PROBABILISTIC MODELS FOR DISSOLUTION OF ETHYLCELLULOSE COATED MICROSPHERES

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ABSTRACT

In the last few decades, a number of probabilistic models for drug delivery have been developed. Of particular interest are those that model controlled release systems to provide targeted dose delivery. Controlled release is achieved by using polymers with different dissolution characteristics. We present here a model based on Monte Carlo and Cellular Automata approaches, for simulating drug release from coated microspheres in the gastro-intestinal tract. Controlled release is obtained using ethylcellulose as the coating polymer. Modelling features, such as the drug and coating dissolution are non-trivial, since material is non-homogenously dispersed and the dissolution exhibits complex behaviour. Important underlying mechanisms of the process, such as erosion, are described here.

INTRODUCTION

Drug delivery systems (DDS) are pharmaceutical systems designed for transporting drugs into the body. The computational modelling of DDS is a constantly developing field, with the potential to become an integral part of pharmaceutical research, as some modern drug formulations are very complex and the influence of system composition and variables on the release profiles is not fully understood. *In-silico* modelling of DDS can, therefore, be of benefit in reducing the cost of experiments, (involving large amount of *in vitro* testing), as well as length of time needed to introduce the drug to the market. Controlled drug delivery systems are a type of DDS, the primary objective of which is to deliver drug at the desired rate to a targeted site in the body. Control is maintained by using polymers of different structures. Consequently, polymer dissolution is one of the most important problems to solve in achieving this type of release.

Here, we present a probabilistic model based on Monte Carlo (MC) and Cellular Automata (CA) approaches, for simulating controlled release from coated microspheres. The work is rooted in an ongoing industrial collaboration and aims to address the release problem for the drug (cyclosporine) in targeting the gastro-intestinal (GI) tract. As one of a number of suitable coating materials, we model the use of ethylcellulose (EC), a generally non-invasive polymer with good film-forming capabilities. It is both an inert and hydrophobic polymer but, when maintained under high humidity, can absorb water in large amounts (Geraghty 2004). In general, properties of ethylcellulose make it ideal for use in matrix agents, for prolonged release, or as a coating material.

THEORY

The first step in modelling the dissolution is to determine the *in vitro* dissolution rate under various external conditions, as measured in the dissolution test apparatus. Standard test methods for measuring those rates are outlined in the pharmacopoeias (European Pharmacopoeia, United States Pharmacopoeia). Here, we used the paddle apparatus II, (USP II), which allows us to mimic metabolic conditions, such as change of temperature, type of solution (pH and dynamic flux of the solution), by varying speed of the paddle, and monitor experimentally their influence on the drug dissolution rate.

Theoretical models will vary according to the type and complexity of the system, and can be used to explore experimental *in vitro* data. Theories are generally divided into three broad groups: mechanistic, empirical and probabilistic (Siepmann and Siepmann 2008). The first two groups take the top-down approach, start from known parameters and use specific deterministic release rate equations for each individual problem, (i.e. to represent physical laws and empirical information). The most important properties must be either known from the manufacturing process or be possible to calculate, which is not straightforward given the complex nature of the formulations. Conversely, for complex detail modelling, bottom-up theories, (incorporating stochastic assumptions), have the potential to yield better predictions while requiring less initial information. These simulate release curves by observing the probabilistic behaviour of individual particles and have the advantage of providing a simplified representation of the system,

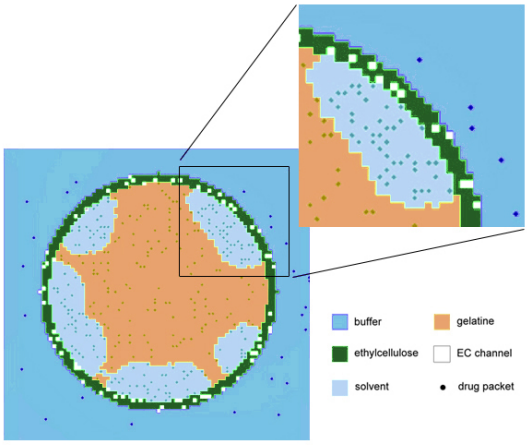

Figure 1: Simplified Internal Morphology of one 3D Sphere Simulating Drug Dissolution through Coating Layer (Ethylcellulose). Enlarged: Part of the Sphere with Definition of Model Cell Types

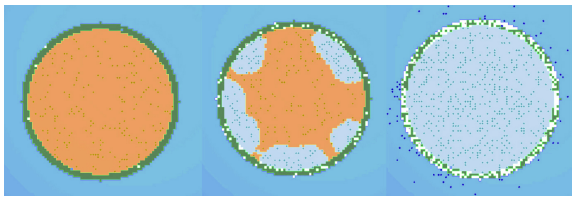

Figure 2: Simulation Stages: Initial Stage (left), During Release, with Gelatine (centre), After all Gelatine is Dissolved (right)

(Barat et al. 2008b).

Monte Carlo methods have numerous applications, ranging from fluid dynamics, space and traffic modelling and statistical physics, to financial analysis (Li et al. 2007, Sopasakis 2004, Tezuka et al. 2005). In one of the first direct MC models of DDS, microstructural changes in bioerodible polymers were simulated (Göpferich and Langer 1993). MC is also often used as a framework for Cellular Automata movement. In a CA system, a discrete grid of individual cells is defined, where each cell can have one of a number of defined states. The behaviour of each cell is governed by a set of rules that describe the local state transitions over discrete time steps, (Zygourakis 1990).

Drug Dissolution Phenomena

Important phenomena in polymeric drug delivery systems include: (i) diffusion: the motion of molecules from a region of higher to one of lower concentration i.e. flux. In the modelling of DDS, diffusion is often described by Fick's laws, (Crank 1975). In one dimension, Fick's first

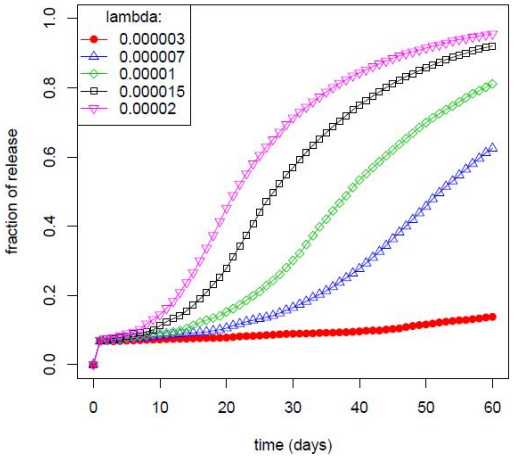

Figure 3: Release Profiles as a Function of the Degradation Rate Lambda (λ)

law can be represented as:

$$J = -D\frac{\delta c}{\delta x} \tag{1}$$

where J is the diffusion flux, D is the diffusion coefficient and c is the concentration; (ii) degradation: the process whereby chain scission occurs causing polymer chains to become oligomers and monomers, facilitating easy release. Degradation is the first step of erosion (Göpferich 1996); (iii) erosion: the loss of material from a polymer due to degradation. It determines the release rate of the drug (Siepmann and Göpferich 2001). When a polymer erodes it leaves space for the drug to be released from the compact, or for water penetration. Two types of erosion are defined (Langer and Peppas 1983): Surface erosion is a homogeneous process and represents the stage during which the size of the compact decreases while the shape remains constant; the compact loses material only from its surface; Bulk erosion is a heterogeneous process with material being lost from the whole compact, although the size remains constant.

MODEL FEATURES

In a previous project (Barat et al. 2008a), (Barat et al. 2008b), microspheres filled with polylactic-co-glycolic acid (PLGA) polymer were modelled. In these, drug is homogeneously dispersed throughout the sphere and contained within a polymer. Understanding the phenomena occurring in polymeric spheres was achieved through dimensional (3D) stochastic Cellular Automata and agent-based modelling. The rationale for introducing the agent-basis is simplification of the interaction of system elements using specifically designed entities (agents), which have simple properties and characteristics. The influence of a number of parameters defining release curves was investigated, including porosity,

drug loading, sphere size and type of neighbourhood, (Von Neumann or Moore). Some of the earlier results are illustrated (Figure 3), which show how the sphere porosity growth dynamics affect the release rate.

Current Work

The modelled device now consists of a drug, non-homogenously dispersed in a coated sphere, where the coating predominantly controls the rate of drug release. The aim of the model is to determine how different properties of the device, such as coating thickness or size of the sphere, affect the release rates. Monte Carlo and Cellular Automata methods are used to describe the system in terms of a 3D grid of cells, with erosion and diffusion as the main release mechanisms. This discrete approach is preferred over a continuous one, (used in mechanistic theories), due to straightforward mimicking of the real system which is discrete by nature. Each cell can have one of several possible states, described in the (Table 1). The state transitions are influenced by the states of all the cells in the Von Neumann neighbourhood for a 3D matrix (i.e. 26 neighbouring cells).
In its initial state, the drug is taken to be randomly dispersed in the form of "packets" inside a gelatinous sphere, coated by a polymer layer. Diffusion of the drug inside the sphere is represented as a random walk of drug packets, influenced by concentration differences between neighbouring cells. The highest probability for movement will be in the direction of the largest concentration gradient, based on the Fick's first law.
Behaviour of coating layer cells is based on work, (Göpferich and Langer 1993), where scission of the polymer chains and formation of pores follows the Erlang distribution:

$$e(t) = \lambda t e^{\lambda t}, t \geq 0 \tag{2}$$

The rate of the pore formation is characterised by λ which defines the lifetime, t, of an individual EC cell:

$$t = \frac{1}{\lambda} ln(U) \tag{3}$$

where U takes randomly distributed values between 0 and 1. When the cell lifetime is reached, the cell is considered to be eroded, and forms a channel through which the drug packet can diffuse. This occurs at a rate slower than the diffusion rate inside the coating, (solvent cells), reflecting the influence of permeability of the membrane (Laaksonen et al. 2009). The release rate is measured by counting the number of packets that reach the buffer zone, which is assumed to have perfect sink conditions.

RESULTS AND EXPLANATIONS

The simulation was developed in C++ with OpenGL used for graphical representation. The matrix size was

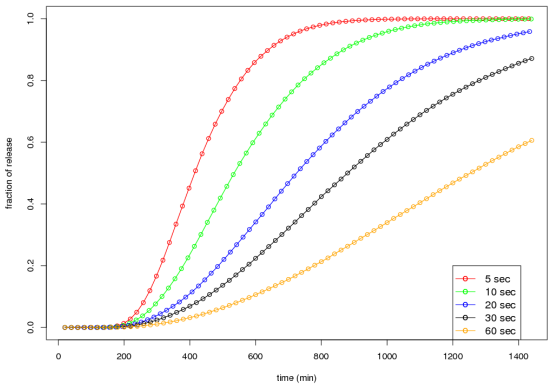

Figure 4: Release Profiles as a Function of the Simulation Time Interval

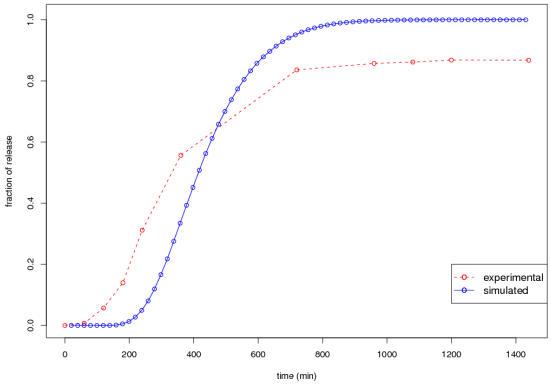

Figure 5: Simulated Release Profiles Against Experimental Release Profiles. Experimental Data Provided by Sigmoid Pharma Ltd.

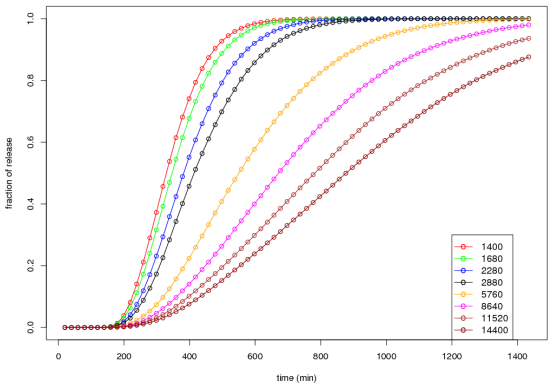

Figure 6: Release Profiles as a Function of the Coating Degradation Rate Lambda

Cell type	Behaviour description
Buffer	Drug is released when it reaches buffer zone. Cell type acts as a perfect sink.
Ethyl-cellulose	Drug-free coating layer. Assigned lifetime based on the λ (degradation rate) parameter. Forms an EC channel cell upon complete erosion.
EC-channel	Gelatine and drug can diffuse through EC channel cells.
Gelatine	Fixed lifetime. During diffusion through solvent cells, facilitates movement of drug "packets".
Solvent	Gelatine erodes into the solvent. Drug can diffuse through the latter.
Drug packet	Drug, initially dispersed in gelatine cells. Each cell can hold a maximum (saturation) amount of drug "packets".

Table 1: Set of Cell Types and Rules of Behaviour.

200 x 200 x 200, with cell size being 10μm. The averaging of the values for 24 repeated runs showed a negligible variation in results for a given set of same parameters.

Model parameters, the effects of which on drug release rates were studied in this work were: the size of the microsphere, the erosion rates of gelatine and ethylcellulose and the effect of coating thickness. The initial values were set according to the available *in vitro* data and unless otherwise stated, the erosion rates of gelatine and ethylcellulose are 90 minutes and 2 days, respectively. The sphere was taken to be 1.43 mm in diameter, and to contain 5% of EC coating. Drug loading is kept constant for all simulations at 10.8% of the mass.

The first step in modelling was to determine the most appropriate time interval in which cell states should be updated. This essential parameter directly determines the diffusion and has order of magnitude in seconds, (from Fick's first law and dimensional analysis). Simulations were then performed for intervals between 5 seconds and 1 minute, (Figure 4). By comparing results against experimental data, (Figure 5), a time interval of 5 seconds was chosen for all subsequent simulations.

The effect of porosity in the coating layer was investigated by varying lifetime of EC cells, (i.e. varying λ), to obtain different release behaviours for different lifetimes of EC chains, (Figure 6). The slower release rate of the drug is due to decreased porosity, i.e. slower channel formation occurring in the coating.

Weight gain of the coating thickness is also one of the primary factors influencing drug formulation and performance. Here, we vary the coating levels from 4% - 8%, (Figure 7). The produced release curves qualitatively reproduce reduction in diffusion rate, but the impact of adjusting the weight gain is somewhat smaller than experienced *in vitro*. This is expected, to some extent, as perfect sink conditions are modelled in this case. In

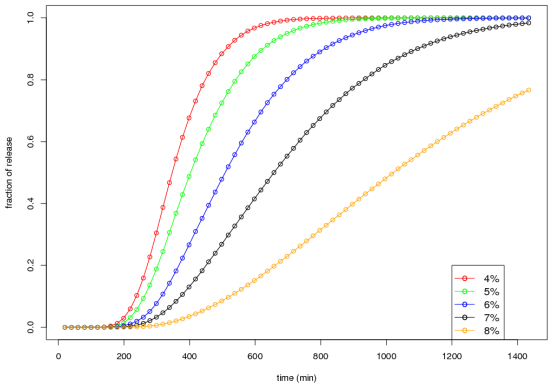

Figure 7: Release Profiles as a Function of Coating Weight Gain

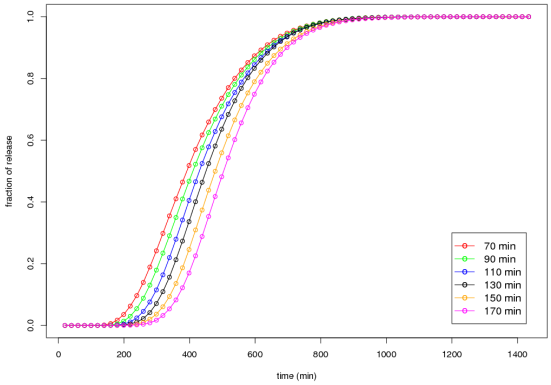

Figure 8: Release Profiles as a Function of Gelatine Lifetime

reality, concentration of ethylcellulose in the boundary layer inhibits movement of drug packets and some local saturation occurs. This phenomenon must be taken into account in future model extensions.

As can be seen, (Figure 8), the lifetime of the gelatine carrier can be considered to be negligible in terms of influence on final release rate. However, gelatine is an important controller of the drug release in the initial stages, as it influences the "burst effect" by accelerating drug transfer through EC channels. The size distribution of microspheres determines the actual mean and variance of release rate, (Figure 9). This feature suggests refinement of initial parameters is necessary, (e.g. coating thickness or drug loading), as these are directly dependent on the size of the sphere. Increasing microsphere size mostly slows down drug release due both to the capability of the device to hold more drug and the fact that larger spheres have heavier and thus less permeable coatings.

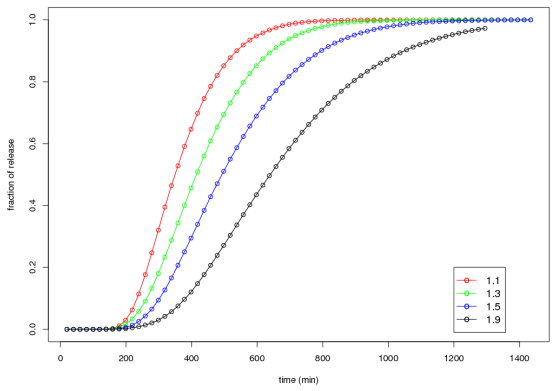

Figure 9: Release Profiles as a Function of Sphere Diameter

FUTURE WORK

Although simulated results do not reflect quantitative *in vitro* data precisely, (Figure 5), results obtained are promising. These show that the model predicts qualitatively similar behaviour compared to that seen for experimental release curves. Results also show that the behaviour of EC cannot be modelled using erosion only, but that other phenomena, such as swelling, which influence volume increase due to the increased hydration of the broken polymer chains, have to be taken into account (Atyabi et al. 2004). A future focus will thus be incorporation, into the model, of the swelling effect, caused by adding additives to the coating structure.

Additionally, the model will be augmented to include the effect of different polymer coatings and different media surrounding the drug (biphasic release) in order to simulate different stages of the GI tract environment. The deduction of unknown parameters from the experimental release curves using reverse engineering and inverse Monte Carlo methods is a long-term aim. Nevertheless, the approach to date enables comparison of a set of simulated and experimental release curves allowing us to determine key parameters and their values for this novel formulation and to reproduce qualitative behaviour. This enables us to compare a large set of simulated release curves with real ones in order to estimate best fit parameter values.

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REFERENCES

Atyabi F.; Vahabzadeh R.; and Dinarvand R., 2004. *Preparation of Ethylcellulose Coated Gelatin Microspheres as a Multiparticulate Colonic Delivery System for 5-Aminosalicilic Acid. Iranian Journal of Pharmaceutical Research*, 2, 81–86.

Barat A.; Crane M.; and Ruskin H., 2008a. *Quantitative multi-agent models for simulating protein release from PLGA bioerodible nano- and microspheres. Journal of Pharmaceutical and Biomedical Analysis*, 48, 361 – 368.

Barat A.; Ruskin H.; and Crane M., 2008b. *3D Multi-agent models for protein release from PLGA spherical particles with complex inner morphologies. Theory in Biosciences*, 127, –.

Crank J., 1975. *Mathematics of Diffusion.* Clarendon: Oxford.

Geraghty M., 2004. *Investigation of ibuprofen release from ethylcellulose matrix compacts.* Ph.D. thesis, University of Dublin, Trinity College.

Göpferich A., 1996. *Mechanisms of polymer degradation and erosion. Biomaterials*, 17, 103 – 114.

Göpferich A. and Langer R., 1993. *Modeling of Polymer Erosion. Macromolecules*, 26, 4105–4112.

Laaksonen T.; Laaksonen H.; Hirvonen J.; and Murtomäki L., 2009. *Cellular automata model for drug release from binary matrix and reservoir polymeric devices. Biomaterials*, 30, 1978 – 1987.

Langer R. and Peppas N., 1983. *Chemical and Physical Structure of Polymers as Carriers for Controlled Release of Bioactive Agents: A Review. Journal of Macromolecular Science*, 23, 61 – 126.

Li D.; Hohne D.; Bortz D.; Bull J.; and Younger J., 2007. *Modeling bacterial clearance from the bloodstream using computational fluid dynamics and Monte Carlo simulation. Journal of Critical Care*, 22, 344 – 344.

Siepmann J. and Göpferich A., 2001. *Mathematical modeling of bioerodible, polymeric drug delivery systems. Advanced Drug Delivery Reviews*, 48, 229 – 247.

Siepmann J. and Siepmann F., 2008. *Mathematical modeling of drug delivery. International Journal of Pharmaceutics*, 364, no. 2, 328 – 343.

Sopasakis A., 2004. *Stochastic noise approach to traffic flow modeling. Physica A: Statistical Mechanics and its Applications*, 342, 741 – 754.

Tezuka S.; Murata H.; Tanaka S.; and Yumae S., 2005. *Monte Carlo grid for financial risk management. Future Generation Computer Systems*, 21, 811 – 821.

Zygourakis K., 1990. *Development and temporal evolution of erosion fronts in bioerodible controlled release devices. Chemical Engineering Science*, 45, 2359 – 2366.

WEB REFERENCES

European Pharmacopoeia, http://www.edqm.eu
United States Pharmacopoeia, http://www.usp.org