Modelling Drug Coatings: A parallel Cellular Automata Model of Ethylcellulose-coated Microspheres

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***Abstract*—Pharmaceutical companies today face a growing demand for more complex drug designs. In the past few decades, a number of probabilistic models have been developed, with the aim of improving insight on microscopic features of these complex designs. Of particular interest are models of controlled release systems, which can provide tools to study targeted dose delivery. Controlled release is achieved by using polymers with different dissolution characteristics. We present here an approach for parallelising a large-scale model of a drug delivery system based on Monte Carlo methods, as a framework for Cellular Automata mobility. The model simulates drug release in the gastro-intestinal tract, from coated ethylcellulose microspheres. The objective is high performance simulation of coated drugs for targeted delivery. The overall aim is to understand the importance of various molecular effects with respect to system evolution over time. Important underlying mechanisms of the process, such as erosion and diffusion, are described.**

Keywords-Drug dissolution, Probabilistic methods, Discrete simulation, Computational modelling, Parallelisation

I. 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 potential to become an integral part of pharmaceutical research. Modern drug formulations can be very complex, while influence of system composition and variables on the release profiles is not fully understood. Modern drug design processes require collaboration between pharmacists, bioengineers and computer scientists. *In silico* modelling addresses the main problems of drug development through (1) reducing experimental cost, (implicit in large amount of *in vitro* testing), (2) accelerating time for drug progression to market, (3) better understanding of drug transport processes and (4) converting the existing approach from a descriptive to a predictive one.

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 making polymer dissolution one of the most important problems to be solved. Here, we present an OpenMP based parallelisation model for simulation of 3D drug systems. The model is based on a combined Monte Carlo (MC) and Cellular Automata (CA) approach and simulates controlled release from coated microspheres. The main novelties in this work include analysis of the effect of the coating structure/material on the drug release and the effort to mimic non-homogeneous dispersion of the drug, thus improving realism of the model. 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, ideal for use in matrix agents, for prolonged release [**Error! Reference source not found.**]. Due to the thin layer of ethylcellulose used, a very fine grained model is required, prompting the need for the parallelisation. The reasons for choosing the particular parallelization framework are outlined, together with its advantages and limitations compared to other industry standard parallelisation approaches, when applied to simulations of complex pharmaceutical systems.

II. THEORY

Theoretical models of DDS vary according to the type and complexity of the system, and can be generally divided into three broad groups: mechanistic, empirical and probabilistic [**Error! Reference source not found.**]. Probabilistic theories have the advantage of applying a bottom-up approach, (incorporating stochastic assumptions and a simplified representation of the system), but requiring less initial information and with the potential to yield better predictions compared to other, top-down theories.

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 these rates are outlined in the pharmacopoeias [**Error! Reference source not found.**], [**Error! Reference source not found.**]. Here, the paddle apparatus II, (USP II), was used to mimic metabolic conditions, (change of temperature, *pH* and dynamic flux), by varying speed of the paddle, and to monitor, experimentally, their influence on the drug dissolution rate. Subsequently, model results are evaluated against these experimental data.

A. Drug Dissolution Phenomena

Important phenomena in polymeric drug delivery systems include: (i) Diffusion: represents the motions 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, [**Error! Reference source not found.**]. In one dimension, Fick's first law can be represented as:

$$J = - D \, \delta c/\delta x \quad (1)$$

where J is the diffusion flux, D is the diffusion coefficient and c is the concentration. (ii) Degradation: the process whereby chain scission occurs during which polymer chains become oligomers and monomers, facilitating easy release. Degradation is the first step of erosion [**Error! Reference source not found.**]. (iii) Erosion: represents the loss of material from a polymer due to degradation. It determines the release rate of the drug [**Error! Reference source not found.**]. 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 [**Error! Reference source not found.**]: (a) 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 looses material only from its surface; (b) Bulk erosion is a heterogeneous process with material being lost from the whole compact, although the size remains constant.

III. CURRENT WORK

This work builds on the basis of a probabilistic model for simulation of PLGA microspheres [**Error! Reference source not found.**]. The modelled device here consists of a drug, nonhomogenously 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 (Figure 1). Microscopic features of the model can be investigated through transitions between cell states. Each cell can have one of several possible states, described (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 Fick's first law). Behaviour of coating layer cells is based on work reported in [**Error! Reference source not found.**], where scission of the polymer chains and formation of pores follow the Erlang probability distribution. The rate of pore formation is characterised by parameter λ, which defines the lifetime, t, of an individual EC cell:

$$t = 1/\lambda \;\; ln(U), U \in Unif[0, 1] \quad (2)$$

When the cell lifetime is reached, the cell is considered to be fully 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 [**Error! Reference source not found.**]. The release rate is measured by counting the number of packets that reach the buffer zone, which is assumed to have perfect sink conditions.

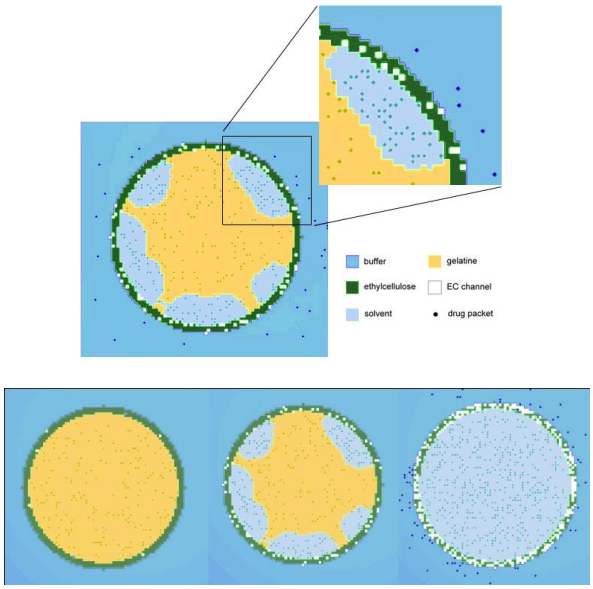


Figure 1. Simplified Internal Morphology of one 3D Sphere Simulating Drug Dissolution through Coating Layer. Enlarged: Part of the Sphere with Definition of Model Cell Types. Bottom: Simulation Stages: Initial (left), Release (centre) and Dissolved (right).

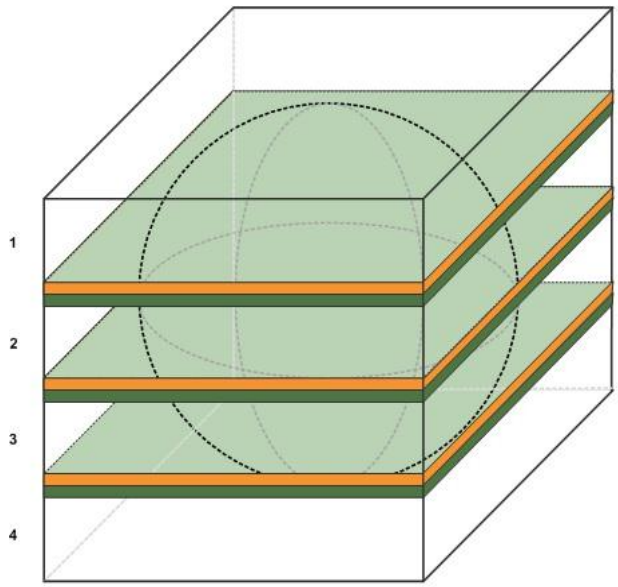
TABLE I. CELL TYPES AND RULES OF BEHAVIOUR

Cell type	***Behaviour description***
Buffer	Drug is released when it reaches buffer zone. Cell type acts as a perfect sink.
Ethylcellulose (EC)	Drug-free coating layer. Assigned lifetime, based on 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".

A. Model Parallelisation

Using high performance computing facilities, (available in-house and at the national centre), we are parallelising the model in order to achieve large-scale short simulation times. The parallelisation scheme is implemented using GNU OpenMP (GOMP). Algorithms are coded using the C++ language and OpenGL libraries for graphic representation where the latter is useful, in particular, for the development and liaison stage.

Initially a sequential, stochastic model for the described drug was implemented [**Error! Reference source not found.**], but the dimensional analysis for fine-tuning of model precision required a significant number of simultaneous runs. However, each run required to produce realistic results was time-consuming, so parallelisation was a logical step forward in obtaining the speedup, with CA models particularly suited to this end, [**Error! Reference source not found.**]. However, special features of the model, such as drug packet movement and cell-state transitions between the layers, proved non-trivial for this implementation. Figure 2 represents the solution for dividing 3D space into layers suitable for parallelisation. Due to high



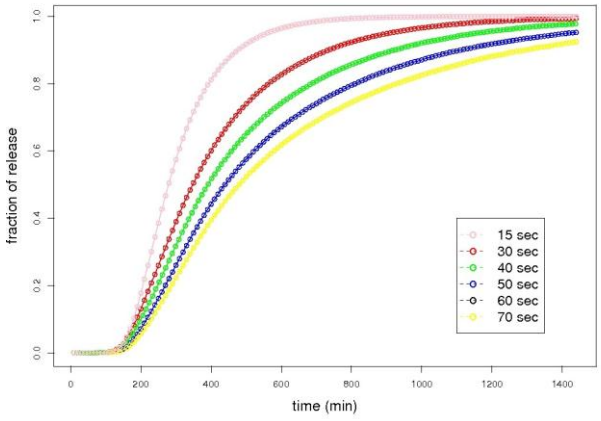
communication demands between the layers, we chose OpenMP, an industry standard for shared-memory parallel programming [**Error! Reference source not found.**], that has an advantage over other frameworks, (e.g. distributed memory, MPI), in that all threads share the same view of the overall problem space. While adequate for cellular automata communication problems, OpenMP is limited by the architecture of the hardware platform used, as it can scale up only to the number of processors that share the same memory.

Figure 2. Parallelisation solution for microsphere geometry for the case of 4 threads. Each thread shares boundary layer with an adjacent thread

Observed also, in upgrading the model from sequential to parallel implementation, is the fact that the standard C++ linear congruential random number generator is unsuitable for large scale parallel models as the implementation of the generator forces a software lock every time the random number generation function is called, causing blocking of threads. Due to this, we used a lock-free implementation of the Mersenne Twister (MT) random number generator which solves the locking problem and also offers a superior period length [**Error! Reference source not found.**].

IV. RESULTS

Based on the available *in vitro* data, initial model parameters were set t: (i) the CA matrix size used was 200 x 200 x 200, with cell size being 10μm simulating millimetre scales of coated microsphere, (ii) maximum lifetimes of individual cells for gelatine and ethylcellulose were 60 minutes and 2 days, respectively, (iii) diameter of the microsphere was 1.43 mm, (iv) default weight gain of EC coating was 5%, and (v) drug loading was kept constant at 10.8% of the mass of the sphere. Unless analysed

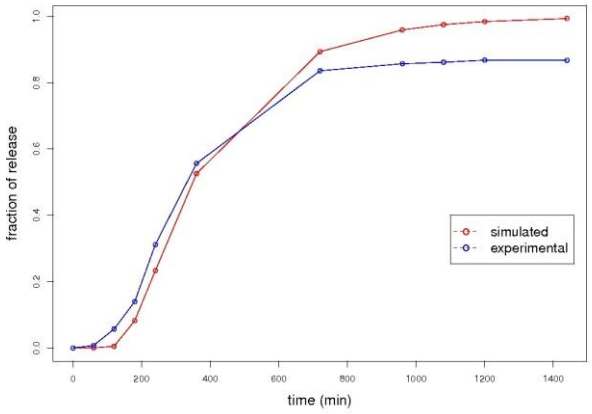


specifically, these values were kept constant for all simulations. The averaging of the drug release curves for these values for 24 repeated runs showed negligible variation. The effectiveness of parallelisation to simulation speeds was measured by comparing total execution times for different number of threads (1, 3, 6 and 12). Results showed linear speedup with increase in the thread number. This allowed both for simulation on very short time intervals and examination of wider ranges of model parameters with the potential to yield deeper insight into the causes of observed system behaviour.

Figure 3. Release Profiles as a Function of the Simulation Time Interval

The first step in modelling was to determine the most appropriate time interval for cell state updates. Since no information was available on the diffusion coefficient from the literature, to our knowledge, the order of magnitude interval was calculated using dimensional analysis based on the average release speed obtained from the *in vitro* data and first Fick's law. To find the best fit interval, we preformed simulations for intervals between 0.5 seconds and 70 seconds, (Figure 3, values higher than 15 sec shown for clarity). Comparing results against experimental data, led to a choice of time interval = 30 seconds which was used for all subsequent simulations. With respect to the physical characteristics of the compact, the effect of porosity in the coating layer was investigated by varying the lifetime of EC cells, (i.e. varying λ parameter), to obtain different release behaviours for different lifetimes of polymer chains, (Figure 5). The slower release rate of the drug observed was due to

decreased porosity, i.e. slower chain scission occurring in the coating. Weight gain of the coating thickness was also one of the primary factors influencing drug formulation and performance. Here, we varied the coating levels from 4% - 8% of the total mass, (Figure 6). The release curves reproduced the reduction in diffusion rate, but the impact was somewhat smaller than experienced *in vitro*. This was

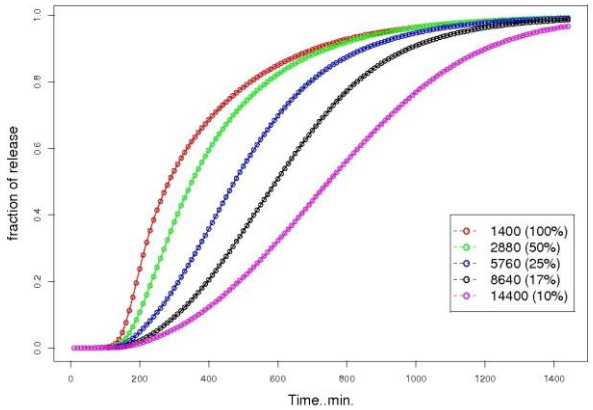


expected, to some extent, as perfect sink conditions were modelled here, whereas these do not really occur. In reality, the concentration of ethylcellulose in the boundary layer inhibits movement of drug packets and some local saturation occurs. This phenomenon must be taken into account in future model extensions. As can be seen, (Figure 7), the lifetime of the gelatine carrier can be considered 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.

Figure 4. Simulated vs experimental results (experimental data provided by Sigmoid Pharma Ltd.)

V. FUTURE WORK

Although simulated results do not reflect quantitative *in vitro* data precisely, (Figure 4), results obtained are promising. These show that the model predicts qualitatively similar behaviour compared to that seen from experiments. Results also show that the behaviour of EC cannot be modelled using erosion only, but that other phenomena, such as swelling, which influences volume increase, due to increased hydration of the broken polymer chains, have to be taken into account [**Error! Reference source not found.**]. Thus, the future focus for the model will be incorporation of the swelling effect, caused by additives to the coating structure. Additionally, the model will be augmented to include the effect of different media surrounding the drug, (biphasic release), in order to simulate different stages of the GI tract environment. Nevertheless, the approach to date facilitates comparison of simulated and experimental release curves, allowing us to determine key parameters and their



values for this novel formulation, and to reproduce qualitative behaviour and best fit. With the introduction of parallelisation, the model became significantly more scalable allowing fast simulation times at fine-grained resolutions.

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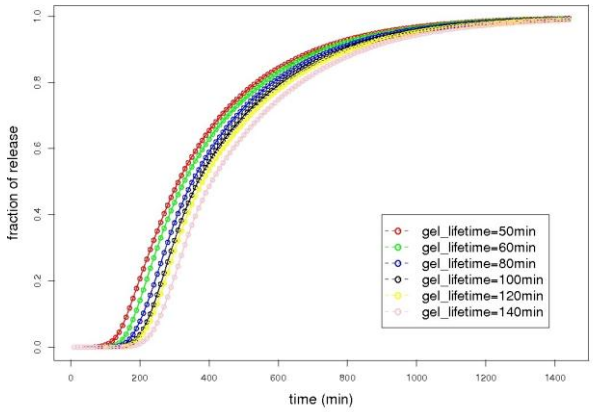
Figure 5. Release Profiles as a Function of the Coating Degradation Rate Lambda. Legend represents inverse lambda values. In brackets: equivalent amount of eroded EC in 24h



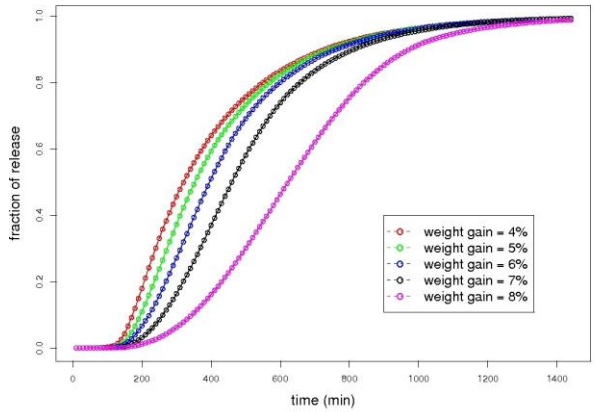


Figure 6. Release Profiles as a Function of Coating Weight Gain.

Figure 7. Release profiles as a Function of Gelatine Lifetime.

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