McMahon, N.M.; Crane, M.; Ruskin, H.J.; Crane L.

The Mechanics of Drug Dissolution

*A numerical method for approximating the mass flux from a dissolving cylindrical drug compact, a tablet, is presented. The tablet consists of alternating layers of drug and inert material. The dissolution takes place in a non-reactive medium using a standard stirring device and is considered to be two dimensional and steady. A finite difference scheme is used to generate an approximation to the concentration boundary layer. By integrating across the velocity*concentration profile at the trailing edge, the mass flux is estimated. This value differs by 0.9% from the recent estimate of Crane et al. who used a Pohlhausen approximation to the concentration boundary layer. The finite difference concentration profile at the trailing edge also agrees very well with the equivalent Lévêque exact solution. We conclude that the finite difference model is behaving as expected.*

1. Introduction

"Drug delivery system" is a modern term used in place of "dosage form" to describe a system for carrying a drug into the body [1]. There are many types of drug delivery system. The common Aspirin tablet, for example, is a system designed to deliver acetylsalicylic acid to the body. The aim of such systems is to control the release rate of the drug with precision (to increase the effectiveness of the therapy and reduce the risk of damage). In dissolution drug delivery systems, the drug release can be controlled with excipients (inert substances that together with the drug form a tablet) whose dissolution properties are known. Previous research has shown that even in the basic case of a drug and excipient dissolving into reactive media, established dissolution models fail to make accurate predictions of the drug mass flux [2]. Recent work by Crane et al. [2], and the PSUDO project [3], has involved modelling the dissolution of simple cylindrical tablets consisting of alternating layers of drug and excipient (figure 1). These simple tablets are used to demonstrate the possibility of modelling state of the art delivery systems. The dissolution takes place in a non-reactive medium using a United States Pharmacopeia (USP) [4] drug dissolution apparatus (a standard stirring device). Mass fluxes computed by Crane et al. agree well with experimental data for both single layered (that is a tablet consisting purely of drug) and multi-layered tablets. A semi-analytical Pohlhausen type approximation to the concentration boundary layer was used. This paper considers an alternative, numerical, approximation to the concentration boundary layer and the mass flux for the trivial case of a single layered tablet undergoing steady state diffusion.

2. Numerical Method

To simulate mass transfer, the time dependent diffusion-advection equation is used with simplifying assumptions [5]. These include a two-dimensional steady state. The equation is discretised using a Forward Time Central Space (FTCS) finite difference scheme [6], second order accurate in space and first order accurate in time. The stream-wise displacement (x) is the time-like independent variable in this case. Initial values are provided by the exact Lévêque solution ([7] cited by Schlichting [5]) in order to avoid the singular nature of the equation's solution at the leading edge ($x = 0$ cm). Lévêque's solution of the diffusion-advection equation is expressed as a ratio of gamma functions and is calculated numerically. The region to be discretised, therefore, extends from $x = 0.1$ cm to $x = 0.85$ cm, the trailing edge. The scheme is stable. The mass flux from the tablet is estimated by integrating across the *velocity*concentration* profile at the trailing edge, from the surface to the edge of the concentration boundary layer. The integral is calculated using the Trapezoidal Rule [8]. The input parameters are: the diffusivity of the drug, the viscosity of the fluid, the main-stream velocity, and the stream-wise length of the tablet. The numerical schemes are implemented using Visual Basic scripts running in MS Excel and using GNU Octave.

3. Results

For a given set of input parameters the finite difference mass flux value, calculated as outlined above, has a relative error of 0.9 % with respect to the Pohlhausen type solution proposed by Crane et al. By comparison, the mass flux approximated with Lévêque's solution has a relative error of 1.0 % with respect to the Pohlhausen type solution. The Lévêque and finite difference mass flux values agree to within 0.1% as demonstrated by the concentration profiles

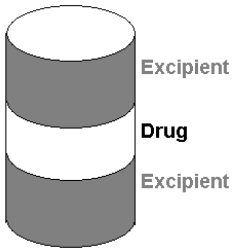

Figure 1: Multi-layer tablet

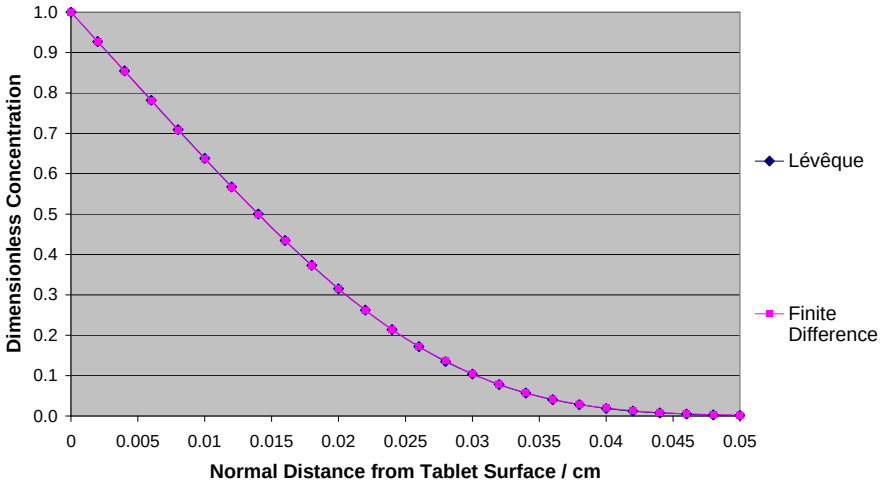

Figure 2: A comparison of drug concentration profiles at $x = 0.85$ cm, the trailing edge of the tablet

shown in figure 2. This good agreement indicates that the finite difference scheme employed is behaving as expected.

This work is currently being improved and extended to model the drug flux from a multi-layered tablet. Future work will consider more realistic systems. Real dissolution systems (those in therapeutic use) have moving boundaries (as the drugs and excipients dissolve) and often the drug is dispersed through a matrix of excipient. Some real systems also use new polymer technologies to protect and deliver the drug. We look forward to these challenges.

Acknowledgements

The authors would like to thank the Irish National Institute for Cellular Biotechnology (NICB) for its support and Dr. Anne-Marie Healy of the School of Pharmacy in Trinity College Dublin who produced the experimental data mentioned in this paper. The authors would also like to thank the people of die Gesellschaft für Angewandte Mathematik und Mechanik (GAMM) and the University of Padua (Università degli Studi di Padova) for the opportunity to present at GAMM 2003.

4. References

1 Robinson, J. R. 1984. Pharmaceutics and the evolving technology of drug delivery - a perspective *IN:* Borchardt, R. T. Repta, A. J. and Stella, V. J. (eds.) *Directed Drug Delivery, a Multidisciplinary Problem.* New Jersey: Humana Press.

2 Crane, M. Crane, L. Healy, A. M. Corrigan, O.I. Gallagher, K.M. McCarthy L.G. 2003. A Pohlhausen Solution for the Mass Flux From a Multi-layered Compact in the USP Drug Dissolution Apparatus. Pending Publication.

3 Parallel SimUlation of Drug release cOde (PSUDO) 2000. (Homepage) [Online]. Available from: <http://www.icetact.tcd.ie/icetact/examples/psudo.html> Access Date [26/05/2003].

4 United States Pharmacopeia 2003. (Homepage) [Online]. Available from: <http://www.usp.org/frameset.htm> Access Date [26/05/2003].

5 Schlichting, H. 1979. *Boundary-Layer Theory* 7th Edition. New York ; London [etc.] : McGraw-Hill. Chap. XII p285 eqn. (12.51c). and p291 eqn. (12.60). *Note: it seems there is a square root missing in the denominator of equation (12.60) in this edition.*

6 Vemuri, V. Karplus, Walter J. 1981. *Digital Computer Treatment of Partial Differential Equations* New Jersey: Prentice-Hall.

7 Lévêque, M. A. 1928. Les lois de la transmission de chaleur par convection (or the laws of heat transmission by convection). Ann. Mines 13, 201 - 239.

8 Spiegel, Murray R. 1974. *Schaum's Outline Series - Theory and Problems of Advanced Calculus* SI (metric) Edition. London: McGraw-Hill.

Mr. Niall McMahon, Dr. Martin Crane, Prof. Heather Ruskin, School of Computer Applications, Dublin City University, Glasnevin, Dublin 9, Ireland

Prof. Lawrence Crane, School of Mathematics, Trinity College Dublin, Dublin 2, Ireland