The Importance of Boundary Conditions in the Simulation of Dissolution in the USP Dissolution Apparatus

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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.

Key words: Drug delivery systems; analytical/numerical simulation; mass-transfer rate; boundary conditions

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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 (Langer, 1993, 2003). 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 (Aulton, 2002). 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 (Crane et al., 2004a).

Ramtoola and Corrigan (1987) showed that for a specific compact consisting of two components, an acid drug and an acid excipient, dissolving in a solvent, classical dissolution theory (Higuchi et al., 1965) fails to make accurate predictions about the drug dissolution rate. The error was attributed to pH changes at the solid-liquid interface, 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 (Healy and Corrigan, 1992) to the hydrodynamics of the dissolution environment (D'Arcy et al., 2005). Healy and Corrigan (1996) 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

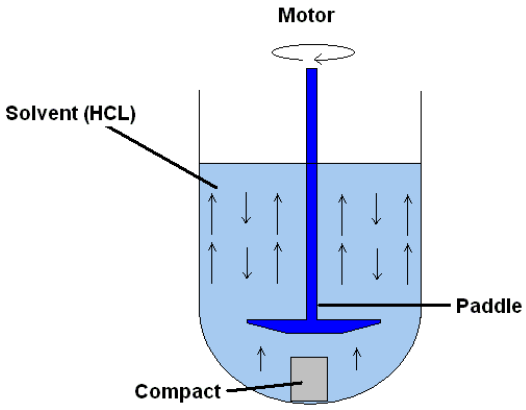

Figure 1: USP type 2 dissolution apparatus.

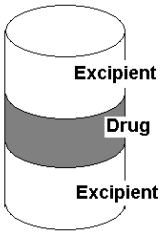

Figure 2: Multi-layer compact.

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 (United States Pharmacopeial Convention, 2000)(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 (Crane et al., 2004a), (ii) techniques used to model this system may be applied to uniformly mixed multi-component compacts (PSUDO, 2000). Layered compacts are uncommon in practice, though similar devices have been proposed as viable delivery systems (e.g. Abdul and Poddar (2004), Qiu et al. (1998)).

Crane et al. (2004b) [2] outlined analytical and numerical predictions for drug release from a compact consisting entirely of drug (a 1-layer system), both approaches giving reasonable agreement with the experimental results of

[2]Results from the fourth framework EU project, PSUDO (2000) (Parallel simulation of drug release code). Its aim was to demonstrate the usefulness of high performance computing in drug delivery system design and development.

Healy et al. (2002). 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. (2004a) 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 1- , 3- and 5-layer systems (Crane et al., 2004a).

Although the dissolution test is widely used, high variability in results have been reported (Qureshi and Shabnam, 2001) and its dynamics are for the most part not well understood (Baxter et al., 2005). In recent years, computational fluid dynamics simulations (Healy et al., 2002; McCarthy et al., 2003, 2004; Kukura et al., 2004; Baxter et al., 2005; D'Arcy et al., 2005) have shown that the flow field in the device is fully three-dimensional and that small displacements of the compact can lead to significant changes in the dissolution rate.

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 5-layer derivative boundary condition and begin with a review of the previous analytical 5-layer model (Crane et al., 2004a). Our aim is to determine the merits of the semi-analytical and finite-difference models.

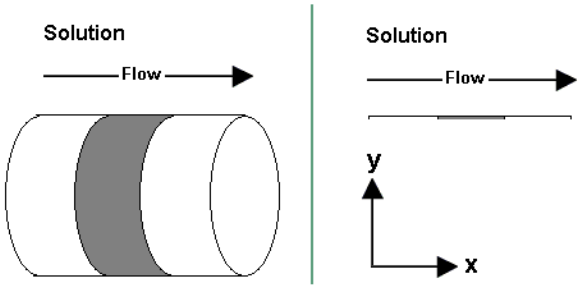

Figure 3: The two-dimensional flat plate approximation.

2 Modelling Compact Dissolution

2.1 Simplifications and Mathematical Description

The advection-diffusion equation, used to model the drug mass transfer from these compacts, is (Incropera and DeWitt, 2002):

$$\frac{\partial c}{\partial t} = -(\vec{v}.\vec{\nabla})c + D\Delta c \tag{1}$$

where c is the concentration of drug, D is its concentration independent diffusion coefficient and $\vec{v}(u, v, w)$ is the fluid velocity field. We maintain a high concentration of the drug in the solid ensuring drug saturation concentration, c_s at the solid-liquid interface (Langer, 1993). If the Schmidt number, S_c, is large[3], the surface curvature may be neglected and the problem reduces to steady two-dimensional dissolution from a flat plate (Fig. 3) with x and y defined in Fig. 4. It is then sufficient to replace the axial velocity profile u by its tangent at the surface since the concentration layer

[3]The velocity boundary-layer is a thin layer of fluid in the immediate vicinity of a surface where the velocity gradients normal to the surface are very large (Prandtl, 1928); it determines the friction on the wall. A concentration boundary-layer also exists that determines the convection mass transfer rate. S_c is the ratio of the momentum and mass diffusivities: for laminar flows, the thickness of the concentration boundary-layer is small compared to the velocity boundary-layer if S_c is large.

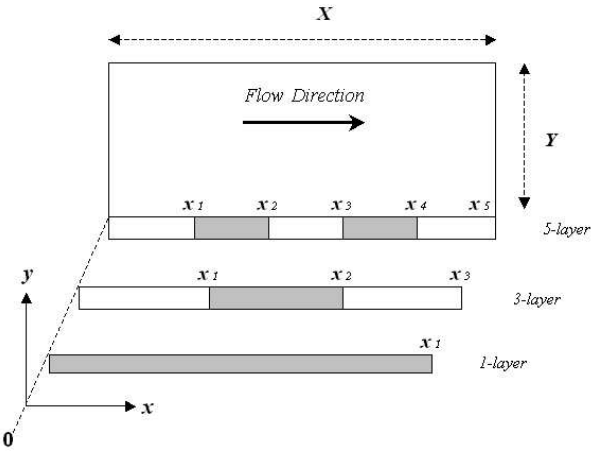

Figure 4: 1-/3-/5-layer configurations with dimensions and coordinate system. The drug layers are coloured grey.

is very thin (Schuh, 1953; Schlichting, 1979) so that

$$u = \frac{\tau_0}{\mu} y \tag{2}$$

where τ_0 is the shear stress at the surface and μ is the dynamic viscosity of the fluid. The freestream fluid velocity past the compact is taken to be axial and steady (Crane et al., 2004a). Diffusion in the x direction may be neglected as for sufficiently fast flows the convection term masks the streamwise diffusion. Surface erosion is assumed to be the primary release mechanism (Siepmann and Gopferich, 2001); this is supported by the linearity of the release rate data reported by Healy et al. (2002) (Heller, 1987). With these assumptions and simplifications, Eq. (1) can be written:

$$u\frac{\partial c}{\partial x} + v\frac{\partial c}{\partial y} = D\frac{\partial^2 c}{\partial y^2} \tag{3}$$

2.2 Boundary Conditions

We are concerned only with the drug mass transfer rate and assume no interaction between the two components, so the boundary conditions are:

		1−Layer	3−Layer	5−Layer
$y = 0$	$0 \leq x \leq x_1$	$c = c_s$	$c = 0$	$c = 0$
$y = 0$	$x_1 \leq x \leq x_2$	–	$c = c_s$	$c = c_s$
$y = 0$	$x_2 \leq x \leq x_3$	–	–	$\left.\frac{\partial c}{\partial y}\right\|_{y=0} = 0$
$y = 0$	$x_3 \leq x \leq x_4$	–	–	$c = c_s$
$y = 0$	$x_4 \leq x \leq x_5$	–	–	–
$y = Y$	$x \geq 0$	$c = 0$	$c = 0$	$c = 0$

where x_1 etc. are defined in Fig. 4.

2.3 Previous Analytical Models

2.3.1 Kestin-Persen Solution (Kestin and Persen, 1962): 1-/3-layer model

Since Sc is large and the concentration boundary-layer is contained entirely within the laminar momentum boundary-layer, we can apply the mathematically equivalent Kestin-Persen (1962) solution to the 1-/3-layer systems. Using the similarity parameter:

$$\eta = \frac{y\sqrt{\frac{\tau_0}{\mu}}}{\left[9D\int_{x_0}^{x}\sqrt{\frac{\tau_0}{\mu}}dx\right]^{\frac{1}{3}}} \tag{4}$$

and noting that $\frac{\partial c}{\partial x} = \frac{\partial c}{\partial \eta}.\frac{\partial \eta}{\partial x}$ and so forth, Eq. (2) can be reduced to an ordinary differential equation whose solution is:

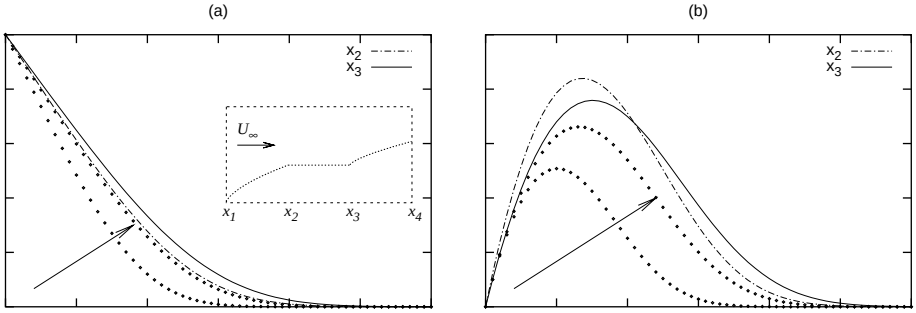

Figure 5: (a) Inset: the variation of drug content in the solution with x-position; (a) The concentration curve at x_3 is varied (by increasing δ_{c_3}) until (b) the areas under the *uc* curves at x_2 and x_3 are the same. The amount of drug in the solution is a function of this area.

$$C = \frac{\Gamma\left(\frac{1}{3}, \eta^3\right)}{\Gamma\left(\frac{1}{3}\right)} \tag{5}$$

$\Gamma\left(\frac{1}{3}, \eta^3\right)$ is the incomplete gamma function (Press et al., 2002). $\Gamma\left(\frac{1}{3}\right)$ is 2.679 (Chang and Jianming, 1996).

2.3.2 Pohlhausen Solution (Crane et al., 2004a): 5-layer model

For the 5-layer case, Crane et al. (2004a) implement the derivative surface boundary condition between x_2 and x_3 by observing that, for a steady state, the total amount of drug in the solution at x_3 must be the same as the total amount of drug in the solution upstream at x_2. They assume, in addition to the assumptions previously outlined, that the *shape* of the concentration-distance curves at x_2 and x_3 are the same and, importantly, that δ_{c_3}, the concentration boundary-layer thickness at x_3, is the only quantity that can be varied to maintain the mass balance between x_2 and x_3 (Fig. 5).

These additional assumptions allow the two separate layers of drug to be treated as one continuous layer and lead to an expression for the total mass transfer from a 5-layer compact:

$$\dot{m}|_{level\ x_4} = \left[2\pi a(0.332U_0)\sqrt{\frac{U_0}{\nu}}c_s\alpha\right](2K)^{\frac{2}{3}}\left(x_4^{\frac{3}{4}} - x_3^{\frac{3}{4}} + x_2^{\frac{3}{4}} - x_1^{\frac{3}{4}}\right)^{\frac{2}{3}} \tag{6}$$

where $\dot{m}$ has units mgs^{-1}, a is the radius of the compact, ν is the kinematic viscosity of the solvent, α is a constant equal to $\left(\frac{1}{2} - \frac{4}{\pi^2}\right)$ and

$$K = \frac{D\pi\nu^{\frac{1}{2}}}{2\alpha 0.332U_0^{\frac{3}{2}}} \tag{7}$$

3 Numerical Method

A rectangular $N \times M$ grid is imposed on the region of interest (Fig. 6), i and j denote the x and y indices respectively. Eq. (2) is linear and parabolic and can be solved using a marching finite difference scheme. We use the well-documented Crank-Nicolson implicit scheme, second order accurate in space and first order accurate in the time-like sense, based on primitive variables and incorporating no numerical diffusion (Dehghan, 2004). x is the time-like independent variable in this case while y is the space variable. The scheme has the advantage of unconditional stability and is evaluated using:

$$-(\epsilon+2s)c_{j-1}^{i}+4(1+s)c_j^i+(\epsilon-2s)c_{j+1}^{i} = (2s+\epsilon)c_{j-1}^{i-1}+4(1-s)c_j^{i-1}+(2s-\epsilon)c_{j+1}^{i-1} \tag{8}$$

$$\epsilon = \frac{v}{u}\frac{\Delta x}{\Delta y}; s = \frac{D}{u}\frac{\Delta x}{(\Delta y)^2} \tag{9}$$

where Δx and Δy are the x and y grid spacings and u and v are calculated at $(i-1,\ j)$. The cell size, $h = \sqrt{\Delta x \Delta y}$.

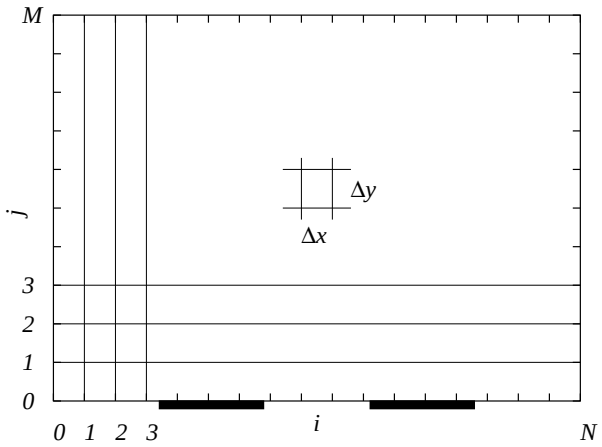

Figure 6: Uniform finite difference grid.

Concentration values at each grid point are calculated using Eq. (8) and the boundary conditions described. The resulting $M-2$ simultaneous equations at every i-position are solved using the tridiagonal matrix algorithm (White, 1991).

Since u and c can be found at each grid point, the drug mass transfer rate from the compact is then estimated using:

$$\dot{m}|_{level\ x} = 2\pi a \int_0^{\delta_c} uc\ dy \tag{10}$$

solved numerically using

$$\dot{m}|_{i_x} = 2\pi a \sum_{j=0}^{j=M-1} u_j^{i_x} c_j^{i_x} \Delta y. \tag{11}$$

Evaluated at the end of the last drug layer, this expression sums the amount of dissolved drug passing level x per second.

3.1 Initial Conditions

For the 1-layer compact, initial concentration values are provided by using the Kestin-Persen solution (1962) to generate a concentration-distance curve at $x = x_0$. This is to avoid the singularity inherent in the solution to the steady-state advection-diffusion equation at $x = 0$. x_0 must be far enough away from the leading edge to have a reasonably well-developed drug concentration profile and so ensure that there is enough information to initialise the finite difference calculation. The rectangular region of interest for a compact consisting entirely of drug extends from $x = x_0$ to $x = X$, the end of the compact. The exact solution is not needed to initialise the 3- and 5-layer solutions and the computational domain for these configurations extends from $x = 0$ to $x = X$.

3.2 Implementing the Neumann Boundary Condition

The derivative boundary condition is implemented as a forward-difference second order approximation, namely (Gavaghan, 1997):

$$\frac{\partial c}{\partial y} = \frac{-c_2 + 4c_1 - 3c_0}{2\Delta y} = 0 \tag{12}$$

$$\Rightarrow c_0 = \frac{4c_1 - c_2}{3} \tag{13}$$

where c_0 is the unknown concentration value at the surface at grid position i, while c_1 and c_2 are the concentration values at Δy and $2\Delta y$ from the surface respectively, also calculated at i. The error associated with this boundary condition, based on a Taylor series expansion, is of the order of at most

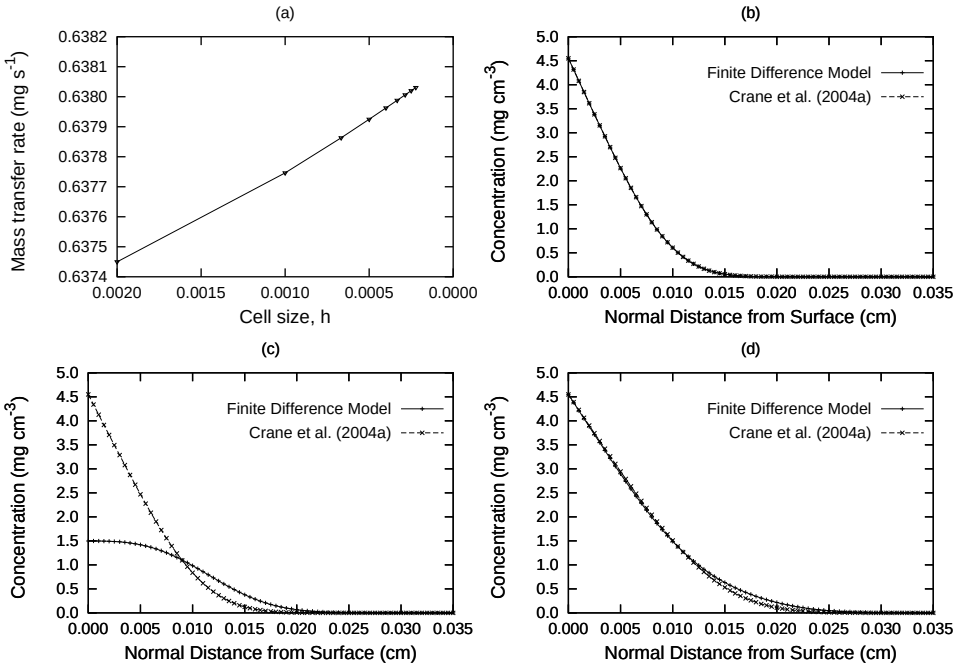

Figure 7: (a) Linear convergence of the 5-layer solution with decreasing cell size; (b) Concentration-distance curve normal to the compact surface at the start of the inert layer, $x = x_2 = 0.34$; (c) At the end of the inert region, at $x = x_3 = 0.51$. The finite difference curve is the more physically realistic; (d) At the end of the second drug layer, $x = x_4 = 0.68$.

$(\Delta y)^2$ (Britz, 1987).

4 Results and Discussion

The drug component was taken to be benzoic acid with a diffusion coefficient of $1.236 \times 10^{-5}\ cm^2/s$ and a solubility in the solvent (0.1N HCL at 37^o) of $4.55\ mg/cm^3$ (Healy et al., 2002). The viscosity of the fluid was assumed to be that of the solvent, $7.867 \times 10^{-5}\ cm^2/s$. The axial freestream velocity past the compact was set as $1.83\ cm/s$ (Crane et al., 2004b). The compacts were $0.85\ cm$ in height and of radius $a = 0.65\ cm$.

The good agreement between the finite difference method and the other

	1-Layer	3-Layer	5-Layer
Experimental (Healy et al., 2002)	**1.46** (-)	**0.64** (-)	**0.73** (-)
Crane et al. (2004b)	1.17 (19.8)	-	-
Kestin and Persen (1962)	1.13 (22.9)	0.50 (21.6)	-
Pohlhausen (Crane et al., 2004a)	1.13 (23.0)	0.51 (21.6)	**0.58 (20.9)**
Finite Difference	1.13 (22.9)	0.51 (21.6)	**0.64 (12.9)**

Table 1: Experimental and theoretical values for the mass transfer rate of benzoic acid from 1/3/5-Layer compacts dissolving in a type 2 USP dissolution test apparatus, $\dot{m}$ $[mg\ min^{-1}]$. Percentage errors with respect to the experimental values are listed in brackets (%). The experimental values for 3/5 layer compacts are inferred from figures for salicylic acid in Crane et al. (2004a).

models[4] for 1-/3-layer compacts, suggests that the finite difference scheme employed is solving Eq. (2) correctly (Table 1). A grid sensitivity analysis (Celik, 2005) indicated that the 5-layer finite difference model converges as $h \rightarrow 0$ with a discretisation error of 0.02 % (Fig. 7a). $t_c = \beta h^2$ where t_c is the computation time, β is a constant. $t_{c_{h=0.001}} = 75s$ (implemented with Python on a 2.4 GHz P4, 512 MB RAM).

The cause of the 10.1% difference between the Pohlhausen and finite difference solutions (Table 2) is illustrated in Figs. 7b - 7d. The drug concentration profiles and corresponding mass transfer rate estimates generated by the Pohlhausen and finite difference solutions almost coincide at the end of the first drug layer, at $x = x_2 = 0.34$ (Fig. 7b). Just before the start of the second drug layer, at $x = x_3 = 0.51$, the concentration-distance curves are quite different (Fig. 7c) but the mass transfer rates based on these curves (calculated using Eq. (8)) are almost the same. Since the same lin-

[4]Crane et al. (2004b) describe a 1-layer solution with a small correction (3%) for the curvature of the compact. If this correction term is dropped, the solution coincides with that of Kestin and Persen.

	1-Layer	3-Layer	5-Layer
Experimental (Healy et al., 2002)	1.00 (29.8)	0.44 (27.5)	0.50 (26.4)
Crane et al. (2004b)	1.00 (4.1)	-	-
Kestin and Persen (1962)	1.00 (0.1)	0.45 (0.1)	-
Pohlhausen (Crane et al., 2004a)	**1.00** (-)	**0.45** (-)	**0.51** (-)
Finite Difference	1.00 (0.1)	0.45 (0.1)	**0.57 (10.1)**

Table 2: Experimental and theoretical values for the mass transfer rate of benzoic acid normalised with respect to 1-layer values. Percentage difference of mass transfer rates with respect to the Pohlhausen values are listed in brackets (%). The 10.1% discrepancy between the Pohlhausen and finite difference methods results from the different implementations of the Neumann boundary condition only.

ear velocity profiles are used in both solutions and we have confidence in the finite difference scheme, it is the difference in the shape of the concentration profiles at $x = x_3 = 0.51$ that gives rise to the slight difference in the drug concentration profiles at $x = x_4 = 0.68$ (Fig. 7d) and the differing mass transfer rates. The shape of the concentration profiles at x_3 only depends on how the Neumann boundary condition within the central layer ($x_2 \leq x \leq x_3$) is implemented. It follows then that the 10.1% difference between the Pohlhausen and finite difference estimates can be entirely attributed to the differing implementations of this boundary condition.

Although the absolute theoretical and experimental mass transfer rate estimates differ (Table 1), if the 3-/5-layer results are presented as fractions of the associated 1-layer solutions, a much better agreement is evident (Table 2). This suggests that much of the underlying physics has been captured by the models. Recent hydrodynamic analyses (McCarthy et al., 2004; D'Arcy et al., 2005) show that for a compact placed centrally in the device the fluid flows across the curved surface, not along it. One implication of this, corresponding with our results, is that the theoretical models will consistently

underestimate the mass transfer rate.

5 Conclusions

The two theoretical estimates for the drug mass transfer rate from the surface of a 5-layer compact are shown to differ by 10.1%, a fact we attribute entirely to the different implementations of the derivative surface boundary condition. Further validation work is necessary but using the finite difference model as a benchmark solution, the analytical Pohlhausen estimate is usefully accurate. The assumption of a steady, axial flow is likely to be the primary reason for the error between the experimental and theoretical results and future work should correct for this.

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References

Abdul, S., Poddar, S., 2004. A flexible technology for modified release of drugs: multi layered tablets. J. Control. Release 97 (3), 393–405.
URL http://dx.doi.org/10.1016/j.jconrel.2004.03.034

Aulton, M., 2002. Pharmaceutics, the science of dosage form design, 2nd Edition. Churchill-Livingstone, Edinburgh etc.

Baxter, J., Kukura, J., Muzzio, F., 2005. Hydrodynamics-induced variability in the usp apparatus II dissolution test. Int. J. Pharm. 292 (1-2), 17–28.

Britz, D., 1987. Investigation into the relative merits of some n-point current approximations in digital simulation. Anal. Chim. Acta 193, 277–285.

Celik, I., 2005. Procedure for estimation and reporting of discretization error in CFD applications. In: Freitas, C. (Ed.), Editorial Policy Statement on the Control of Numerical Accuracy. ASME J. Fluids Eng.
URL http://journaltool.asme.org/Templates/JFENumAccuracy.pdf

Chang, S.-C., Jianming, J., 1996. Computation of special functions, 2nd Edition. Wiley-Interscience, New York.

Crane, M., Crane, L., Healy, A.-M., Corrigan, O., Gallagher, K., McCarthy, L., 2004a. A pohlhausen solution for the mass flux from a multi-layered compact in the USP drug dissolution apparatus. Simul. Model. Pract. Th. 12 (6), 397–411.
URL http://dx.doi.org/10.1016/j.simpat.2004.06.004

Crane, M., Hurley, N. J., Crane, L., Healy, A.-M., Corrigan, O. I., Gallagher, K. M., McCarthy, L. G., 2004b. Simulation of the USP drug delivery problem using CFD: Experimental, numerical and mathematical aspects. Simul. Model. Pract. Th. 12 (2), 147–158.

D'Arcy, D., Corrigan, O., Healy, A., 2005. Hydrodynamic simulation (computational fluid dynamics) of asymmetrically positioned tablets in the paddle dissolution apparatus: impact on dissolution rate and variability. J. Pharm. Pharmacol. 57 (10), 1243 – 1250(8).

Dehghan, M., 2004. Weighted finite difference techniques for the one-

dimensional advection-diffusion equation. Appl. Math. Comput., 307 – 319.

Gavaghan, D., 1997. How accurate is your two-dimensional numerical simulation? Part 1. an introduction. J. Electroanal. Chem. 420(1-2), 147–158. URL http://dx.doi.org/10.1016/S0022-0728(96)04797-3

Healy, A.-M., Corrigan, O., July 1992. Predicting the dissolution rate of ibuprofen-acidic excipient compressed mixtures in reactive media. Int. J. Pharm. 84 (2), 167–173.

Healy, A.-M., Corrigan, O., 1996. The influence of excipient particle size, solubility and acid strength on the dissolution of an acidic drug from two-component compacts. Int. J. Pharm. 143, 211–221.

Healy, A.-M., McCarthy, L., Gallagher, K., Corrigan, O., 2002. Sensitivity of dissolution rate to location in the paddle dissolution apparatus. J. Pharm. Pharmacol. 54 (3), 441–444.

Heller, J., 1987. Fundamentals of polymer science. In: Robinson, J. R., Lee, V. H. (Eds.), Controlled Drug Delivery, Fundamentals and Applications, 2nd Edition. Vol. 29. Dekker, New York, p. 206.

Higuchi, W., Mir, N., Desai, S., 1965. Dissolution rates of polyphase mixtures. J. Pharm. Sci. 54, 1405 – 1410.

Incropera, F. P., DeWitt, D. P., 2002. Fundamentals of Heat and Mass Transfer, Fifth Edition. John Wiley & Sons, New York.

Kestin, J., Persen, L., 1962. The transfer of heat across a turbulent boundary layer at very high prandtl numbers. Int. J. Heat Mass Transfer 5, 355–371.

Kukura, J., Baxter, J., Muzzio, F., 2004. Shear distribution and variability in the usp apparatus 2 under turbulent conditions. Int. J. Pharm. 279 (1-2), 9 – 17.

Langer, R., 1993. Polymer-controlled drug delivery systems. Accounts Chem. Res. 26, 537–542.

Langer, R., April 2003. Where a pill won't reach. Sci. Am. 288 (4), 32 – 39.

McCarthy, L., Bradley, G., Sexton, J., Corrigan, O., Healy, A., 2004. Computational fluid dynamics modeling of the paddle dissolution apparatus: Agitation rate, mixing patterns, and fluid velocities. AAPS PharmSciTech. 5 (2).

McCarthy, L., Kosiol, C., Healy, A.-M., Bradley, G., Sexton, J., Corrigan, O., 2003. Simulating the hydrodynamic conditions in the united states pharmacopeia paddle dissolution apparatus. AAPS PharmSciTech. 4 (2).

Prandtl, L., 1928. Motion of fluids with very little viscosity. TM 452, NACA.
URL http://naca.larc.nasa.gov/digidoc/report/tm/52/NACA-TM-452.PDF

Press, W. H., Teukolsky, S. A., Vetterling, W. T., Flannery, B. P., 2002. Numerical Recipes in C, The Art of Scientific Computing, 2nd Edition. Cambridge University Press, Cambridge etc.
URL http://lib-www.lanl.gov/numerical/bookcpdf.html

PSUDO, 2000. Final report. Tech. rep., Parallel Simulation of Drug release code (PSUDO) Project.
URL http://icetact.tchpc.tcd.ie/icetact/examples/PSUDOfinal.html

Qiu, Y., Chidambaram, N., Flood, K., 1998. Design and evaluation of layered diffusional matrices for zero-order sustained release. J. Control. Release 51 (2-3), 123–130.
URL http://dx.doi.org/10.1016/S0168-3659(97)00119-3

Qureshi, S. A., Shabnam, J., 2001. Cause of high variability in drug dissolution testing and its impact on setting tolerances. Eur. J. Pharm. Sci. 12 (3), 271 – 276.

Ramtoola, Z., Corrigan, O., 1987. Dissolution characteristics of benzoic acid and salicylic acid mixtures in reactive Media. Drug Dev. Ind. Pharm. 13, 1703–1720.

Schlichting, H., 1979. Boundary-Layer Theory, 7th Edition. McGraw-Hill, New York.

Schuh, H., 1953. On asymptotic solutions for the heat transfer at varying wall temperatures in a laminar boundary layer with Hartree's velocity profiles. Jour. Aero. Sci. 20(2), 146–147.

Siepmann, J., Gopferich, A., 2001. Mathematical modeling of bioerodible, polymeric drug delivery systems. Advanced Drug Delivery Reviews 48, 229–247.
URL http://dx.doi.org/10.1016/S0169-409X(01)00116-8

United States Pharmacopeial Convention, 2000. USP XXIV. Rockville, MD, Ch. Dissolution < 711 >, p. 1941.

White, F., 1991. Viscous Fluid Flow, 2nd Edition. McGraw-Hill, New York.