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The importance of boundary conditions in the simulation of dissolution in the USP dissolution apparatus

N. McMahon [a,*], M. Crane [a], H.J. Ruskin [a], L. Crane [b]

[a] School of Computing, Dublin City University, Dublin 9, Ireland
[b] School of Mathematics, Trinity College, Dublin 2, Ireland

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Abstract

As shown in previous papers, mathematical simulation can be useful in the design of drug delivery systems. We present a finite-difference approximation to the drug mass transfer rate from dissolving cylindrical drug-containing compacts, consisting of alternating layers of drug and inert material. Results are compared with a recent analytical solution to the same problem and with experiment. The two theoretical estimates differ by about 10%, a result of different implementations of a derivative surface boundary condition. The finite-difference model is more physically realistic but the analytical solution is usefully accurate.

Keywords: Drug delivery systems; Analytical/numerical simulation; Mass transfer rate; Boundary conditions

1. Introduction

There are many types of drug delivery system. Aspirin tablets, or *compacts*, for example, are designed to deliver acetylsalicylic acid to the body. Controlled release systems deliver drug at a predetermined rate, maximising the drug's effectiveness while minimising the risk of overdose [18,19]. In dissolution controlled systems, the drug release rate is modified with excipients of known dissolution properties. Excipients are the generally biologically inert materials that together with the drug(s) form the delivery system [2]. Compacts often consist of uniform, compressed mixtures of drug and excipient. Dissolution simulations can give physical insight and reduce the costs of researching new dissolution controlled delivery systems [6].

Ramtoola and Corrigan [25] showed that for a specific compact consisting of two components, an acid drug and an acid excipient, dissolving in a solvent, classical dissolution theory [15] fails to make accurate predictions about the drug dissolution rate. The error was attributed to pH changes at the solid–liquid interface,

* Corresponding author. Tel.: +353 (0) 87 683 9648.
E-mail addresses: nmcmahon@computing.dcu.ie (N. McMahon), mcrane@computing.dcu.ie (M. Crane), hruskin@computing.dcu.ie (H.J. Ruskin).

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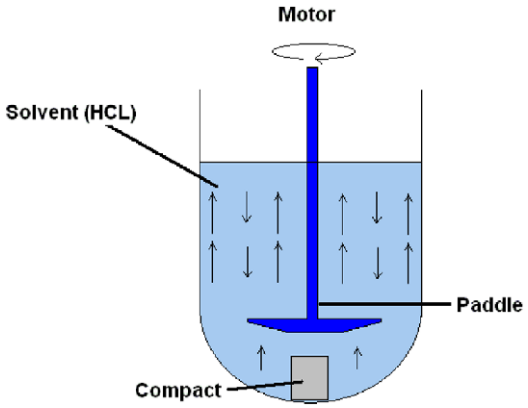

Fig. 1. USP type 2 dissolution apparatus.

an effect not captured by Higuchi's non-interacting component model. Healy and others have investigated further aspects of dissolution behaviour that standard models do not include, from compact composition [11] to the hydrodynamics of the dissolution environment [8]. Healy and Corrigan [12] concluded that large particles of fast-dissolving excipient increase the drug dissolution rate. Once dissolved, large particles leave behind large pores on the compact surface, increasing the effective surface area of drug exposed to the solvent. This suggested an investigation into how drug and excipient dissolution properties affect the surface area of drug and its delivery rate during dissolution. To this end, recent work has involved modelling simple one or two component cylindrical compacts, dissolving in a type 2 USP dissolution test apparatus [29] (Fig. 1). The two component compacts consist of equally spaced alternating layers of one drug and one excipient (Fig. 2).

The multi-layer configuration was chosen for reasons including: (i) it is a simple starting point, with well-defined regions of drug and excipient [6], and (ii) techniques used to model this system may be applied to uniformly mixed multi-component compacts [23]. Layered compacts are uncommon in practice, though similar devices have been proposed as viable delivery systems [1,24].

Crane et al. [7][1] outlined analytical and numerical predictions for drug release from a compact consisting entirely of drug (a one-layer system), both approaches giving reasonable agreement with the experimental results of Healy et al. [13]. The authors concluded with two recommendations for building improved models: (i) to incorporate the three dimensional fluid motion of the USP apparatus, and (ii) to develop the analytical model to take account of the compact's finite size and its increasing axial curvature as it dissolves. Crane et al. [6] describe an improved analytical model, derived using a simpler method and agreeing to within 5% of the previous analytical result. Importantly, despite neglecting the axial curvature and finite volume of the compact, this model has a significant advantage in that it tackles the surface boundary conditions necessary to model multi-layer compacts. Mass transfer rates computed using this improved model agree reasonably well with experimental data for one-, three- and five-layer systems [6].

We present further considerations about the surface boundary conditions and describe a numerical approximation to drug dissolution from the curved surface of single- and multi-layer compacts. We consider, in particular, the five-layer derivative boundary condition and begin with a review of the previous analytical five-layer model [6]. Our aim is to determine the merits of the semi-analytical and finite-difference models.

[1] Results from the fourth framework EU project, PSUDO [23] (parallel simulation of drug release code). Its aim was to demonstrate the usefulness of high performance computing in drug delivery system design and development.