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A multi-scale stochastic drug release model for polymer-coated targeted drug delivery systems

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Abstract

A multi-scale mathematical model for drug release of oral targeted drug delivery systems was developed and applied to a commercially available delayed release tablet (Asacol®) that delivers 5-aminosalicyclic acid (5-ASA) to the colon. Underlying physical and biochemical principles governing the involved processes (diffusion and dissolution) were employed to develop the mathematical description. Finite element formulation was used to numerically solve the model equations. Molecular dynamics (MD) simulations were used to predict macro-scale transport properties of the drug and the biologic fluid. The effect of pH variability in the gastrointestinal tract environment on the dissolution of the polymeric enteric coating was investigated using the Monte Carlo method. The direct coupling method employed (MD) predicted a sufficiently accurate diffusion coefficient (5.7×10^{-6} cm^2 s^{-1}) of the drug molecules in reasonable (3 h) computation times. The model was validated using experimental data from in vitro dissolution experiments and provided accurate prediction of the drug release from the delivery system (root mean square error of 5%). The amount of drug entering the systemic circulation, computed from the predicted drug release in varying pH environments in the small bowel, was 15–24%. This range was in good agreement with clinical in vivo data (13–36%) obtained from literature. This research shows that in silico experiments using mechanistic models and stochastic approaches can be used for drug design and optimization and as a decision making tool for physicians.

Keywords: Drug release; Multi-scale; Stochastic; Modeling; Colon; Targeted delivery

1. Introduction

Drug delivery via the colon or distal portion of the small intestine is advantageous in that the drug is not destroyed by the hostile environment of the upper gastro-intestinal tract (GIT) [1]. Besides treatment of local diseases, drug delivery to the lower GIT has gained importance due to the potential to deliver proteins and therapeutic peptides via the colon [2–4]. One of the primary ways to target drug release to the distal portion of the small intestine and the colon is to prepare film-coated pellets or tablets that protect the drug during transit through the upper GIT. The drug is released at the target by exploiting unique features of the target site [5]. These features include transit time, physiological conditions of the GIT, bacterial enzymes and targeting moieties [2]. Ashford and co-workers [6] argue that the effectiveness of most of these triggering mechanisms, especially transit time and physiological conditions, are limited by the large variations in the GIT (intra/inter subject). Because the pH gradient along the GIT forms the basis of several targeted lower intestinal delivery systems, understanding how this gradient varies in health and disease states is important [7]. Application of mechanistic computational models can be instrumental in investigating the effects of GIT environmental variability to design alternative and more efficient smart delivery systems.

A true mechanistic model is one that: (i) considers the underlying physical principles to describe the observed phenomena, (ii) considers the stochastic nature of the involved processes, (iii) addresses the empiricism that is often assumed in estimating the model parameters, and (iv) incorporates the

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true geometry of the domain under consideration. Few studies have been devoted to the mathematical description of drug release from hydrophilic (reviewed in Ref. [8]) and non-hydrophilic [9–12] coated polymeric systems (pellets or tablets). Most of the latter works describe non-dissolving and non-swelling systems and the involved model parameters are often estimated empirically and assumed constant. Moreover, assumptions that ignore one or more of the involved processes and simplified geometries are often considered. Frenning [13] argues that surprisingly few works exist that consider pharmaceutically relevant geometries. These factors limit the ability of the models to address underlying physical mechanisms of the transient drug delivery, relying heavily on in vitro and in vivo experiments. To fully understand the drug–carrier and drug–solvent interaction behaviors and mechanisms, study at the molecular level must be conducted in concert with the traditional macroscopic effort. In this respect, few studies have been carried out that derive the model parameters from their molecular descriptors. Recently, Clement and co-workers [14] have studied the interaction of pure solvents with polymeric membranes using molecular dynamics (MD) simulation.

The objective of the present paper is to develop a mechanistic drug release model for targeted oral drug delivery (TODD) systems by considering biological variability to give clinically relevant predictions. A continuum approach was pursued to model the processes involved by considering the relevant geometry of the delivery device. The structure–property relationship of the interaction of dissolution medium with the drug molecules was characterized using MD simulations. Parameters that characterize the interaction of the polymeric coating with the medium were derived from free volume theory [15]. A stochastic approach (Monte Carlo method) was employed to incorporate the effect biological variability in the GIT on the drug release behavior in the model, By means of a mathematical model that considers the pertinent physico-chemical processes and biological variability of the GIT environment, in silico experiments that accurately replicate in vivo clinical experiments can be performed. Moreover, such a model can be used for design and optimization of broad range of new and existing targeted and controlled release formulations to the distal intestine and colon.

2. Materials and methods

2.1. Multi-scale modeling

2.1.1. Continuum model

Drug release from polymer-coated oral delayed-release systems includes a number of mass transfer processes involving multiple species as the capsule transits through the GIT. A complete model would include the transport of the diffusing species through the boundary layer, the polymeric coating and the core matrix, and dissolution of solid drug. The polymeric coating dissolves and eventually disappears releasing the payload, as the dosage form is subjected to different media in the GIT. One or more of the above processes can be the rate determining mechanisms at different stages of the drug release process. The changing and deforming geometry of the dosage form should also be accounted for during transit. In the present model, the convective flux of the diffusing species was ignored because of limited convective flow inside the delivery device. Moreover, due to sufficient agitation, there is no boundary layer formation, thus no boundary layer film was considered. Given these assumptions, the mathematical description of the processes is expressed by:

$$\frac{\partial c_i}{\partial t} = -\nabla\left(D_{i,k}\nabla c_i\right) + R_i, \tag{1}$$

where c is concentration of the species [g cm^{-3}]; the subscript i represents the species, (biologic fluid $i=1$, dissolved drug $i=2$); t is time [s]; D is the diffusion coefficients [cm^2 s^{-1}]; the subscript k denotes the different domains of the tablet (core $k=1$, coating $k=2$; Fig. 1) and R is the source

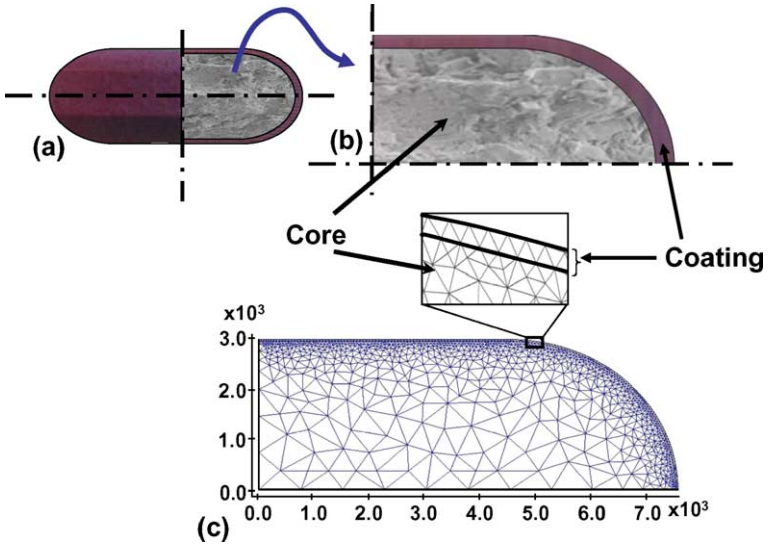

Fig. 1. (a) Cartoon of the tablet (Asacol®); (b) one-quarter of the tablet considered for modeling due to symmetric assumption; (c) geometric mesh model for one quarter of the tablet (dimensions in μm).