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

Laurent Simon[a,*], Juan Ospina[b]

[a] Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering, New Jersey Institute of Technology, Newark NJ 0702, USA
[b] Logic and Computation Group, Physics Engineering Program, School of Sciences and Humanities, EAFIT University, Medellin, Colombia

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

* Corresponding author.
E-mail address: laurent.simon@njit.edu (L. Simon).

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.

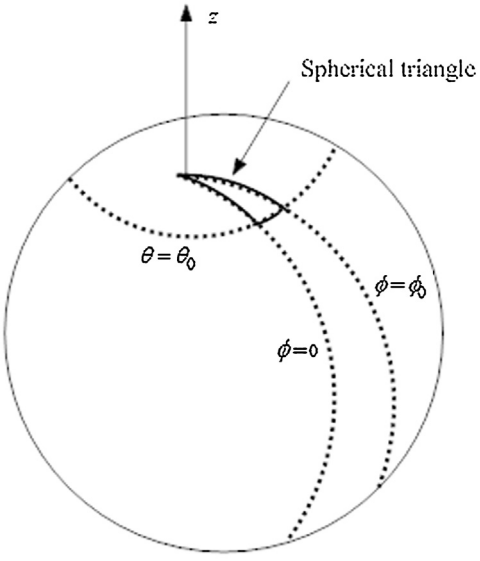

Fig. 1. The surface of the device is impermeable to drug diffusion except through a region delimited by a spherical triangle with $\theta_0 \le \theta < \pi$and $\phi_0 \le \phi < 2\pi$.

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

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