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On the effusion time of drugs from the open pore of a spherical vesicle

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HIGHLIGHTS

- The effusion time was calculated for a spherical device.
- An analytical solution was derived for the fraction of drug released.
- The effusion time contained geometric characteristics of the device.

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ABSTRACT

Solute permeation through a spherical liposomal vesicle was analyzed using Fick's second law and a mixed Neumann–Dirichlet boundary condition. The first-principles approach was necessary to help calculate the effusion time of a medication through a pore located on the surface of the device. An infinite series of Bessel functions represented the concentration in the Laplace domain. This method yielded closed-form expressions for the characteristic time and the Laplace-transformed fraction of drug released, which was approximated by the first term of the series. The time constant was inversely proportional to the diffusion coefficient in the system and decreased as the pore size increased. It took 4 times the effusion time to unload nearly ninety-eight percent of the pharmaceutical ingredient.

1. Introduction

Several controlled-release products, such as liposomal vesicles, are spherical [1]. These liposomes are filled with a drug, or a gene, designed to treat a disease. 5-Fluorouracil (5-FU) was delivered to androgen receptor-positive tumors using testosterone coupled liposomes [2]. The carriers have also been employed to transport spironolactone, a specific aldosterone antagonist, for the treatment of heart failure [3].

An important problem that arises when evaluating these systems is the effusion time (also called efflux time) of the medication through an open pore of the vesicle [4]. To the best of our knowledge, no analytical expression has been derived to calculate the time for unloading the drug completely from the device. The development of such a formula may be exploited to design products with specific requirements. For example, because the size of the pore affects the drug release rate, it can be used to achieve therapeutic action for either a short or extended period. Previous works show that reducing the orifice diameter in a cylindrical device is an effective way of retarding the transport of the pharmaceutical ingredient [5].

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Although systems with releasing holes have widespread applications, the development of reliable computational tools to determine the time required to release the drug from the vehicle (τ) has received little attention in the literature. After assuming that the process is governed by Fick's second law, Levin et al. proposed an analytical approach to estimate τ [6]. They modeled the system as two spheres, one serving as a sink, to circumvent a mixed boundary condition that is closer to the real geometry. Contrary to devices where the osmotic pressure drives the active ingredient out of an opening in the tablet [7], drug transport was mainly due to diffusion in their study.

There is growing interest in understanding how drug molecules are delivered through liposome pores [8]. While several models have been developed to explain release due to either ruptured liposomes or membrane stretching [9,10], only a few theoretical contributions have tried to explain the mounting evidence of release through transient or permanent pores [8,11,12]. Modeling and simulation of the process would help manufacturers assess the specific role of each mechanism (e.g., permeation through the membrane and release from the pores). Whether the pore size or diffusion through the medium has a discernible impact on the release kinetics is critical in designing efficient vesicular drug-delivery systems that meet end-user requirements. The mathematical model and solution would make it possible to test several designs in a controlled manner and at a relatively inexpensive cost, compared to laboratory tests. Numerical simulations may provide complementary information and valuable insight into the physical phenomena.

Following the work in Ref. [6], a spherical device is considered in this contribution. Transport of the medication through the matrix is governed by Fick's second law. One important departure from this approach is the application of a mixed Neumann–Dirichlet boundary condition to represent material transfer at the surface. A mathematical representation of the problem is first presented followed by an analysis of the dynamic characteristics of the system. Simulation results are reported and discussed.

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 cone (cone and a spherical cap) with apex angle θ_0 (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. Consequently, the governing equation is

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

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

$$\rho\,(r,\theta,0) = \rho_0 \tag{2}$$

and the combined Neumann and Dirichlet boundary conditions are

$$\left.\frac{\partial \rho\,(r,\theta,t)}{\partial r}\right|_{r=R} = 0, \quad \theta_0 \le \theta < \pi \tag{3}$$

and

$$\rho\,(R,\theta,t) = 0, \quad 0 \le \theta < \theta_0 \tag{4}$$

with

$$\sin\theta_0 = \frac{a}{R} \tag{5}$$

where R is the radius of the sphere and a is the base radius of the cap. Azimuthal symmetry is satisfied because the initial concentration is independent of θ.

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

$$M\,(t) = \frac{\rho_0 \frac{4}{3}\pi R^3 - 2\pi \int_0^{\pi}\int_0^{R}\left[\sin(\theta)\,r^2\rho\,(r,\theta,t)\right]\mathrm{d}r\mathrm{d}\theta}{\rho_0 \frac{4}{3}\pi R^3} \tag{6}$$

or

$$M\,(t) = 1 - \frac{2\pi \int_0^{\pi}\int_0^{R}\left[\sin(\theta)\,r^2\rho\,(r,\theta,t)\right]\mathrm{d}r\mathrm{d}\theta}{\rho_0 \frac{4}{3}\pi R^3} \tag{7}$$

which represents the fractional amount of drug released.

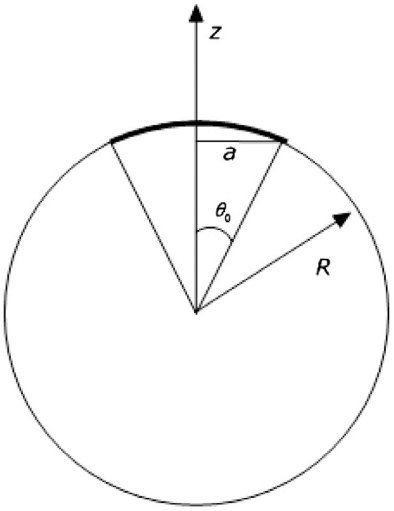

Fig. 1. Schematic representation of the spherical vesicle. R is the radius of the sphere and a is the base radius of the cap; angle θ_0 is the apex angle of the spherical cone.

2.2. Dynamic characteristics

2.2.1. Development of an analytical solution

To solve the system formed by Eqs. (1) and (4), Eq. (1) is first written as

$$\frac{\partial}{\partial t}\rho\left(r,\theta,t\right)=D\left(2\,\frac{\frac{\partial}{\partial r}\rho\left(r,\theta,t\right)}{r}+\frac{\partial^2}{\partial r^2}\rho\left(r,\theta,t\right)+\frac{\cos\left(\theta\right)\frac{\partial}{\partial\theta}\rho\left(r,\theta,t\right)}{r^2\sin\left(\theta\right)}+\frac{\frac{\partial^2}{\partial\theta^2}\rho\left(r,\theta,t\right)^2}{r}\right). \tag{8}$$

Application of the Laplace operator leads to

$$sP\left(r,\theta\right)-\rho_0=D\left(2\,\frac{\frac{\partial}{\partial r}P\left(r,\theta\right)}{r}+\frac{\partial^2}{\partial r^2}P\left(r,\theta\right)+\frac{\cos\left(\theta\right)\frac{\partial}{\partial\theta}P\left(r,\theta\right)}{r^2\sin\left(\theta\right)}+\frac{\frac{\partial^2}{\partial\theta^2}P\left(r,\theta\right)^2}{r}\right) \tag{9}$$

where

$$P\left(r,\theta\right)=\int_0^\infty\rho\left(r,\theta,t\right)\mathrm{e}^{-st}\mathrm{d}t \tag{10}$$

using the initial condition (2). We look for a solution to Eq. (8) of the form

$$P\left(r,\theta\right)=f\left(r\right)g\left(\theta\right)+\frac{\rho_0}{s} \tag{11}$$

with

$$\frac{\mathrm{d}^2}{\mathrm{d}r^2}f\left(r\right)=-\frac{c_1f\left(r\right)}{Dr^2}+\frac{-2D\left(\frac{\mathrm{d}}{\mathrm{d}r}f\left(r\right)\right)+sf\left(r\right)r}{Dr} \tag{12}$$

and

$$\frac{\mathrm{d}^2}{\mathrm{d}\theta^2}g\left(\theta\right)=\frac{c_1g\left(\theta\right)}{D}-\frac{\cos\left(\theta\right)\left(\frac{\mathrm{d}}{\mathrm{d}\theta}g\left(\theta\right)\right)}{\sin\left(\theta\right)} \tag{13}$$

where c_1 is a separation-of-variables constant. Solving Eqs. (12) and (13) yields

$$\begin{aligned}f\left(r\right)g\left(\theta\right)=\;&\frac{1}{\sqrt{r}}\left(C_1I_{\frac{1}{2}\sqrt{\frac{D-4c_1}{D}}}\left(r\sqrt{\frac{s}{D}}\right)+C_2K_{\frac{1}{2}\sqrt{\frac{D-4c_1}{D}}}\left(r\sqrt{\frac{s}{D}}\right)\right)\\&\times\left(C_3P_{-\frac{1}{2}\frac{\sqrt{D}-\sqrt{D-4c_1}}{\sqrt{D}}}\left(\cos\left(\theta\right)\right)+C_4Q_{-\frac{1}{2}\frac{\sqrt{D}-\sqrt{D-4c_1}}{\sqrt{D}}}\left(\cos\left(\theta\right)\right)\right).\end{aligned} \tag{14}$$

To form a solution without singularities, we make $C_2 = 0$, $C_4 = 0$ and $C_3 = 1$. Note that the Bessel function K has a singularity at $r = 0$ and the Legendre function Q has singularities at $\theta = 0$ and $\theta = \pi$. Thus, Eq. (14) is reduced to

$$f(r)\, g(\theta) = \frac{1}{\sqrt{r}} \left(C_1 I_{\frac{1}{2}\sqrt{\frac{D-4c_1}{D}}} \left(r\sqrt{\frac{s}{D}} \right) P_{-\frac{1}{2}\frac{\sqrt{D}-\sqrt{D-4c_1}}{\sqrt{D}}} (\cos(\theta)) \right). \tag{15}$$

The Legendre function P becomes a polynomial by setting

$$\frac{1}{2}\frac{\sqrt{D-4c_1}-\sqrt{D}}{\sqrt{D}} = n \tag{16}$$

where n is an integer. From Eq. (16), we derive

$$c_1 = -\frac{\left(2n\sqrt{D}+\sqrt{D}\right)^2}{4} + \frac{D}{4}. \tag{17}$$

Therefore, Eq. (15) becomes

$$f(r)\, g(\theta) = \frac{1}{\sqrt{r}} \left(C_1 I_{n+\frac{1}{2}} \left(r\sqrt{\frac{s}{D}} \right) P_n(\cos(\theta)) \right). \tag{18}$$

Applying the superposition principle to Eq. (18), Eq. (11) is rewritten as

$$P(r,\theta) = \frac{1}{\sqrt{r}} \left(\sum_{n=0}^{\infty} A_n I_{n+\frac{1}{2}} \left(r\sqrt{\frac{s}{D}} \right) P_n(\cos(\theta)) \right) + \frac{\rho_0}{s}. \tag{19}$$

After combining Eq. (19) and the Laplace transform of boundary condition (3), the resulting expression is

$$\sum_{n=0}^{\infty} \frac{A_n P_n(\cos(\theta)) \left(R\sqrt{s} I_{n+\frac{3}{2}} \left(R\sqrt{\frac{s}{D}} \right) + n\sqrt{D} I_{n+\frac{1}{2}} \left(R\sqrt{\frac{s}{D}} \right) \right)}{R^{\frac{3}{2}}\sqrt{D}} = 0. \tag{20}$$

A similar operation performed on Eqs. (4) and (19) yields

$$\left(\sum_{n=0}^{\infty} \frac{A_n I_{n+\frac{1}{2}} \left(R\sqrt{\frac{s}{D}} \right) P_n(\cos(\theta))}{\sqrt{R}} \right) + \frac{\rho_0}{s} = 0 \tag{21}$$

which, after a first-order approximation, becomes

$$\frac{A_0\sqrt{2}}{\sqrt{R\sqrt{\frac{s}{D}}\sqrt{R\pi}}} \sinh\left(R\sqrt{\frac{s}{D}} \right) + \frac{A_1\sqrt{2}\cos(\theta)\left(\cosh\left(R\sqrt{\frac{s}{D}} \right)\sqrt{s}R - \sinh\left(R\sqrt{\frac{s}{D}} \right)\sqrt{D} \right)}{\sqrt{\pi RD}\left(R\sqrt{\frac{s}{D}} \right)^{3/2}} + \frac{\rho_0}{s} = 0. \tag{22}$$

The integral of Eq. (22) with respect to θ from 0 to θ_0 gives

$$\frac{\left(\begin{array}{c} -A_0\sqrt{2}\sinh\left(R\sqrt{\frac{s}{D}} \right)\theta_0 s^{3/2}R - A_1\sqrt{2}\sin(\theta_0)\, s^{3/2}\cosh\left(R\sqrt{\frac{s}{D}} \right)R \\ + A_1\sqrt{2}\sin(\theta_0)\, s\sinh\left(R\sqrt{\frac{s}{D}} \right)\sqrt{D} - \rho_0\theta_0\left(R\sqrt{\frac{s}{D}} \right)^{3/2}\sqrt{\pi RD} \end{array} \right)}{s\sqrt{\pi RD}\left(R\sqrt{\frac{s}{D}} \right)^{3/2}} = 0 \tag{23}$$

and the integral of the first-order approximation of Eq. (20) with respect to θ from θ_0 to π yields

$$\frac{\left(\begin{array}{l} A_0 s^{3/2}\theta_0 R^2 D^2 \cosh\left(R\sqrt{\frac{s}{D}}\right) - A_0 s\theta_0 R D^{5/2}\sinh\left(R\sqrt{\frac{s}{D}}\right) \\ \quad + A_1 \sin(\theta_0)\, D^2 s^{3/2} R^2 \sinh\left(R\sqrt{\frac{s}{D}}\right) + 2A_1 \sin(\theta_0)\, D^3\sqrt{s}\sinh\left(R\sqrt{\frac{s}{D}}\right) \\ \quad - 2A_1 \sin(\theta_0)\, D^{5/2} sR\cosh\left(R\sqrt{\frac{s}{D}}\right) - R^2\pi\, A_0 D^2 s^{3/2}\cosh\left(R\sqrt{\frac{s}{D}}\right) \\ \quad + R\pi\, A_0 D^{5/2} s\sinh\left(R\sqrt{\frac{s}{D}}\right) \end{array}\right)}{\left(R\sqrt{\frac{s}{D}}\right)^{5/2}\frac{\sqrt{\pi R D^{7/2}}}{\sqrt{2}}} = 0. \tag{24}$$

The coefficients A_0 and A_1 are obtained by solving Eqs. (23) and (24):

$$A_0 = -\sqrt{2\pi R}\rho_0\theta_0\sqrt{s}\,\frac{\left(\begin{array}{l} -D^2 s^{3/2}R^2\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 + D^2 s^{3/2}R^2 - 2D^3\sqrt{s}\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 \\ \quad + 2D^3\sqrt{s} + 2D^{5/2}sR\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 + 2D^{5/2}sR \end{array}\right)}{\left(\begin{array}{l} 4s^3R^2\theta_0 D^2\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 - s^2D^3\theta_0 - s^2D^3\pi \\ \quad - s^2D^3\left(e^{R\sqrt{\frac{s}{D}}}\right)^4\theta_0 + 2s^2D^3\left(e^{R\sqrt{\frac{s}{D}}}\right)^2\theta_0 - s^2D^3\left(e^{R\sqrt{\frac{s}{D}}}\right)^4\pi \\ \quad + 2s^2D^3\left(e^{R\sqrt{\frac{s}{D}}}\right)^2\pi - s^3R^2\pi D^2 + 2s^{5/2}D^{5/2}\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 R\pi \\ \quad - 2s^{5/2}D^{5/2}R\pi - 2s^3R^2\pi D^2\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 - s^3R^2\left(e^{R\sqrt{\frac{s}{D}}}\right)^4\pi D^2 \end{array}\right)}\sqrt{R\sqrt{\frac{s}{D}}}e^{R\sqrt{\frac{s}{D}}} \tag{25}$$

and

$$A_1 = -\frac{R^{3/2}\sqrt{2}\rho_0\theta_0\sqrt{s}\sqrt{\pi}}{\sin(\theta_0)}\,\frac{\left(\begin{array}{l} -s\theta_0 D^{5/2}\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 + s\theta_0 D^{5/2} + s^{3/2}\theta_0 RD^2\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 \\ \quad + s^{3/2}\theta_0 RD^2 - R\pi\, D^2 s^{3/2}\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 - R\pi\, D^2 s^{3/2} \\ \quad + \pi\, D^{5/2} s\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 - \pi\, D^{5/2} s \end{array}\right)}{\left(\begin{array}{l} 4s^3R^2\theta_0 D^2\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 - s^2D^3\theta_0 - s^2D^3\pi \\ \quad - s^2D^3\left(e^{R\sqrt{\frac{s}{D}}}\right)^4\theta_0 + 2s^2D^3\left(e^{R\sqrt{\frac{s}{D}}}\right)^2\theta_0 \\ \quad - s^2D^3\left(e^{R\sqrt{\frac{s}{D}}}\right)^4\pi + 2s^2D^3\left(e^{R\sqrt{\frac{s}{D}}}\right)^2\pi - s^3R^2\pi D^2 \\ \quad + 2s^{5/2}D^{5/2}\left(e^{R\sqrt{\frac{s}{D}}}\right)^4 R\pi - 2s^{5/2}D^{5/2}R\pi \\ \quad - 2s^3R^2\pi D^2\left(e^{R\sqrt{\frac{s}{D}}}\right)^2 - s^3R^2\left(e^{R\sqrt{\frac{s}{D}}}\right)^4\pi D^2 \end{array}\right)}\sqrt{R\sqrt{\frac{s}{D}}}e^{R\sqrt{\frac{s}{D}}}. \tag{26}$$

As a result, $P(r,\theta)$ is given as

$$P(r,\theta) = \frac{1}{\sqrt{r}}\left(\sum_{n=0}^{1} A_n I_{n+\frac{1}{2}}\left(r\sqrt{\frac{s}{D}}\right)P_n(\cos(\theta))\right) + \frac{\rho_0}{s} \tag{27}$$

and the Laplace transform of $M(t)$ is

$$\bar{M}(s) = \frac{4\sqrt{2\pi R}A_0\left(-\sqrt{D}Rs\cosh\left(R\sqrt{\frac{s}{D}}\right) + D\sqrt{s}\sinh\left(R\sqrt{\frac{s}{D}}\right)\right)}{\left(\frac{4}{3}R^3\pi\rho_0\right)s^{3/2}\sqrt{R\sqrt{\frac{s}{D}}}}. \tag{28}$$

In theory, additional terms can be included in the series solution. However, the procedure becomes computationally expensive and the expression for τ_{eff}, too complex for practical implementation. The first-order approximation is exact when θ_0 approaches 0. In this case, the entire amount of the drug remains in the device. From Eq. (25), we obtain $A_0 = 0$ yielding $\bar{M}(s) = 0$ (Eq. (28)), as expected.

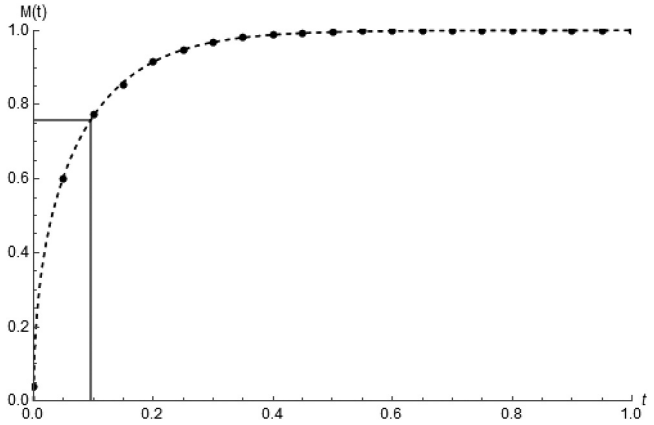

Fig. 2. Cumulative amount of drug released $M(t)$ through the pore of the vesicle when $\theta_0 = \pi$. The profile generated after inverting Eq. (28) (- - - -) was compared to the numerical solution (•) of the function "NDSolveValue". The intersection of the straight lines represents the effusion time.

2.2.2. Derivation of the effusion time

The concept of a time constant [13,14] is applied to evaluate the characteristic time for effusion. It is estimated in this work by the method proposed by Collins [15]:

$$\tau_{\text{eff}} = \int_0^\infty t\Omega(t)\,\mathrm{d}t \tag{29}$$

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

$$\Omega(t) = \frac{(M(\infty) - M(t))}{\int_0^\infty (M(\infty) - M(t))\,\mathrm{d}t}. \tag{30}$$

Eq. (29) is written in terms of Laplace variables as

$$\tau_{\text{eff}} = \lim_{s\to 0}\left(\frac{M(\infty)}{s^2} + \frac{\mathrm{d}\bar{M}(s)}{\mathrm{d}s}\right)\left[\lim_{s\to 0}\left(\frac{M(\infty)}{s} - \bar{M}(s)\right)\right]^{-1}. \tag{31}$$

It can be shown that

$$\tau_{\text{eff}} = \frac{1}{21}\frac{R^2\left(2\theta_0^2 + 35\pi^2 - 35\pi\theta_0\right)}{D\theta_0\left(-4\theta_0 + 5\pi\right)} \tag{32}$$

after using Eqs. (28) and (31). The effusion is $\tau_{\text{eff}} = \frac{2R^2}{21D}$ when $\theta_0 \to \pi$.

3. Results and discussions

***Case* 1**. $\theta_0 = \pi$

When $\theta_0 = \pi$, the system takes the form of a one-dimensional problem with a perfect sink boundary condition (4). The following normalized parameters are chosen: $\bar{R} = R/R = 1$ and $\bar{t}_{fin} = Dt_{fin}/R^2 = 1$, where t_{fun} represents the simulation time. A numerical technique [16] was employed to invert Eq. (28). The result was compared to a solution produced by the function "NDSolveValue", from Mathematica (Wolfram Research, Inc.). This validation step is important to ensure the reliability of Eq. (32). The profiles for the cumulative amount of drug released profiles are indistinguishable (Fig. 2) and the characteristic time for effusion is 0.095. It is worth noting that $M(4 \times \tau_{\text{eff}}) = 98.6\%$, which agrees with the observation that it takes approximately 4 time constants for the response of a first-order process to reach 98% of its final value after a unit step input change [17,18].

***Case* 2**. $\theta_0 = 0.2\pi$

Consider the case where the apex angle is small (e.g., 0.2π). This scenario is equivalent to setting a equal to $0.31R$ (see Eq. (5)). Fig. 3 shows a small discrepancy between the profiles from "NDSolveValue" and Eq. (28) at small times. But, as the time increases, the prediction becomes more accurate. Note that $M(4 \times \tau_{\text{eff}}) = 98.4\%$ and the effusion time is 1.59, which is greater than the value reported when $\theta_0 = \pi$. As the size of the release hole decreases, it takes more time for the drug to escape through the pore of the vesicle. In fact, Eq. (32) shows that τ_{eff} approaches infinity as θ_0 approaches zero.

The proposed model and solution procedure have immediate implications in several areas. The framework can be applied directly to (i) explain drug release from microspheres [19], (ii) study the mechanism by which a ligand escapes from a protein [20] and (iii) estimate the time it takes for a diffusing receptor to be attached at its final location on a

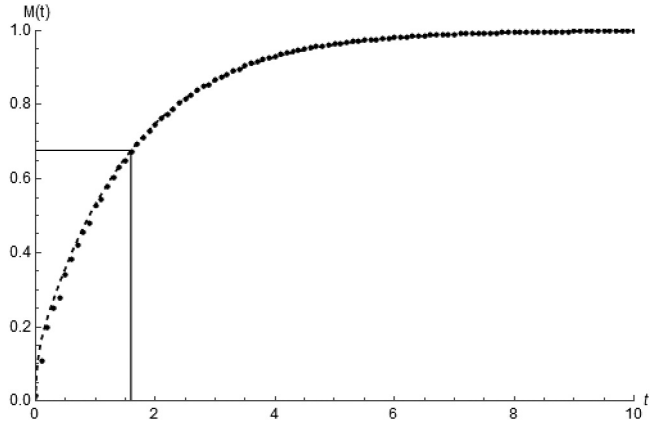

Fig. 3. Cumulative amount of drug released $M(t)$ through the pore of the vesicle when $\theta_0 = 0.2\pi$. The profile generated after inverting Eq. (28) (- - - -) was compared to the numerical solution (•) of the function "NDSolveValue". The intersection of the straight lines represents the effusion time.

postsynaptic membrane after insertion into the membrane [21]. The last two examples are part of the narrow escape problem, encountered in biophysics and biology. In this context, a brownian particle, such as a protein, is confined to a bounded domain and can only escape through a small window [22]. Mixed Dirichlet–Neumann boundary conditions, similar to Eqs. (3) and (4), are enforced to help estimate the mean escape time.

4. Conclusions

The effusion time of a drug from a spherical device, such as a vesicle, was analyzed in this work. Fick's second law was applied to model permeation of the medication through the matrix. Mass transfer at the surface of the vehicle was captured by a mixed Neumann–Dirichlet boundary condition. The governing equations were solved by a Laplace transform-based method and the concentration was expressed as an infinite series in the frequency domain. After retaining the first term of the series, the fractional amount of drug released was derived and inverted using a numerical method. The result was compared to that reported by Mathematica. The effusion time was estimated and contained geometric characteristics of the device and the diffusion coefficient. Two case studies show that a decrease in the size of the release hole results in a lower time constant.

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