Physica A 451 (2016) 366–372

Contents lists available at ScienceDirect

Physica A

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

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.

ARTICLE INFO

Article history:
Received 31 October 2015
Received in revised form 1 January 2016
Available online 8 February 2016

Keywords:
Effusion time
Effective time constant
Controlled release
Spherical device
Laplace transform
Bessel function

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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http://dx.doi.org/10.1016/j.physa.2016.01.097
0378-4371/

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.