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A two-phase model for drug release from microparticles with combined effects of solubilisation and recrystallisation

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ABSTRACT

The present study aims to provide a comprehensive mathematical model for drug release from microparticles to the adjacent tissues. In the elucidation of drug release mechanisms, the role of mathematical modelling has been depicted thereby facilitating the development of new therapeutic drug by a systematic approach, rather than expensive experimental trial-and-error methods. In order to study the whole process, a two-phase mathematical model describing the dynamics of drug transport in two coupled media is presented. Drug release is described taking into consideration both solubilisation dynamics of drug crystallites and diffusion of the solubilised drug through the microparticle. In the coupled media, reversible dissociation/recrystallisation processes are taking place. The model has led to a system of partial differential equations that are solved analytically. The model points out the important roles played by the diffusion, mass-transfer and reaction parameters, which are the main architects behind drug kinetics across two layers. The dependence of drug masses on the main parameters is also analysed.

1. Introduction

Sometimes, patients consciously or unconsciously change their prescribed drug dosage schedules and many a time physicians are not informed of this. Forgetfulness, is one of the major reasons behind this non-compliance by the patients, which leads to serious consequences in their treatment. New drug delivery systems certainly offer the opportunity to reduce patient non-compliance by tailoring some of the conventional dosage forms. Not only non-compliance by the patients, but also drug distribution, absorption and metabolism vary among individuals. Controlled drug release mechanism provides much relief to these problems. It increases patient's comfort by reducing the frequency of doses. A major advantage of controlled drug release is that besides prolonging the action of the drug, it maintains drug levels within the therapeutic windows (range of drug dosages which can treat diseases effectively while staying within the safety range) of the drug.

Controlled release systems can be classified into three parts, namely passively programmed, actively programmed and actively self-programmed systems [1]. In passively programmed system, the release rate of drug is predetermined and it does not depend on any external biological stimuli. In actively programmed system, the release rate can be controlled by some external mechanism. Now, the third category i.e. actively self- programmed system is in the main focus of medical doctors and pharmacists as it represents the new generation of delivery systems neglecting the administration route. These types of delivery systems regulate release behaviour of drugs depending upon the external stimuli, such as concentration of a fixed solute. One of the most common practises to get controlled release is to encapsulate a drug in microparticles or any matrix to enhance or reduce the kinetics behind drug release mechanism depending on the anticipated healing target.

Particles with a size in a range of 1–1000 μm are generally termed as microparticles. The drug is embedded in the microparticle matrix. Due to the potential for the microparticles to spend an extended time in the body relative to that for naked drug, good biocompatibility and biodegradability of the microparticles, particularly those with polymeric coating such as polylactic acid (PLA), polyglycolic acid (PGA) and polylactic-*co*-glycolic acid (PLGA), are reliably used in recent years as potential drug delivery devices. Since these are long–circulating particles, they have the ability to circulate for a prolonged duration of time in the vicinity of the organ at which they are targeted either by injecting or through some other targeting mechanism. There are several advantages of using microparticle as a controlled drug release device [2]. Firstly, particle size and the characteristics of the surface can be varied according to the necessity to have both passive and active self-programmed controlled release system. Secondly, since microparticles have biodegradable polymeric coating, they are particularly attractive for use in drug delivery, as once introduced into the body the microparticle matrix is degraded into non-toxic

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by-products leading to reduction of side effects. Thirdly, encapsulation of drug in the polymeric matrix is done in such a way that the drug and its polymeric coating are chemically inert, mutually, thus preserving the stability and biological activities of the drug. Moreover, this system can be used through various paths of administration, including oral, nasal etc.

Mathematical modelling of drug release process is a subject that is in the limelight of recent medical development. Due to the advancement in computer science and technology, the models are now easier to apply. An extremely helpful, yet challenging aspect is to combine mathematical theories with models quantifying drug transport in the living cells [3]. Besides, controlled drug release is also an important part of the recent medical research. Many attempts have been made to control drug release through various approaches and different theories. The polymeric gel is a chamber of drug and it provides a good example of controlled drug release to the tissues [4]. In the controlled release of drug from drug eluting stent, the therapeutic effect of the drug depends greatly on the amount of drug release and its binding nature with the receptors [5]. Many studies on drug delivery devices, for controlled drug release, have been done in order to obtain an optimal device design through either experimental methods or numerical modelling or with the combined effect of both [6–9]. Recently, an important work is done by Pontrelli and Monte [10], where drug association/dissociation aspect is taken into account while dealing with transdermal drug delivery. A recent work of Casalini et al. [11] on drug release process is described as —water penetrates inside the polymeric microparticle and wets drug crystals, allowing solubilisation of the drug, which diffuses through the microparticle. There is an assumption that no significant recrystallisation of solubilised drug occurs during its release.

In the present study, an improved model of controlled drug release is proposed. In this improved model, some of the simplifying assumptions made in the work of Pontrelli and Monte [10], Casalini et al. [11] are not taken into account to make the model, a more realistic one. The process of drug release is described by taking into account the solubilisation dynamics of drug crystallites and diffusion of the solubilised drug through the microparticle. The reversible drug binding process both in the microparticle and in tissue is also addressed. An important aspect of this type of modelling is to have correct judgement of the main parameters such as diffusion coefficient, mass transfer coefficient, drug association and dissociation rates. A significant perspective of the present work is that the model is solved analytically. The numerical results and their graphical representations provide trustworthy predictions about various aspects of controlled drug release kinetics, which can be utilised by pharmacists to revive their ideas and make few tweaks to the prevailing drug delivery technique.

2. Formulation of the problem

In order to model the release kinetics of drug from a microparticle, a two layered system composed of (a) the matrix (microparticle) and (b) the tissue (the collection of living cells which is being acted upon by the drug) (Fig. 1) is considered. The drug is encapsulated in the matrix coated with some biodegradable polymer.

The polymeric microparticles are assumed to be in perfect spherical shape having a fixed volume with only radial variations in concentration. Distribution of diameter of the microparticle is not considered and assumed that all the particles are of same dimensions. It is also assumed that there is uniform distribution of drug concentration inside the microparticle. Lastly, it is presumed that there is no re-distribution of drug back into the tissue from the systemic circulation.

Water enters into the polymeric matrix and wets the drug loaded inside it, allowing solubilisation of the drug crystals which diffuses through the microparticle. When the drug diffuses through the

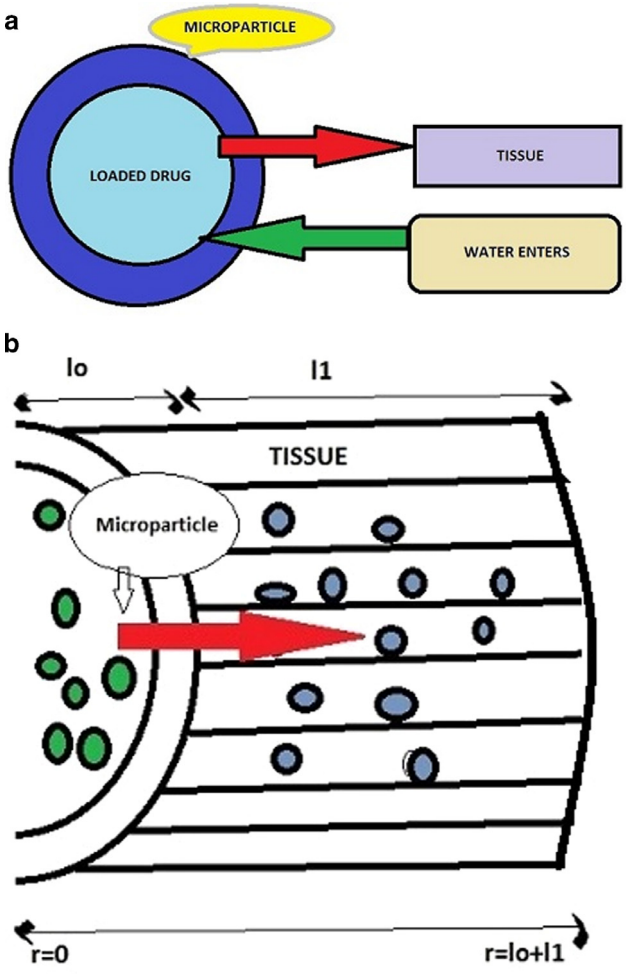

Fig. 1. (a) Schematic representation of drug release kinetics. (b) Schematic representation of drug release in the tissue.

microparticle, it is the outcome of an unbinding process (solubilisation). Initially, the drug is present inside the microparticle at maximum concentration, being in bound phase (c_l) cannot be transferred to the tissue. Then a fraction of this drug ($\beta_0 c_l$) is transferred to an unbound (free) drug particles (c_0) which has the ability to diffuse into the tissue. Conversely, by a recrystallisation process, a fraction of the free drug ($\delta_0 c_0$) is again back to the bound state. At the same instant, a portion of the free drug (c_1) diffuses into the tissue. In the tissue also, a fraction of the free drug ($\beta_1 c_1$) is bound by the cell receptors and converted into bound phase (c_b) (this is due to the absorption phenomena by the cells in the tissue). From the bound state (c_b), a portion ($\delta_1 c_b$) is transferred to the unbound state (Fig. 2). The diffusion of the free drug is assumed to follow Fick's law. The dissolution of the drug is described by the aid of Noyes–Whitney equation [12,13]. Since the density of binding sites is much higher than the local free drug concentration, the use of a linear relationship is quite reasonable.

Now, the equations represent modelling of drug dynamics in the first layer i.e. microparticle in the following manner

$$\frac{\partial c_l}{\partial t} = -k(c_{lim} - c_0) - \beta_0 c_l + \delta_0 c_0 \quad \text{in } (0,\ l_0) \tag{2.1}$$

$$\frac{\partial c_0}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(D_0 r^2 \frac{\partial c_0}{\partial r}\right) + k(c_{lim} - c_0) + \beta_0 c_l - \delta_0 c_0 \quad \text{in } (0,\ l_0) \tag{2.2}$$