Multi-scale drug release modeling for Targeted Oral Drug Delivery (TODD)

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ABSTRACT

A multi-scale mathematical model of the drug release from commercially available (Asacol®) delayed release capsules that deliver 5-ASA is developed. In this system, diffusion and dissolution processes were considered. The interaction of drug molecules with biologic fluid was characterized using molecular descriptors of the capsule components to predict macro-scale transport properties using molecular dynamics simulations. The direct coupling method employed provides sufficiently accurate diffusion coefficient ($5.7x10^{-6}$ cm^2s^{-1}) prediction of the drug molecules in decent computation times. The effect of pH variability in the Gastrointestinal Tract environment on the dissolution of the polymeric coating was investigated using Monte Carlo method. A 10% deviation at 95% confidence interval in the decrease of the thickness of the coating was obtained. Experimental data obtained from in-vitro dissolution experiment showed a good agreement between predicted and measured fractional drug release profiles.

Keywords: drug release, multi-scale, stochastic, modeling, colon, targeted delivery

1 INTRODUCTION

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) considers the true geometry of the domain under consideration. Targeted oral drug delivery (TODD) systems involve a matrix of active drug core coated with pH dependent enteric coating that protects the drug from being released in the upper gastrointestinal tract (GIT). Some studies, few as they are, have been devoted to the mathematical description of drug release from hydrophilic (reviewed in ref. [1]) and non-hydrophilic [2], [3], [4], [5] 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. In fact, [6] argues that surprisingly few works exist that consider pharmaceutically relevant geometry. 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, [7] have studied the interaction of pure solvents with polymeric membranes using molecular dynamics simulation. Often, such multi-scale methods are hindered by un-bridged gaps between the macro and molecular scales in both the spatial and temporal dimensions. In an attempt to arrive at higher mechanistic levels, first step are taken in this work by considering the continuum approach to model the involved processes in the drug release of TODD systems and to derive the structure-property relationship of the interaction of dissolution medium with the drug molecules by considering the exact geometry of the involved tablet. The parameters that characterize interaction of the polymeric coating with the medium were derived from free volume theory [8] at this stage. In the future these parameters will also be predicted using molecular dynamics simulation. To characterize the diffusion coefficient of the drug molecules molecular level simulation using MD (molecular dynamics) is carried out which was in turn used as a coupling parameter with the continuum macro-scale simulation.

2 MATERIALS AND METHODS

2.1 Multi-scale modeling

Continuum model

Drug release from film coated oral delayed systems includes a number of different mass transfer processes involving multiple species as the capsule transits through the GIT. A complete model would include medium transport through the film coat and the core matrix, dissolution of solid drug, mass transport of the dissolved drug in the core matrix and the polymeric coating. The polymeric coating dissolves and eventually disappear releasing the payload as the dosage form is subjected to different media in the GIT. The analytical treatment of the drug release requires the consideration of the above processes, which one or more can be rate determining processes at different stages of the drug release step, and the accounting for the changing and deforming geometry of the dosage form during transit. Assuming the convective

flux due to the diffusing species can be ignored, the mathematical description of the processes can generally be given by:

$$\frac{\partial \bar{c}_i}{\partial t} = -\frac{1}{r}\left[\nabla\left(rD_i\nabla\bar{c}_i\right)\right] + R_i \quad (1)$$

where $\bar{c}$ is concentration of the species (the overbars indicate a random variable) [g cm^{-3}]; the subscript i represents the species, (biologic fluid $i=1$, dissolved drug $i=2$); t, time [s]; r, the coordinate vector [cm]; D, the diffusion coefficients [cm^2 s^{-1}]; and R, source density [g cm^{-3} s^{-1}]. The source term results from drug dissolution and can be given by the Whitney-Noyes equation.

$$R_2 = \frac{\partial \bar{C}_2}{\partial t} = k_2 A_t \Delta\bar{c}_2 \quad (2)$$

where C is the concentration of solid un-dissolved drug [g cm^{-3}]; k_i, the dissolution rate constant [cm s^{-1}]; A_t is the time dependent surface area per unit volume [cm^{-2} cm^{-3}]; and $\Delta\bar{c}_2 = c_s - \bar{c}_2$, the driving force for the dissolution of the drug, where c_s is the solubility of the drug. This term applies only to the drug and is only valid as long as water has diffused into the matrix and the dissolution is incomplete. The thickness of the polymeric coating decreases over time. After it disappears, drug diffusion is very fast and the matrix starts to disintegrate. In targeted delivery dosage forms the dissolution rate of the polymeric coating is a function of the pH of the medium. Hence, this involves a moving boundary problem. As a result, the initial and boundary conditions can be posed as follows for the different domains (polymeric coating and drug core):

$$c_1(0,r) = 0 \quad (3)$$

$$c_2(0,r) = 0 \quad (4)$$

$$C_2\begin{cases}(0, 0 < r < R_{dc}) = C_{2o} & \text{where } R_{dc} \text{ is the radius of} \\ (0, R_{dc} < r < R_0) = 0 & \text{the core drug and } R_0 = r\big|_{t=0}\end{cases} \quad (5)$$

$$c_1(t, r = R_t) = c_1^* \quad (6)$$

$$\left.\frac{\partial c_1}{\partial r}\right|_{r=0} = 0 \quad (7)$$

$$c_2(t, r = R_t) = 0 \quad (8)$$

$$\left.\frac{\partial c_2}{\partial r}\right|_{r=0} = 0 \quad (9)$$

The boundary condition in eq. (6) is the critical moisture content of the polymeric film and the equilibrium moisture content of the matrix once the coating has dissolved.

Model parameters

Required parameters are the diffusion coefficients D_i in domains (polymeric coating and drug core), the solubility and related kinetic parameter of the drug (c_s and k_2). The boundary conditions involve parameters that characterize the interaction between biologic fluid and drug coating as well as the drug matrix. These are the critical and equilibrium penetrant concentrations. Diffusion coefficients of the drug in the biologic fluid and the biologic fluid in the drug core are predicted using molecular dynamics simulation. The parameters quantifying interaction of the biologic fluid with the coating polymer were estimated using molecular free volume theory. Rheological properties of the coating polymer were obtained from ref [9] and the glass transition temperature was determined using DSC measurements. The dissolution parameters of the drug (c_s and k) were obtained from literature [10].

Variability

The drug release of pH-dependent TODD systems is highly dependent upon the dissolution of the coating which depends on the pH of the GIT. Inter/intra subject variability affects the site specificity of the drug release. One example is the inherent variability of fed/fast situation. Therefore, to incorporate this effect, the pH dependent dissolution rate constant of the coating polymer was considered as a random parameter sampled from a normal distribution and a Monte Carlo (MC) simulation [11] was performed. The Monte Carlo method was selected for its simplicity of implementation and robustness despite the extended computation time.

Method of solving

A standard finite element methodology was used to describe the dynamic of the concentration fields in the drug release device. Since the boundary surrounding the device is unknown *a priori* due to dissolution, its location was determined as a moving boundary problem using Arbitrary Euleurian-Lagrangian (ALE) formulation [12]. The edge of the mesh followed the edge of the drug release device as its location changed due to dissolution. The edge motion was governed by the rate of dissolution of the coating polymer. Due to the limitation of the ALE formulation to handle excessive deformation, the disintegration of the core drug was not followed in the present study. FEMLAB 3.0a software (COSMOL AB.) was employed and was run on a Pentium IV 3.06GHz with 1GB RAM PC.

Molecular dynamics simulation

In the present work, the interaction of the drug molecule (5-ASA) with water was investigated using MD simulation to predict the diffusion properties of the drug. The topology of the drug molecule was obtained by using the PRODRG [13] tool and energy minimization and MD simulations were carried out using GROMACS [14]. The steepest descent method was used to do energy minimization, which removes too close contacts and unrealistic initial atomic positions. Only polar hydrogen atoms are included in our simulation and the number of total atoms considered was 597. The cutoff distance was set at 0.9nm and a simulation temperature of 310K was considered. To compute the diffusion coefficients, the Ernestine relation, based on Mean Square Displacement, was used. The mass ratio of drug molecules in water was 18.5%.

2.2 Experiment

DSC Measurements

DSC patterns for the coating polymer (Eudragit® S-100, kindly provided by Röhm pharma polymers) used to measure the glass transition temperature were obtained from a Mettler DSC30 (Heightstown, NJ) equipped with a Mettler TC11 TA processor. The DSC patterns were run at 20°C/min with a pre-scan of 30-170°C in nitrogen environment to evaporate solvent. The 5-10mg sample was quickly cooled to room temperature and scanned between 30-280°C at scan rate of 20°C min^{-1}. The glass transition temperature was calculated as the mid point of the heat capacity transition between the upper and lower points of deviation from the extrapolated glass and liquid lines.

Dissolution

Dissolution studies were performed in triplicate using a USP II paddle apparatus according to USP standard for mesalamine [USP standard] using artificial intestinal fluid. Commercially available delayed release mesalamin (Asacol) tablets were used. The fractional release was determined by CARY 50 spectroscopy (Bio Varian Australia Pty Ltd. Victoria, Australia)

3 RESULTS AND DISCUSSION

The computation of the MD simulation yielded diffusion coefficients of $5.7x10^{-6}$ and $3.39\ x10^{-6}$ $cm^2\ s^{-1}$ for the drag molecule in water and vise versa, respectively. This values are in the same order of magnitude with the effective diffusion coefficients used in literature [15] for similar drugs. Therefore, these values were used in the continuum model as model parameters.

In Figure (1) the simulated dissolution of the polymeric coating in different intestinal buffers is shown. In the stomach where the pH is low (1.2), the dissolution of the coating is almost non-existent even after 2 h of simulation. In the jejunum, were the pH is raised to 6.8, limited amount of dissolution of the polymeric coating is observed. At the terminal ileum (pH = 7.2) the dissolution of the coating is very fast and the pay load of the tablet is released quickly once the coating disappears, as can be seen in Figure (3). It should be noted here that due to the limited deformation level the ALE formulation could handle, the simulation of the coating dissolution was stopped before the entire coating had dissolved and was then considered fully dissolved for subsequent simulation. Poor mesh quality due to excessive deformation caused numerical anomalies and convergence problems where the moving boundary was constrained.

In Figure (2a), the effect of variation of pH in the jejunum on the dissolution of the polymeric coating is depicted by means of stochastic Monte Carlo simulation (N=100). Here, the range of pH used was [6.3-7.3] [16]. Average coating decrease of 20% of the original thickness with 95% confidence interval of 10% at the end of 1h is obtained. The simulation assumed a uniform coating, however, as can be observed from the SEM images (Fig 2b-d) of the tablet further variation in the release can be caused by the non-uniformity and holes that exist in the coating. Dincer and Ozdurmus [17] report a variation of 6 to 28 min in disintegration time of polymeric coating in simulated intestinal fluid due to variation in process variables that result is the non-uniformity of the coat. Therefore, it is imperative to include this non-uniformity together with the GIT environmental stochastics to analyze the joint effect on the drug release.

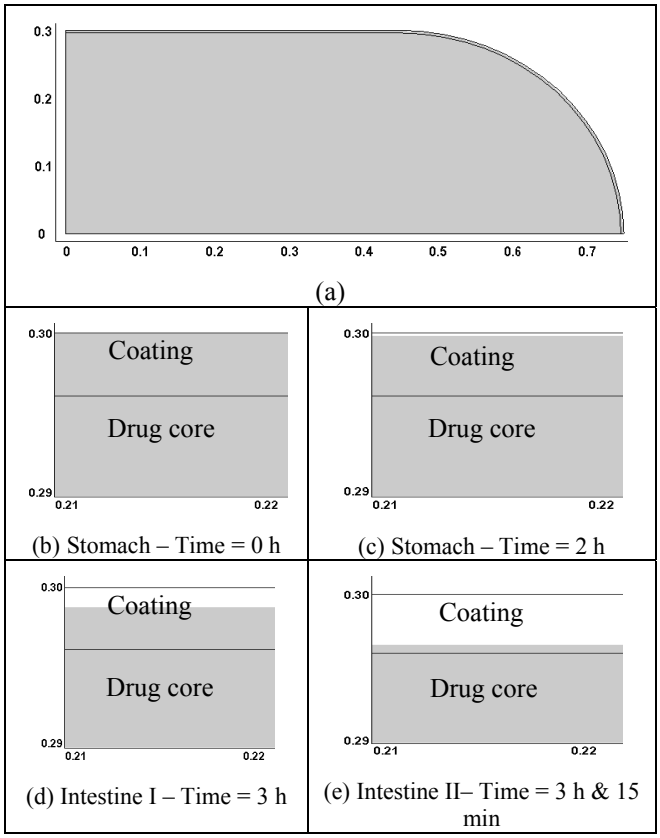

Fig 1. Simulation of the polymeric coating (Eudragit® S-100) of Asacol® a) the simulation domain (one quarter of the tablet); b) enlarged section of the interface between the drug core and coating at *t = 0* h; c) after 2 h in the stomach fluid at pH = 1.2; d) after 1 h in the intestinal fluid I (jejunum) at pH = 6.8; e) after 15 min in the intestinal fluid II (jejunum) at pH = 7.2.

In Figure 3 the simulated and experimental fractional cumulative drug release are depicted. As can be observed, the tablet remained intact in the stomach and Intestine I fluids. As was evident from Figure 1, the model predicts no release in these regions. The model predicts the drug release slightly earlier than the actual release. This could be due to the fact that the dissociation of the particles happens before their actual dissolution in to the medium.

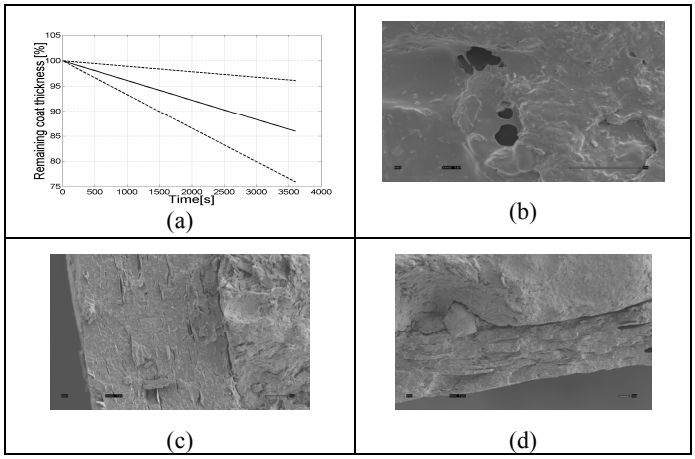

Fig 2. (a) Confidence interval of the MC simulation for the coating polymer in the ileum; (b) SEM image showing the holes in the coating polymer (c) & (d) non-uniform thickness of the coating at different positions in the cross section

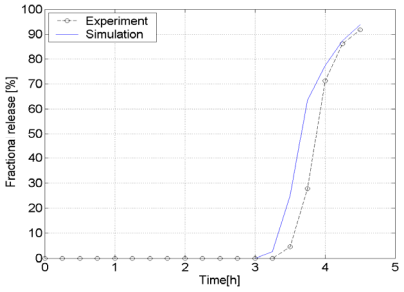

Fig 3. Simulated and experimental fractional cumulative drug release

4 CONCLUSION

A multi-scale model for prediction of the drug release of TODD systems was presented. It was attempted to represent the involved transport processes using continuum model and predict some of the model parameters using molecular properties of the drug and the biologic fluid. Moreover, the effect of regional variability of the GIT on the dissolution of the delayed release coating and in turn on the drug release was addressed. The model provides fairly accurate prediction of the drug release from delayed release. A theoretical analysis of the variability in terms of the variation in pH which is inherent in the GIT due to different situations (for example fed/fast) can be carried out to analyze the delayed or early release of the drug. This is an ongoing work and at the moment the limitations of the ALE formulation is being addressed to achieve a better resolution to predict the deforming drug core as well as improvement in computation time for the MC simulation (100 MC runs take about 48 h). Such modeling effort plays a significant role to achieve mechanistic models for better design and administration of controlled release systems towards patient specific treatment regimen.

Acknowledgements

Prof. Kinam Park, Mr. Jeong Seonghoon, Prof. Cliff Jonston and Dr. Premachandra Gnanasiri are acknowledged for their advice and assistance.

REFERENCES

[1] J. Siepmann and N.A. Peppas, *Advanced Drug Delivery Reviews*, 48:139-157, 2001.

[2] S.M. Lu and S.R. Chen, *Journal of Controlled Release*, 23:105-121, 1993.

[3] T. Koizumi, G.C. Ritthidej and T. Phaechamud, *Journal of Controlled Release*, 70:277-284, 2001.

[4] P. Borgquist, G. Zackrisson, B. Nilsson and A. Axelsson, *Journal of Controlled Release*, 80:229-245, 2002.

[5] G. Frenning, A. Tunon and G. Alderborn, *Journal of Controlled Release*, 92:113-123, 2003.

[6] G Frenning, *Journal of Controlled Release*, 95:109-117, 2004.

[7] R. Clement, A. Jonquieres, I. Sarti, M.F. Sposata, M.A.C. Teixidor and P. Lochon, *Journal of Membrane Science*, 232:141-152, 2004.

[8] P.J. Flory, Cornell University, 1953.

[9] J.D. Ferry, John Wiley & Sons, Inc., 1980.

[10] D.L. French and J.W. Mauger, *Pharmaceutical Research*, 10:1285-1290, 1993.

[11] G.S. Fishman, Springer Verlag; 1996.

[12] J. Donea, A. Huerta, J-P Ponthot and A. Rodriguez-Ferran, (Chapter 14), In: *Encyclopedia of Computational Mechanics, Volume 1: Fundamentals.* Wiley & Sons, Ltd., 2004.

[13] A.W. Schuttelkopf and D.M.F. van Aalten, *Acta Crystallographica Section D-Biological Crystallography,* 1355-1363, 2004.

[14] E.B.H. Lindahl and D. van der Spoel, *Journal of Molecular Modeling*, 7:306-317, 2001.

[15] S. Kiil and K. Dam-Johansen, *Journal of Controlled Release*, 90:1-21, 2003.

[16] G. Chaela, P. Gupta, V. Koradia and A. Bansal: *Pharmaceutical Technology,* July 2003.

[17] S. Dincer and S. Ozdurmus, *Journal of Pharmaceutical Sciences*, 66:1070-1073, 1977.