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A mathematical model for pulsatile release: Controlled release of rhodamine B from UV-crosslinked thermoresponsive thin films

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ABSTRACT

A controlled drug delivery system fabricated from a thermoresponsive polymer was designed to obtain a pulsatile release profile which was triggered by altering the temperature of the dissolution medium. Two stages of release behaviour were found: fast release for a swollen state and slow (yet significant and non-negligible) release for a collapsed state. Six cycles of pulsatile release between 4 °C and 40 °C were obtained. The dosage of drug (rhodamine B) released in these cycles could be controlled to deliver approximately equal doses by altering the release time in the swollen state. However, for the first cycle, the swollen release rate was found to be large, and the release time could not be made short enough to prevent a larger dose than desired being delivered. A model was developed based on Fick's law which describes pulsatile release mathematically for the first time, and diffusion coefficients at different temperatures (including temperatures corresponding to both the fully swollen and collapsed states) were estimated by fitting the experimental data with the theoretical release profile given by this model. The effect of temperature on the diffusion coefficient was studied and it was found that in the range of the lower critical solution temperature (LCST), the diffusion coefficient increased with decreasing temperature. The model predicts that the effective lifetime of the system lies in the approximate range of 1–42 h (95% of drug released), depending on how long the system was kept at low temperature (below the LCST). Therefore this system can be used to obtain a controllable pulsatile release profile for small molecule drugs thereby enabling optimum therapeutic effects.

1. Introduction

Most local drug delivery systems aim to maintain the drug concentration at some appropriate therapeutic level for a specified period of time, and this objective is frequently achieved using sustained release dosage forms. However, for some drugs, an optimum therapeutic effect comes from a periodically fluctuating drug concentration (Kikuchi and Okano, 2002). To realise such behaviour, pulsed or pulsatile drug release systems have been developed (Bae et al., 1991; Coughlan et al., 2004; Ishino et al., 1992; Lowman and Peppas, 1999; Mundargi et al., 2010; Siegel and Pitt, 1995; Vertommen et al., 2008). This type of release system possesses a cycle with two distinct release stages; off/slow release and on/fast release. Usually, the release duration time for the slow release stage is much longer than that for the fast stage, and the release rate is much smaller.

The majority of existing pulsatile release systems can be classified into two categories (Kikuchi and Okano, 2002); time-controlled systems (Intra et al., 2008; Kashyap et al., 2007; Liu et al., 2007; Makino et al., 2000) and stimuli-induced systems (Li and D'Emanuele, 2001; Mohamad and Dashevsky, 2006; Satarkar and Hilt, 2008; Schellekens et al., 2008). Time-controlled release systems can only release at pre-programmed time points, whereas stimuli-induced pulsatile release systems are more easily manipulated. Stimuli-induced systems have been developed based on thermal, chemical, and electrical stimuli. However, systems based on thermal stimuli are particularly convenient since they can be designed and operated without significantly affecting other critical parameters of the system.

Thermoresponsive polymers undergo dramatic changes in conformation in response to a small change in temperature. They

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possess a lower critical solution temperature (LCST) in aqueous solution, below which they are hydrophilic and absorb water to become swollen, and above which they are hydrophobic and expel water to become dense and dry. The thermoresponsive polymer, poly(*N*-isopropylacrylamide) (pNIPAm) has been extensively studied. Its LCST (Heskins and Guillet, 1968) is near physiological temperature (37 °C), and the highly temperature-sensitive transition between the hydrophobic and hydrophilic states (also known as the volume phase transition) is independent of other factors, such as pH (Pei et al., 2004). This polymer has been used in the construction of many pulsatile drug release systems that are triggered by altering the temperature, such as hydrogel matrices (Caykara et al., 2006; Coughlan et al., 2004), microspheres (Fundueanu et al., 2009b; Mundargi et al., 2010; Wei et al., 2009), membranes (Li and D'Emanuele, 2001), porous systems (Fundueanu et al., 2009a; Vertommen et al., 2008) and thin films (Doorty et al., 2003; Kavanagh et al., 2005). The release time for a single cycle for these various delivery systems ranged from approximately 20 min (Fundueanu et al., 2009b) to 15 h (Coughlan et al., 2004). In the current study, the release profiles indicate that the behaviour is diffusion dominated, although some behaviour characteristic of zero-order release was also observed (Fundueanu et al., 2009b). The parameters that can be used to control drug release from the system include the initial drug loading concentration, the geometrical dimensions of the system (such as thickness and surface area), and the durations the device is left switched on/off; the governing mathematical model described here incorporates all of these quantities.

A few models have previously been developed to describe the release behaviour from swelling delivery systems (Brazel and Peppas, 2000; Crank, 1975; Fujita, 1961; Grassi and Grassi, 2005; Kikuchi and Okano, 2002; Lee, 1985; Siegel and Pitt, 1995; Siepmann et al., 1998; Siepmann and Siepmann, 2008), and diffusion from thin films has been well studied (Cooke and Chen, 1995; McCaig et al., 2000; Sanches Silva and Cruz, 2007; Wang et al., 2007). However, in this paper, the first model to incorporate release from a system that alternates between a swollen hydrophilic state and a film-like hydrophobic state is described.

In this work, a fabrication procedure is described for thin hydrogel films loaded with rhodamine B, and the drug release behaviour from these films is analyzed. The objective of the study is to develop a new controllable drug delivery system based on thin UV-crosslinked thermoresponsive films, which can be characterised and tuned with the aid of a mathematical model.

2. Modelling pulsatile release

A one-dimensional model is formulated for drug diffusion in the film, and the release behaviour is considered for the case in which the temperature of the film is quickly and repeatedly switched between a value above the LCST and a value below the LCST. The motion of the drug molecules through the film is assumed to be governed by Fick's law and we denote by $c(x, t)$ the concentration of drug at penetration x and time t in the film. When the film is held at a temperature above the LCST, it is in a condensed state, and we denote by H_c, D_c the constant thickness and diffusivity of the condensed film, respectively. If the film is held at a temperature below the LCST, it is in a swollen state, and we denote by H_s, D_s the constant thickness and diffusivity of the swollen film, respectively. The lateral dimensions of the film are fixed because they are constrained by the wall of the containing well, and swelling/collapsing can only occur in the x direction. We shall find, as would be expected, that $D_c \ll D_s$, so that alternating the temperature between values above and below the LCST results in a release profile with an on/off pulsatile character.

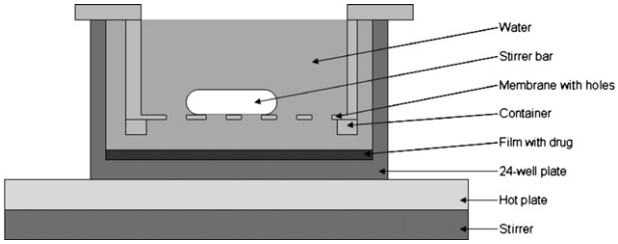

Fig. 1. The experimental setup for the drug release experiment at the start.

The time the polymer was left in either the fully swollen or fully collapsed state was typically of the order of minutes. However, in the experimental work for this paper, the time it took for the thin polymer film to either fully swell or fully collapse was considerably shorter than a minute. Hence, in the current model, we assume that the swelling and collapsing processes occur instantaneously. This assumption simplifies the problem considerably since incorporating the detail of the swelling or collapsing behaviour in the model would require the tracking of moving boundaries (Siepmann and Siepmann, 2008). This would lead to a much more challenging mathematical problem, from which an analytical expression for the release profile could not be in general obtained.

We suppose that at time $t = 0$ the film is at the temperature above the LCST and is fully collapsed. At time $t = t_1$ the temperature of the film is taken to instantaneously switch to the value below the LCST and the film is fully swollen; at time $t = t_2$ the film instantaneously reverts to the collapsed state, and so on (collapsed → swollen → collapsed → ...).

If $H(t)$, $D(t)$ denote the thickness of the film and the drug diffusivity at time t, respectively, then under the assumptions stated above, the concentration $c(x, t)$ of drug in the film is governed by:

$$\frac{\partial c}{\partial t} = D(t)\frac{\partial^2 c}{\partial x^2} \quad \text{for} \quad 0 < x < H(t), \tag{1}$$

where

$$D(t) = \begin{cases} D_c, 0 \le t < t_1, \\ D_s, t_1 \le t < t_2, \\ D_c, t_2 \le t < t_3, \\ \vdots \end{cases} \quad \text{and} \quad H(t) = \begin{cases} H_c, 0 \le t < t_1, \\ H_s, t_1 \le t < t_2, \\ H_c, t_2 \le t < t_3, \\ \vdots \end{cases} \tag{2}$$

Eqs. (1) and (2) are solved subject to the following conditions.

(i) The film is initially uniformly loaded with drug, so we take $c = c_0$ at $t = 0$ in $0 < x < H_c$ where c_0 is constant.
(ii) The bottom of the film (see Fig. 1), $x = 0$, is attached to a plastic cover slip substrate, which is taken to be impermeable to the drug, and so we impose $-D(\partial c/\partial x) = 0$ on $x = 0$.
(iii) Perfect sink conditions are assumed for the drug at the top surface of the film which is in contact with the eluting medium, and so we set $c = 0$ on $x = H(t)$.

The model (1) and (2) is readily solved subject to (i)–(iii) by separating variables (Crank, 1975) and the amount of drug released per unit area from the film by time t, $M(t) = H_c c_0 - \int_0^{H_c} c(x, t)dx$,