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, for the purpose of giving a better insight into the microscopic features of these complex designs. Of particular interest are those models that simulate controlled release systems to provide targeted dose delivery. Controlled release is achieved by using polymers with different dissolution characteristics. We present here a model of a drug delivery system based on Monte Carlo methods, as a framework for Cellular Automata mobility, and show a solution for model enhancement through parallelisation. The objective is the high performance simulation of targeted drug release in the gastro-intestinal tract, from a capsule composed of ethylcellulose coated microspheres. 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, OpenMP parallelisation

I. INTRODUCTION

Pharmaceutical systems designed to transport active substances into the body are known as drug delivery systems (DDS). The computational modelling of DDS is a constantly developing field, with the potential to become an integral part of pharmaceutical research development. Newer 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, (implicitly high in large amount of *in vitro* testing), (2) accelerating the 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 designed to deliver active substance, (i.e. drug), at the desired rate over a prolonged period to a targeted site in the body. Numerous research studies over the past three decades have resulted in a number of novel controlled delivery formulations, [1]. 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 the analysis of the effect of the coating structure on the drug release and the effort to mimic non-homogeneous dispersion of the drug, thus improving realism of the model. The research is performed in an ongoing collaboration with the industrial partner and aims to address the questions surrounding the release of 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, (hence ideal for use in matrix agents), for prolonged release, [2]. 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 parallelisation 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, [3]. 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. To emulate these conditions, a dissolution test apparatus is used, with standardised measuring methods outlined in the pharmacopoeias, [4], [5]. Here, metabolic conditions in the intestine stomach, (change of temperature, *pH* and dynamic flux), are mimicked in the paddle apparatus II, (USP II), by varying speed of the paddle, and monitoring, experimentally, their influence on the drug dissolution rate (Figure 1). Subsequently, model results are evaluated against these experimental data.

Monte Carlo methods have numerous applications, ranging from fluid dynamics, space and traffic modelling and statistical physics generally, to financial and business analysis, [6], [7], [8]. In one of the first direct MC models of

DDS, microstructural changes in bioerodible polymers were simulated [9], while 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 state transitions. Time is discrete, and the state at different time steps is defined according to local relations, [10].

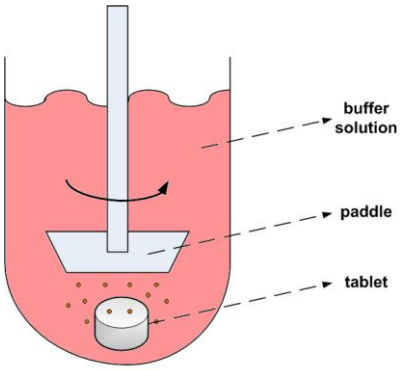

Figure 1. Schematic representation of the USP II Paddle Apparatus

A. *Drug Dissolution Phenomena*

Important phenomena in polymeric drug delivery systems, and used in this work, 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, [11]. In one dimension, Fick's first law can be represented as:

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

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, [12]. (iii) Erosion - represents the loss of material from a polymer due to degradation and determines the release rate of the drug, [13]. When a polymer erodes it leaves space for the drug to be released from the device, or for water penetration. Two types of erosion are defined, [14]: (a) Surface erosion is a homogeneous process and represents the stage during which the size of the device decreases while the shape remains constant; the device loses material only from its surface; (b) Bulk erosion is a heterogeneous process with material being lost from the whole device, although the size remains constant.

III. CURRENT WORK

This work builds upon a basis of a probabilistic model for simulation of PLGA microspheres, [15]. The DDS we are modelling here is a polymer coated sphere, with a nonhomogenously dispersed drug. The purpose of the model is to evaluate the drug release rates depending on different properties of the device with the emphasis on the influence of coating characteristics. The spherical geometry of the device is represented as a 3D grid of cells, where microscopic features can be investigated through transitions between cell states. Cells are initialised and simulated using Monte Carlo methods combined with Cellular Automata rules. Erosion and diffusion are assumed as the main release mechanisms (Figure 2). Each cell can have one of several possible states, described (Table 1). The transitions are influenced by the states of all nearest neighbour cells for a 3D grid (i.e. Von Neumann neighbourhood with each cell having 26 neighbours). The drug is randomly dispersed within a gelatinous sphere in the form of "packets" where the latter represent quantities of drug that can diffuse in each simulation interval. Diffusion of the drug inside the sphere is represented as a random walk of packets, influenced by concentration differences. Each packet has probability of transition between neighbouring cells, weighted by the value of the concentration gradient, based on Fick's first law (i.e. the highest probability for movement will be in the direction of the largest concentration gradient). In the coating layer, scission of the polymer chains occurs and formation of pores follows the Erlang probability distribution, as reported in [9]. The rate of pore formation is characterised by a parameter λ, which defines the lifetime, t, of an individual EC cell:

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

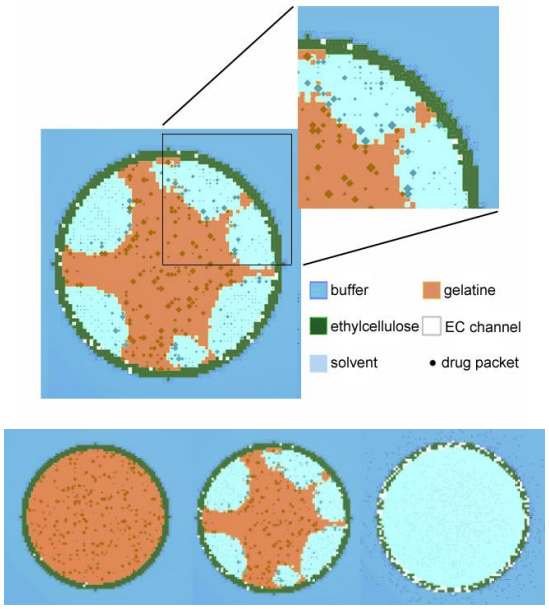

Figure 2. Simplified Internal Morphology of one 3D Sphere Simulating Drug Dissolution through Coating Layer. Enlarged: Part of the Sphere with Definition of Model Cell Types. Bottom: Simulation Stages: Initial (left), Release (centre) and Dissolved (right).

Cells erode, forming a channel through which the drug packet can diffuse, when cell lifetime expires. The diffusion through these channels occurs at a rate slower than the diffusion in solvent, (inside the coating layer), reflecting the influence of permeability of the membrane, [16]. The release

rate is measured by counting the number of packets that reach the buffer zone, assuming perfect sink conditions.

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 reconstructing the model to suit a shared memory, multi-threaded paradigm in order to achieve short large-scale 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 [17], but the dimensional analysis for fine-tuning of model precision required a significant number of simultaneous runs. However, requirements for producing realistic results proved to be time-consuming for large model scales, so parallelisation was a logical step forward in obtaining the speedup, with CA models particularly suited to this end, [18]. However, special features of the model, such as drug packet movement and cell-state transitions between the layers, appear to be non-trivial for this implementation. Figure 3 represents the solution for dividing 3D space into layers suitable for parallelisation. Due to the high communication demands between the layers, we chose OpenMP, an industry standard for shared-memory parallel programming [19], that has an advantage over other solutions, (e.g. distributed memory and message passing frameworks), in that all threads share the same view of the overall problem space. While adequate for CA 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.

Observed also, in upgrading the model from sequential to parallel implementation, is the fact that the standard C++ linear congruential random number generator was unsuitable for large scale parallel models as the implementation of the generator forces thread locking [1] every time the random number generation function is called, causing excessive synchronization overhead between the threads. Instead, we used a lock-free implementation of the Mersenne Twister (MT) random number generator for each thread, which solved the locking problem while also offering a superior period length, [20].

[1] A thread lock is a situation where one or more threads have to wait to enter a critical section of the code. If another thread is currently executing the critical section, the operating environment will block the other threads until the executing thread leaves it.

IV. RESULTS

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

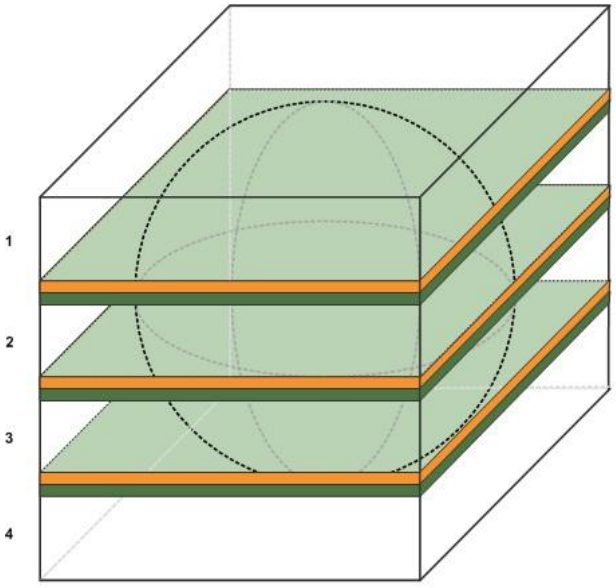

Figure 3. Parallelisation solution for microsphere geometry for the case of 4 threads. Each thread shares boundary layer with an adjacent thread

The main step for initial model calibration was to determine the most appropriate time interval for cell state updates, which represents the speed of drug diffusion characterised by its diffusion coefficient. Since coefficient value was not available from the literature, to our knowledge, the order of magnitude interval was estimated 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 performed simulations for intervals between 0.5 seconds and 100 seconds, (Figure 4, with representative values only shown, for clarity). Comparing results against experimental data (Figure 5), led to a choice of time interval of 30 seconds for all subsequent simulations. This comparison showed good model prediction. In analysing the results, it should be remembered that measurements of the *in vitro* release rates using different dissolution media in USP II may have certain limitations in terms of sensitivity. The insolubility of the cyclosporine, causes fragmentational release which requires adding surfactants to the dissolution media in order to solubilise the drug. If suitable amount of surfactants is not present, equipment used will not be able to detect exact release rates, [21]. As a result, the release curve may reach a platform at 80% of total release, (although 100% is accounted for in the experiment), also in agreement with simulated predictions.

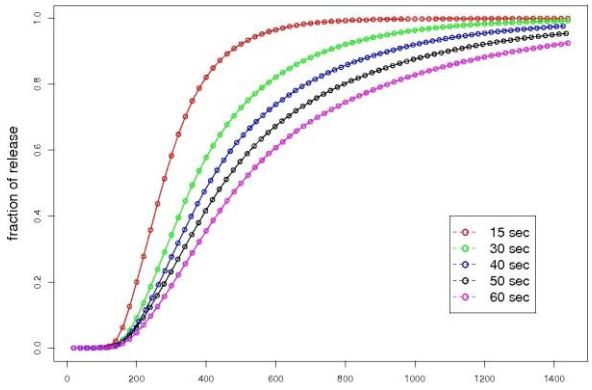

Figure 4. Release Profiles as a Function of the Simulation Time Interval

With respect to the physical characteristics of the device, release behaviour due to the effects of coating layer porosity was investigated. The lifetime of EC cells was varied by changing the λ parameter, in order to simulate different lifetimes of polymer chains, (Figure 6). As expected from the *in vitro* data, decreased porosity, i.e. slower chain scission occurring in the coating influenced slower release rate of the drug. Among the primary factors influencing drug formulation and performance is the weight gain of the coating. Here, we varied the coating weight gains from 4% - 8% of the total mass, (Figure 7). 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 assumed, whereas these do not really occur. In reality, the concentration of the dissolved device material 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. Also, differences of only 1% in coating thickness could be significantly more visible with finer model resolutions. With speedup accomplished using parallelisation, this will be investigated further.

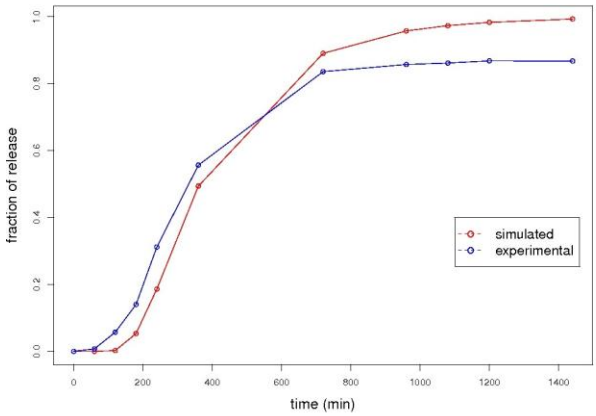

Figure 5. Simulated vs experimental results (experimental data provided by Sigmoid Pharma Ltd.)

On the other hand, the lifetime of the inner, gelatine, carrier can be considered negligible in terms of influence on final release rate, as can be seen, (Figure 8). However, gelatine was shown to be an important controller of the drug release in the initial stages, as it influences the "burst effect" by accelerating the buffer penetration inside the coating and therefore drug transfer through EC channels.

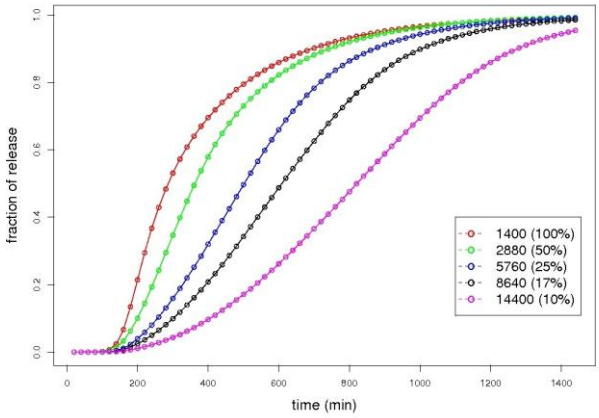

Figure 6. Release Profiles as a Function of the Coating Degradation Rate Lambda. Legend represents inverse lambda values. In brackets: equivalent amount of eroded EC in 24h

V. FUTURE WORK

With the introduction of parallelisation, the model became significantly more scalable, allowing fast simulation times at fine-grained resolutions. Current simulated results showed qualitatively similar behaviour to *in vitro* data, (Figure 5). Although, quantitative data is not obtained precisely, which is to be expected, given the simplified dissolution model, the overall results are promising and form a good base for future extensions. As noted, the modelled EC phenomena can not focus only on erosion, but must include polymer swelling due to increased hydration of broken polymer chains, [22]. This swelling is caused by additives to

the coating structure. Additionally, the model needs be augmented to include the effect of different media surrounding the drug, (biphasic release), in order to mimic 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.

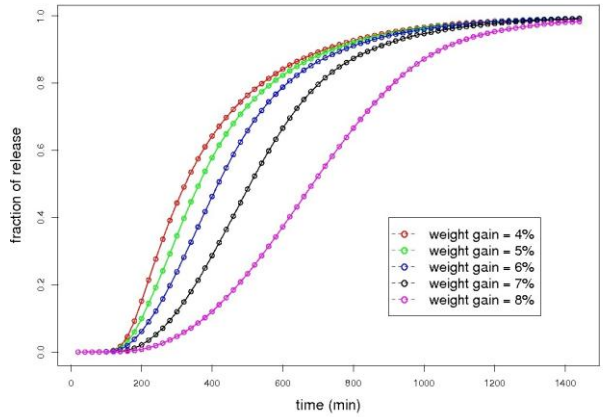

Figure 7. Release Profiles as a Function of Coating Weight Gain.

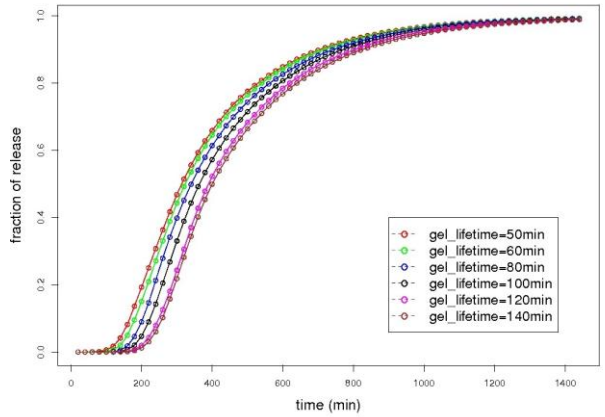

Figure 8. Release Profiles as a Function of Gelatine Lifetime.

ACKNOWLEDGMENT

MB acknowledges financial support from the Irish Research Council for Science, Engineering and Technology (IRCSET), under the Enterprise Partnership Scheme, grant number P07669, with Sigmoid Pharma as Enterprise Partner, and access to ICHEC (Irish Centre for High-End Computing) facilities.

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