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Controlled Release of Drugs from Polymeric Devices

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Abstract

Mathematical modeling of polymeric controlled drug release systems can be used to predict drug release rates and drug diffusion characteristics to reduce the number of experiments. These models also provide an insight into physical mechanisms of drug transport by comparing the experimental data with the model simulations. Clinical use of these polymeric devices requires that the drug release follows a given profile. Release of drugs in a controlled manner can be facilitated by designing polymeric devices with optimal geometry and diffusivity property. In this paper the convexity properties of the drug release profile are analyzed. Such an analysis is important to formulate the design problem in an optimization framework and select appropriate solution techniques to ensure global optimality.

Keywords: Drug delivery, design of devices, convexity analysis.

1. Introduction

Drug delivery covers a very broad range of techniques for getting the therapeutic agents into the human body [1-8]. Ingested tablets and injections are the most commonly used modes of delivery. For the case of ingested tablets, since the drug enters the bloodstream through the hepatic system it has low bioavailability and can even damage the liver. The injection mode allows delivery of any size of drug molecule but its main drawbacks are the short

duration for drugs, with small half-lives, and being invasive and painful. To summarize, the major shortcomings of these methods are the duration for which the drug is active in the body and its control. The objective of controlled drug delivery systems is not only to increase the amount of drug entering the bloodstream but also to maintain the desired plasma profile of the drug. Other modes of delivery have been devised to overcome some of these limitations, these include transdermal, transmucosal, transocular, transalveolar, implantable and injectable; use of nanoparticles for delivering DNA or genes to cells has also been reported. In this work polymeric devices for controlled release of drugs are considered.

Intelligent drug delivery devices can be used to release precise amount of drugs at specific sites and at specific times, to meet the therapeutic needs of patients. These devices usually comprise of a drug carrier and an appropriate amount of drug dispersed within the carrier. Polymeric materials are the most widely used carriers, primarily due to their biocompatibility, biofunctionality and biodegradability properties. These devices are expected to provide effective therapy, reduce toxicity and increase patient comfort levels. Design of these devices comprises of following main problems: selection of appropriate materials, optimal geometrical configuration of the device and optimal distribution of the drugs within the device.

An aim of this work is to underpin the development of computational techniques for designing devices for controlled release of drugs. The design problem can be formulated as an optimization problem [9-10] where the objective is to minimize the difference between the actual drug release profile and the desired profile, and the main optimization variables are the initial drug loading and distribution, and the geometry of the device. Constraints can also be introduced to avoid overdosing and underdosing of drugs. This paper analyses the convexity properties of the equation describing the drug release profile; this equation appears in the design problem. Rest of the paper is organised as follows. Next section presents an overview of the drug release from polymeric materials. Section 3 presents convexity analysis of the equation describing the drug release profile and finally concluding remarks are presented in section 4.

2. Drug Diffusion from Polymeric Materials

For delivery devices where the active agent is dissolved in the polymer matrix the diffusion of the agent from the matrix to the external surroundings is given by:

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \tag{1}$$

where c is concentration of the drug in the polymer, t is time and D is the diffusivity coefficient of the drug in the polymer. Solution of this equation subject to following boundary and initial conditions (Figure 1):

$$
\begin{aligned}
c = c_0 \quad & t = 0 \quad 0 < x < L \\
c = c_s \quad & t > 0 \quad x = 0, L \\
\frac{\partial c}{\partial x} = 0 \quad & t > 0 \quad x = L/2
\end{aligned}
\tag{2}
$$

where c_s is the concentration of the drug in the medium surrounding the device, is given by:

$$\frac{c - c_s}{c_0 - c_s} = \frac{4}{\pi} \sum_{n=0}^{\infty} \frac{1}{2n+1} \exp\left(-\frac{D(2n+1)^2 \pi^2 t}{L^2} \right) \sin\left(\frac{(2n+1)\pi x}{L} \right) \tag{3}$$
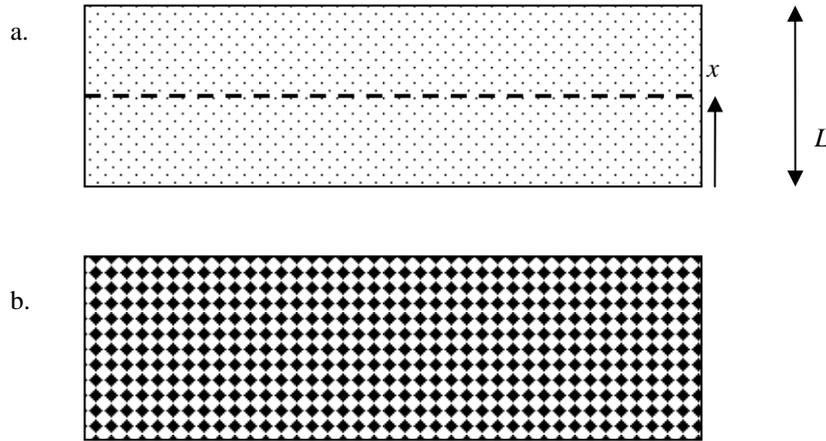

Figure 1. Polymer matrix systems for controlled drug delivery: (a) drug dissolved in the matrix material and (b) drug particles dispersed to form the composite material [11].

The cumulative amount of the active agent released from the matrix at time t is given by:

$$E_t = c_0 AL - \int_0^L c(x,t) A \, dx \qquad (4)$$

where $E_\infty = c_0 AL$ is initial amount of drug in the matrix and A is the exposed area of the external surface of the device. The above equation provides the cumulative fractional release [11-12] (Figure 2):

$$\frac{E_t}{E_\infty} = 1 - \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp\left(-\frac{D(2n+1)^2 \pi^2 t}{L^2} \right) \qquad (5)$$
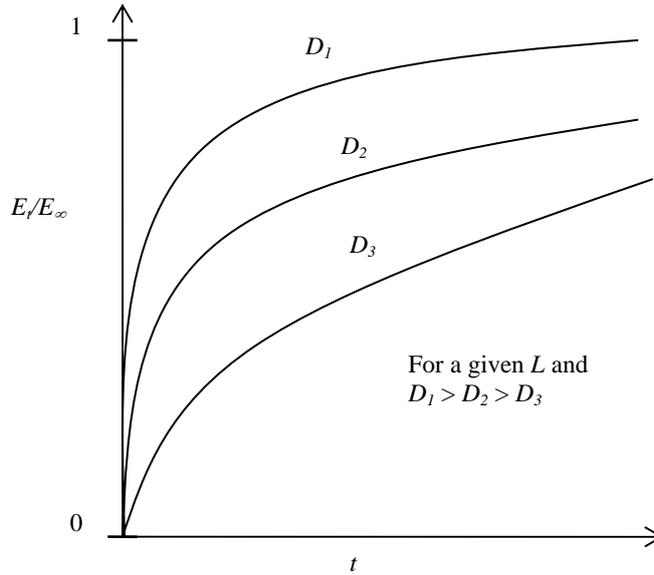

Figure 2. Cumulative drug release profiles for fixed *L* and varying *D*.

3. Convexity Analysis

Design of polymer matrix devices involves determining appropriate polymeric material and its dimensions, *L*, so as to meet the clinical requirements of the desired active agent release profile. Polymeric material must be biocompatible and non-toxic and have suitable diffusivity, *D*. The design problem can be

formulated as an optimization problem where the objective is to minimize the deviation between the desired release profile and the profile given by the above equation, subject to lower and upper bounds on D and L. The convexity of such an optimization problem and various formulations for the optimization problem will be discussed in a separate and extended paper; in this paper we discuss the convexity properties of the fractional release profile, E_t/E_∞, which participates in the optimization problem. Considering D and L as the optimization variables, the terms in this equation are analyzed.
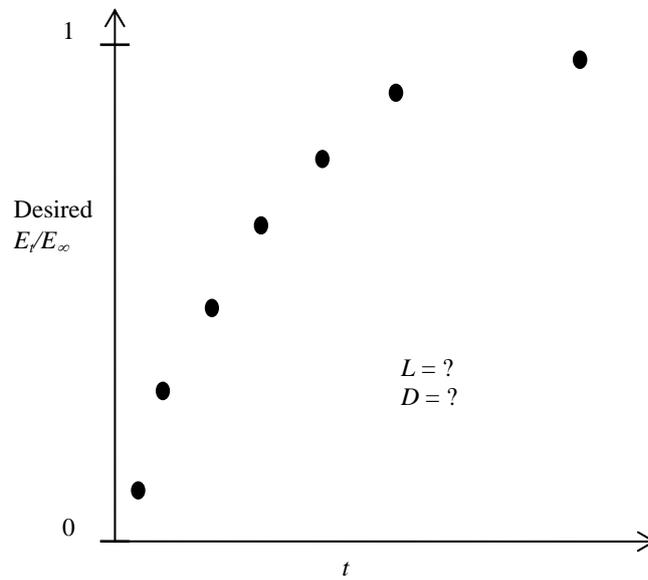

Figure 3. Desired drug release profile given at finite number of time points.

The equation involves a summation of n terms in the series and a term can be rewritten as $a.\exp(-b.D.t /L^2)$, where a and b are positive constants. For example, for $n = 0$, $a = 8/\pi^2$, $b = \pi^2$. The desired drug release profile can be specified at discrete points in time and therefore t appears as constant time points (see Figure 3). The terms in the series can be rewritten as $a.\exp(-c.D /L^2)$, where $c = b.t$ is a positive constant. Define $z = D/L^2$; it can be shown that $a.\exp(-c.z)$ is a convex function of z since second derivative of $a.\exp(-c.z)$ with respect to z is given by $a.c^2.\exp(-c.z)$ which is always positive. The summation of the terms in the series is therefore a convex function of z and since there is a negative sign in front of this summation, the drug release profile, E_t/E_∞, is a concave function of z. Note that for a given value of z, the solution of the design problem is not unique since different sets of values of D and L can provide the

same value of z. In this case it is important to consider other factors such as lower and upper bounds on D and L and cost of manufacturing of the devices.

4. Concluding Remarks

Polymeric devices are widely used in delivering active agents at controlled rates. Design of these devices can be formulated as an optimization problem and in this paper the convexity properties of the drug release profile have been analyzed. It is shown that the drug release profile is a concave function of D/L^2 where D is the diffusion coefficient and L is the thickness of the device. This analysis paves the way for systematically analyzing the convexity properties of the device design problems and exploring possibilities of existence of multiple solutions of the design problem. Future work will also consider the cases where D and L vary with time and optimization variables also include initial drug concentration and cross section area of the device. Effect of the number of terms in the series on the accuracy of the solution will also be analyzed. It is envisaged that the developments presented in this work will lead to novel process and product designs.

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