameter $\overline{\tau}_{eff}$ is the dimensionless time constant ($\overline{\tau}_{eff} = D\tau_{eff}/R^2$).

Data for drug released from a spherical bead matrix were taken from the literature (Kim, 2000) to test the results. An infinite sink condition was maintained. The original bead diameter was 1.0 mm and a diffusion coefficient of 4.76×10^{-6} mm^2/sec was determined (Kim, 2000). The solution predicted the experimental release kinetics successfully (Fig. 3).

Case 2. Effect of hole size on the release kinetics

The release was simulated with $\theta_0 = \frac{2\pi}{5}$ and $\phi_0 = \frac{4\pi}{5}$ and the results were compared to the "NDSolveValue" solution (Fig. 4). Convergence between the two methods was better at longer times. The time constant $\overline{\tau}_{eff}$ and the fractional release were 2.2 and 98.2, respectively. The dynamic profile was compared with one for which $\theta_0 = \frac{4\pi}{5}$ and $\phi_0 = \frac{8\pi}{5}$ (Fig. 5). The following values were computed for this case: $\overline{\tau}_{eff} = 0.25$ and $M(4 \times \overline{\tau}_{eff}) = 98.6\%$. As expected, a larger hole leads to a smaller effusion time. The agreement between "NDSolveValue" and the analytical method improved as the size of the aperture increased.

The method outlined in this work finds important applications, from drug-delivery systems (Siepmann et al., 1998) to the mechanism of a ligand escaping from a protein (Sheu and Yang, 2000). Note that the region where the drug is released is described by a spherical triangle with $\theta_0 \leq \theta < \pi$ and $\phi_0 \leq \phi < 2\pi$ (Fig. 1). To extrapolate the results to a device with a circular hole on the surface, we seek a relationship between the radius r of a circle and the dimensions of the orifice, defined in this contribution, such that both representations share the same area:

$$\pi r^2 = R^2\phi_0(1 - \cos\theta_0) \tag{39}$$

As a result,

$$r = R\sqrt{\frac{\phi_0(1 - \cos\theta_0)}{\pi}} \tag{40}$$

The expression for τ_{eff} is too large for practical calculations. However, it can be shown that for $\phi_0 = 2\pi$, we have the following two-dimension-based time constant:

$$\tau_{eff,2} = \frac{1}{21}\frac{R^2\left(2\theta_0^2 + 35\pi^2 - 35\pi\theta_0\right)}{D\theta_0(-4\theta_0 + 5\pi)} \tag{41}$$

which leads to the following approximation:

$$\tau_{eff} = \frac{2\pi}{\phi_0}\frac{1}{21}\frac{R^2\left(2\theta_0^2 + 35\pi^2 - 35\pi\theta_0\right)}{D\theta_0(-4\theta_0 + 5\pi)} \tag{42}$$

after using Eq. (41) and assuming that τ_{eff} is inversely proportional to ϕ_0: $\tau_{eff} = \frac{2\pi}{\phi_0}\tau_{eff,2}$. When adapted to the two aforementioned cases, Eq. (42) yields $\overline{\tau}_{eff}$ values of 0.11, 1.9, 0.34 compared to 0.095, 2.2 and 0.25, respectively.

4. Conclusions

The mathematical model described a medicament uniformly distributed within a spherical device. The encapsulated drug could only escape through a region delimited by a spherical triangle. A mixed Neumann-Dirichlet condition was prescribed at the boundary. The solution procedure involved the use of Laplace transforms. The cumulative amount of drug released was then calculated after invoking the orthogonal properties of the Legendre and modified Bessel functions. An effective time constant was developed to estimate the time required for releasing ninety-eight percent of the amount of drug. As expected, a larger surface pore yielded a smaller time constant. A numerical solution, using built-in Mathematica functions, matched the semi-analytical method, especially for larger holes. Suggestions were offered to help implement the techniques to controlled-release devices with a circular hole on the surface. A simpler expression was derived for the time constant to promote widespread adoption of the approach.

References

Bug, A.L.R., Grossman, E.L., Morgan, D.D., Berne, B.J., 1992. Diffusion-limited reactions in spherical cavities. J. Chem. Phys. 96, 8840–8852.

Champion, J.A., Katare, Y.K., Mitragotri, S., 2007. Particle shape: a new design parameter for micro- and nanoscale drug delivery carriers. J. Controlled Release 121, 3–9.

Collins, R., 1980. The choice of an effective time constant for diffusive processes in finite systems (Thermal conduction and sputtering examples). J. Phys. D: Appl. Phys. 13, 1935.

Collins, R., Paul, Z., Reynolds, D.B., Short, R.F., Wasuwanich, S., 1997. Controlled diffusional release of dispersed solute drugs from biodegradable implants of various geometries. Biomed. Sci. Instrum. 33, 137–142.

Crank, J., 1975. The Mathematics of Diffusion, 2d ed. Clarendon Press, Oxford, Eng.

Ferreira, J.A., de Oliveira, P., da Silva, P., Simon, L., 2011. Flux tracking in drug delivery. Appl. Math. Modell. 35, 4684–4696.

Ferreira, J.A., Grassi, M., Gudiño, E., Oliveira, P.D., 2014. A 3D model for mechanistic control of drug release. SIAM J. Appl. Math. 74, 620–633.

George, K., 2005. A two-dimensional mathematical model of non-linear dual-sorption of percutaneous drug absorption. Biomed. Eng. Online 4, 40.

George, K., Kubota, K., Twizell, E.H., 2004. A two-dimensional mathematical model of percutaneous drug absorption. Biomed. Eng. Online 3, 18.

Jerri, H.A., Dutter, R.A., Velegol, D., 2009. Fabrication of stable anisotropic microcapsules. Soft Matter 5, 827–834.

Kim, C.-J., 2000. Controlled Release Dosage Form Design, 1st ed. Technomic Publishing Co., Lancaster, PA.

Levin, Y., Idiart, M.A., Arenzon, J.J., 2005. Random walk to freedom: the time of effusion. Phys. A: Stat. Mech. Appl. 354, 95–100.

McGinty, S., 2014. A decade of modelling drug release from arterial stents. Math. Biosci. 257, 80–90.

Rice, R.G., Do, D.D., 1995. Applied Mathematics and Modeling for Chemical Engineers. Wiley, New York.

Roy, A., Roy, K., Roy, S., Deb, J., Ghosh, A., Ali, K.A., 2012. Response surface optimization of sustained release metformin-hydrochloride matrix tablets: influence of some hydrophillic polymers on the release. ISRN Pharm. 2012, 364261.

Shefeeq, T., Ahmad, N., Ravins, Singh, R.K., 2012. Theoretical modeling of diffusional release of a dispersed solute from a cylindrical polymeric matrix. J. Nanosci. Nanotechnol. 12, 7167–7172.

Sheu, S.-Y., Yang, D.-Y., 2000. Gated escaping of ligand out of protein. J. Chem. Phys. 112, 408–415.

Siepmann, J., Ainaoui, A., Vergnaud, J.M., Bodmeier, R., 1998. Calculation of the dimensions of drug-polymer devices based on diffusion parameters. J. Pharm. Sci. 87, 827–832.

Siepmann, J., Gopferich, A., 2001. Mathematical modeling of bioerodible, polymeric drug delivery systems. Adv. Drug Deliv. Rev. 48, 229–247.

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.

Simon, L., 2013. Control of Biological and Drug-delivery Systems for Chemical, Biomedical, and Pharmaceutical Engineering. Wiley, Hoboken, N.J.

Simon, L., Ospina, J., 2012. Two-dimensional solution and analysis of a cylindrical matrix device with a circular release area. Chem. Eng. Commun. 200, 115–138.

Simon, L., Ospina, J., 2015. Closed-form Solutions for Drug Transport Through Controlled-release Devices in Two and Three Dimensions. John Wiley & Sons Inc, Hoboken, New Jersey.

Smith, C.A., Corripio, A.B., 2006. Principles and Practice of Automatic Process Control, 3rd ed. Wiley, Hoboken, NJ.

Tojo, K., Miyanami, K., 1983. Controlled release from a cylindrical matrix device. Bulletin of University of Osaka Prefecture. Series A. Eng. Nat. Sci. 31, 149–157.