International Journal of Pharmaceutics, 96 (1993) 167–174

IJP 03208

A numerical convective-diffusion model for dissolution of neutral compounds under laminar flow conditions

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(Received 11 November 1992)
(Modified version received 27 January 1993)
(Accepted 28 January 1993)

Key words: Convective-diffusion; Dissolution; Laminar flow; Neutral compound; Numerical model

Summary

The convective-diffusion model reported earlier by Shah and Nelson (*J. Pharm. Sci.*, 64 (1975) 1518–1520) described the dissolution of neutral compounds under laminar flow conditions. A linear velocity profile over the tablet surface was assumed to allow calculation of an analytical solution. In the present study, dissolution under laminar flow conditions was modified to include the actual parabolic velocity profile. The modified model was solved numerically using finite difference approximations. The numerical solution to the model predicted dissolution rates to be within 10% of experimental values for benzocaine, a neutral compound, and for benzoic acid and naproxen at suppressed ionization conditions. The modified model predictions were slightly better at high flow rates (100 ml/min) when compared to the earlier model. Overall, however, the Shah-Nelson simplified assumption was found to predict the experimental results as closely as the numerical solution. Using the same apparatus as described earlier by Shah and Nelson (1975), the flow conditions in the device were characterized over the entire range of flow rates considered (1.10–110 ml/min). Flow was found to be in the laminar region from Reynolds number calculations and to be fully developed, devoid of entrance effects, before reaching the tablet surface. As expected, the concentration boundary layer thickness grew with distance from the leading edge of the tablet, but stayed within the dimensions of the flow chamber even at the lowest flow rates employed (1.10 ml/min).

Introduction

The absorption rate of sparingly aqueous soluble drugs from the gastro-intestinal tract (GIT) can be limited by dissolution rate. The importance of understanding the dissolution phenomena is very well appreciated, and various theoretical treatments have been presented since the middle of this century (King and Brodie, 1937; Hixson and Baum, 1944). One of the main factors that affect the dissolution process is the hydrodynamics, or flow characteristics, surrounding the dissolving surfaces. Researchers have used the rotating disk as a model hydrodynamic system to study the intrinsic dissolution rate of sparingly soluble compounds (Wood et al., 1965; Mooney et al., 1980; McNamara and Amidon, 1986). Although this system generates a constant boundary layer thickness through which transport of dis-

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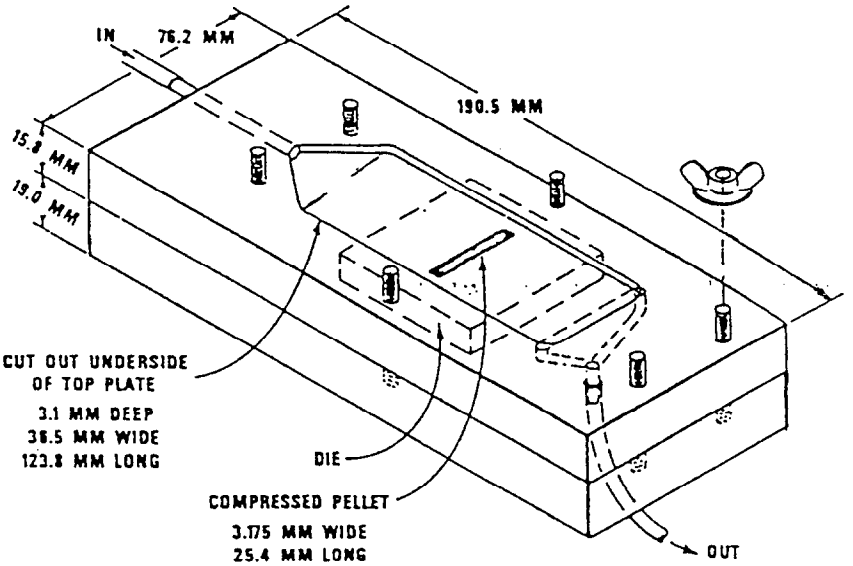

Fig. 1. Schematic diagram of the laminar dissolution cell of Shah and Nelson (1975) used in the present study.

solved drug occurs, the fluid flow patterns generated by disk rotation are complex and have been difficult to use in computation (Southard et al., 1992). It is also unreasonable to expect the cylindrical flow patterns of the rotating disk to simulate flow in the small intestine, where laminar flow is more likely to exist (Hirtz, 1985).

An experimental system with laminar flow characteristics was proposed earlier by Shah and Nelson (1975), shown in Fig. 1, and used to study dissolution of non-reactive neutral compounds. The authors proposed a convective-diffusion drug dissolution model by assuming a linear velocity profile over the tablet surface (Fig. 2). The linear velocity profile was described by assuming that the rate of shear across the thin boundary layer is constant. The liquid velocity term was given by Eqn 1:

$$V_x = \alpha y \tag{1}$$

where y is the position across the boundary layer, perpendicular to the tablet surface and α, the rate of shear (Nelson and Shah, 1975). An analytical solution (Eqn 2) for the dissolution rate (R) of a rectangular tablet with length L (in the direction of flow) and width b was derived:

$$R = 0.808 D^{2/3} C_o \alpha^{1/3} b L^{2/3} \tag{2}$$

where D is the diffusion coefficient of the drug molecule and C_o, the saturated solubility of the compound.

The above assumption of a linear velocity profile is an approximation to the actual situation, where a parabolic velocity profile exists (Bird et al., 1975). Therefore, the main purpose of this study was to reassess this convective-diffusion model by including the actual parabolic velocity profile. Since this actual velocity is not a simple

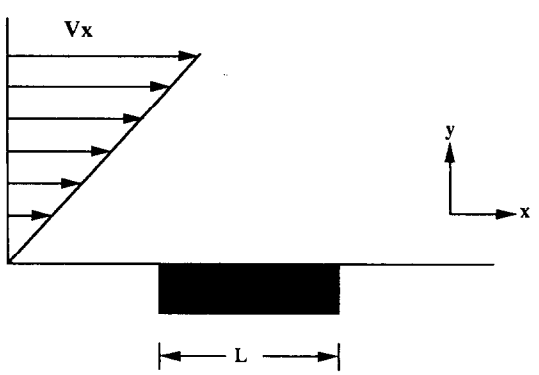

Fig. 2. Linear fluid velocity profile as defined by Eqn 1 (Nelson and Shah, 1975).

linear function, it was necessary to solve the transport equations numerically.

Model Development and Solution

Transport equations and velocity function

The transport of dissolved non-reacting drug occurs by convection and diffusion. The governing equation describing the concentration of such a drug in the laminar flow system is given by Eqn 3:

$$\frac{\partial C_i}{\partial t} = D_i \frac{\partial^2 C_i}{\partial y^2} - V_x \frac{\partial C_i}{\partial x} \tag{3}$$

by assuming that diffusion in the direction of flow (x) and convection perpendicular to it (y) are negligible. The latter assumption can be made since the velocity components in the y- and z-directions are negligible. To verify the former assumption, the diffusion term for the x-direction was included in Eqn 3 and solved separately. The results will be discussed later. The boundary conditions corresponding to Eqn 3 are given by Eqns 3a–d:

$$C = C_o \quad \text{at} \quad y = 0 \quad \text{for} \quad 0 < x \leqq L \tag{3a}$$
$$C = 0 \quad \text{at} \quad y = \delta \quad \text{for all} \quad x \tag{3b}$$
$$C = 0 \quad \text{at} \quad x = 0 \quad \text{for all} \quad y \tag{3c}$$
$$C = 0 \quad \text{at} \quad y = 0 \quad \text{for} \quad x > L \tag{3d}$$

where δ is the boundary layer thickness over the tablet surface as defined by Levich (1962) (Eqn 4):

$$\delta = 3(D/\nu)^{1/3}(\nu x/V_{\max})^{1/2} \tag{4}$$

where ν is the kinematic viscosity of the bulk solution, $V_{\max}$, the maximum fluid velocity and x, the distance from the leading edge of the tablet in the direction of flow.

Instead of employing a linear velocity profile (Nelson and Shah, 1975), the actual parabolic profile (Bird et al., 1975) was employed, where 'no-slip' conditions were assumed to exist at the walls of the device, i.e., zero velocity at the solid surface and maximum fluid velocity at the center (Fig. 3). For a rectangular duct, the velocity profile is parabolic in both cross-sectional dimensions (y and z) as described by Levich (1962), and given by Eqn 5:

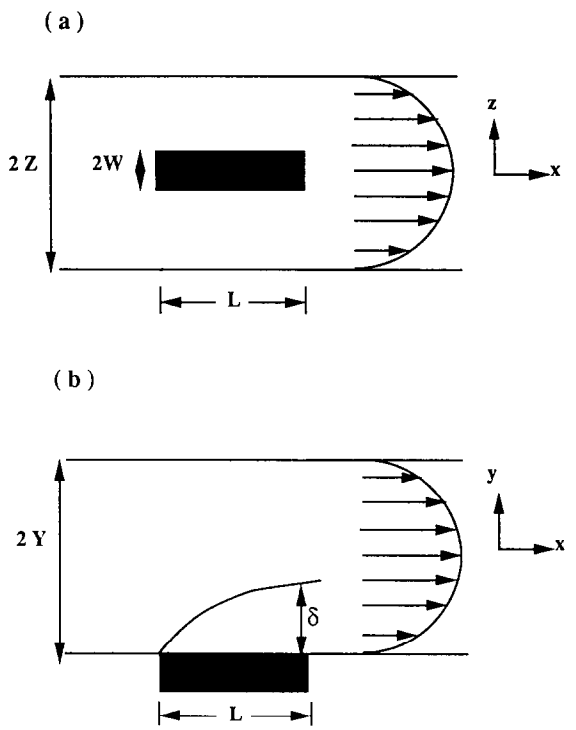

Fig. 3. Schematic diagram of the dissolution cell illustrating the device and tablet geometry, parabolic fluid flow and boundary layer characteristics. (a) Top view; (b) side view.

$$V_x(y,z) = V_{\max}(1 - y^2/Y^2)(1 - z^2/Z^2) \tag{5}$$

From Fig. 1, it is apparent that the width of the device ($2Z$) is significantly larger than the height of the device ($2Y$) and width of the tablet ($2W$; defined as b in the earlier work). Hence, the velocity changes minimally over the width of the tablet and was averaged to simplify the model (Eqn 6; Appendix):

$$V_x(y) = V_{\max}(1 - W^2/3Z^2)(1 - y^2/Y^2) \tag{6}$$

Numerical solution

The system of equations describing our model (Eqns 3, 4 and 6) is difficult to solve analytically

because of the parabolic velocity function. Hence, a numerical solution method using finite difference approximations (Carnahan et al., 1969) was sought. Backward differences were used to approximate the first derivatives and a centered difference was used for the second derivative. The governing equation, Eqn 7, is of the form:

$$\frac{C_{i,j,k+1} - D_{i,j,k}}{\Delta t} = \frac{D}{\Delta y^2}(C_{i,j-1,k} - 2C_{i,j,k} + C_{i,j+1,k}) - \frac{V_x}{\Delta x}(C_{i,j,k} - C_{i-1,j,k}) \quad (7)$$

where i and j are position counters in the x- and y-directions, respectively, and k represents the present time step. This formulation is explicit in time since all position derivatives are expressed at the present time step (k). The finite differences Δt, Δy and Δx are set by the user of the routine, which was coded in FORTRAN.

Imposing the boundary conditions (Eqns 3a–d), the concentration of the drug was calculated at every point within the boundary layer at the new time step $k + 1$. Because there is no flow at the surface of the tablet, the drug flux is purely diffusive, and is calculated at $k + 1$ according to Eqn 8:

$$J = -D\left(\frac{\partial C}{\partial y}\right) \quad (8)$$

which can be numerically approximated by Eqn 9:

$$J = -D\sum_{i=1}^{L} \frac{C_{i,1,k+1} - C_{i,0,k+1}}{\Delta y} \quad (9)$$

where $j = 0$ is the point at the surface of the tablet and $j = 1$ is the point just above the surface.

The rate of dissolution (R) can then be calculated from Eqn 10:

$$R = J \times A \quad (10)$$

where A is the surface area of the tablet. As the solution proceeded in time, a steady-state condition was reached. This was indicated in the routine when the fractional change in rate of dissolution between time steps was less than a given convergence criterion (generally 1×10^{-5}). Computation was completed when this criterion was satisfied.

Experimental Method

The dissolution studies were performed as reported earlier with the laminar flow cell of Shah and Nelson (1975). In the present study, the dissolution of benzoic acid and naproxen were studied with the bulk solution adjusted to a pH of 2.0 using HCl solution and the ionic strength adjusted to 0.5 and 0.1, respectively, using potassium chloride. The solution was pumped through the cell at varying flow rates using an infusion syringe pump (Model 220, Sage Instruments).

Samples from the above studies were analyzed by HPLC using an ODS Hypersil C18, 5 mm column at 1 ml/min and ambient temperature. For benzoic acid, the mobile phase used was acetonitrile-0.01 M phosphate buffer (PB), adjusted to pH 7.0 (10:90 v/v) with detection at 255 nm while, for naproxen, the mobile phase used was acetonitrile-0.05 M PB, pH 7.0 (23:77 v/v) with detection at 222 nm.

Results and Discussion

Flow and boundary layer profiles

The flow profile in the device can be verified by calculating the Reynolds number (Re) for a rectangular duct (Perry and Green, 1984) which is defined by Eqn 11:

$$\mathrm{Re} = \frac{4YZ\bar{V}}{\nu(Y+Z)} \quad (11)$$

where $\bar{V}$ is the average velocity of the fluid, ν denotes the kinematic viscosity and Y and Z are the half height and width of the duct, respec-

tively. At a high flow rate of 108 ml/min, Re was calculated to be approx. 91, and at lower flow rates Re is even smaller, indicating that the flow is very much in the laminar range (Re = 0–2000) at all flow rates in use. This flow should also be fully developed before it reaches the tablet surface, devoid of any entrance effects. The hydrodynamic entrance length (L_{hy}), which is the distance required to reach 99% of fully developed velocity from the inlet, for a rectangular duct was defined by Perry and Green (1984) (Eqn 12):

$$L_{hy} = 2Y(0.625 + 0.022\ \mathrm{Re}) \qquad (12)$$

Again, for the worst case, at high flow rate (108 ml/min), L_{hy} was calculated to be 0.82 cm, while the actual distance from the inlet to the tablet surface is about 4 cm. Thus, the entrance effects dissipate and fully developed laminar flow exists before the tablet surface is reached.

The concentration boundary layer, as defined in Eqn 4, should be within the annulus so that all the mass that is being transported is accounted for. From this equation it is apparent that the largest boundary layer is at low flow rates and far downstream (outlet). At the lowest flow rate employed (1.1 ml/min), δ was calculated to be 0.40 cm at the outlet, which is approximately the thickness of the annulus. Thus, for all other cases, the annulus is significantly larger than the boundary layer under consideration.

Numerical model results

The properties of the model compounds listed in Table 1 and the model parameters (step sizes) were given as input to the computer program. The numerical model routine was run for various flow rates. For benzoic acid and naproxen, suppressed ionization conditions (pH 2.0) were used so they exist only in neutral form. Table 2 summarizes the dissolution results from the numerical model and compares them with experimental results and the analytical model of Shah and Nelson (1975).

From Table 2 it is apparent that both the analytical model and the present numerical model predict the dissolution rate quite accurately, within the range of experimental error. When the long axis of the tablet was aligned to be parallel to the flow, the numerical model deviated by an average of 3.7% for benzocaine, 6.5% for benzoic

TABLE 1

Physico-chemical properties of the model compounds at 25°C and ionic strength adjusted with potassium chloride

Model compound	Intrinsic solubility (M)	Diffusivity (cm^2/s)	pK_a
Benzoic acid ($\mu = 0.5$) [a]	2.15×10^{-2}	9.70×10^{-6}	4.03
Naproxen ($\mu = 0.1$) [b]	1.37×10^{-4}	3.90×10^{-6}	4.57
Benzocaince [c]	7.26×10^{-3}	9.48×10^{-6}	–

[a] From Southard et al. (1992).
[b] From McNamare and Amidon (1986).
[c] From Shah and Nelson (1975).

TABLE 2

Comparison of model predictions with experimental dissolution rates at different flow rates for the compounds under investigation

Compound	Flow rate (ml/min)	Dissolution rate ($\times10^7$ mol/min)		
		Experimental	Calculated from Eqn 2	Numerical model prediction
(a) Case when the long axis of the tablet is parallel to the flow				
Benzocaine [a]	1.54	0.522	0.547	0.530
	2.28	0.629	0.623	0.613
	6.33	0.887	0.875	0.876
	10.00	1.073	1.019	1.031
	13.33	1.180	1.121	1.140
	17.50	1.320	1.228	1.240
	31.30	1.634	1.491	1.524
	107.3	2.550	2.248	2.386
Benzoic acid	1.10	1.455	1.337	1.385
	3.48	2.162	1.957	2.008
	5.10	2.607	2.230	2.298
	8.49	2.816	2.642	2.747
	13.41	3.392	3.076	3.242
Naproxen	1.10	0.0044	0.0047	0.0045
	3.48	0.0071	0.0069	0.0067
	5.10	0.0075	0.0079	0.0076
(b) Case when the long axis is perpendicular to flow				
Benzocaine [a]	1.37	1.051	1.052	0.993
	11.70	2.037	2.148	2.145
	31.20	3.031	2.978	3.134
	108.46	4.655	4.512	4.978

[a] The experimental values correspond to those reported in Shah and Nelson (1975).

acid and 3.0% for naproxen, while the corresponding deviations for the analytical model were 5.4, 9.5 and 4.8%, respectively. When the long axis of the tablet was perpendicular to the flow the numerical model deviated by an average of 5.3% for benzocaine and the analytical model by an average of 2.6%. The benzocaine results indicate that either model prediction is slightly better when the long axis is parallel to the flow, where edge velocity changes at the side walls of the device are minimized. However, the numerical model prediction at high flow rates is better, since the change in the rate of shear is significant, i.e., the parabolic profile is more pronounced and the linear velocity assumption may not be appropriate.

As stated earlier, the model equation with a diffusion term in the x-direction (along the flow) was also solved numerically. The dissolution rates calculated were not significantly different, with less than 0.5% improvement from the model described by Eqn 3. This implies that the diffusion along the flow contributes to a negligible extent to the dissolution and justifies its exclusion from the model.

The validity of imposing the Levich boundary layer thickness (Eqn 4) was tested by removing that condition and giving sink conditions at the top wall, far removed from the tablet. The concentration was calculated at all points within the annulus. The concentration profile thus calculated for benzoic acid at 3.48 ml/min, as shown in Fig. 4, indicates the formation of a parabolic shape. The Levich boundary layer thickness at each point above the tablet was calculated and the concentration at that thickness was found to be less than 0.5% of the saturated solubility. This indicated that assuming sink conditions at the

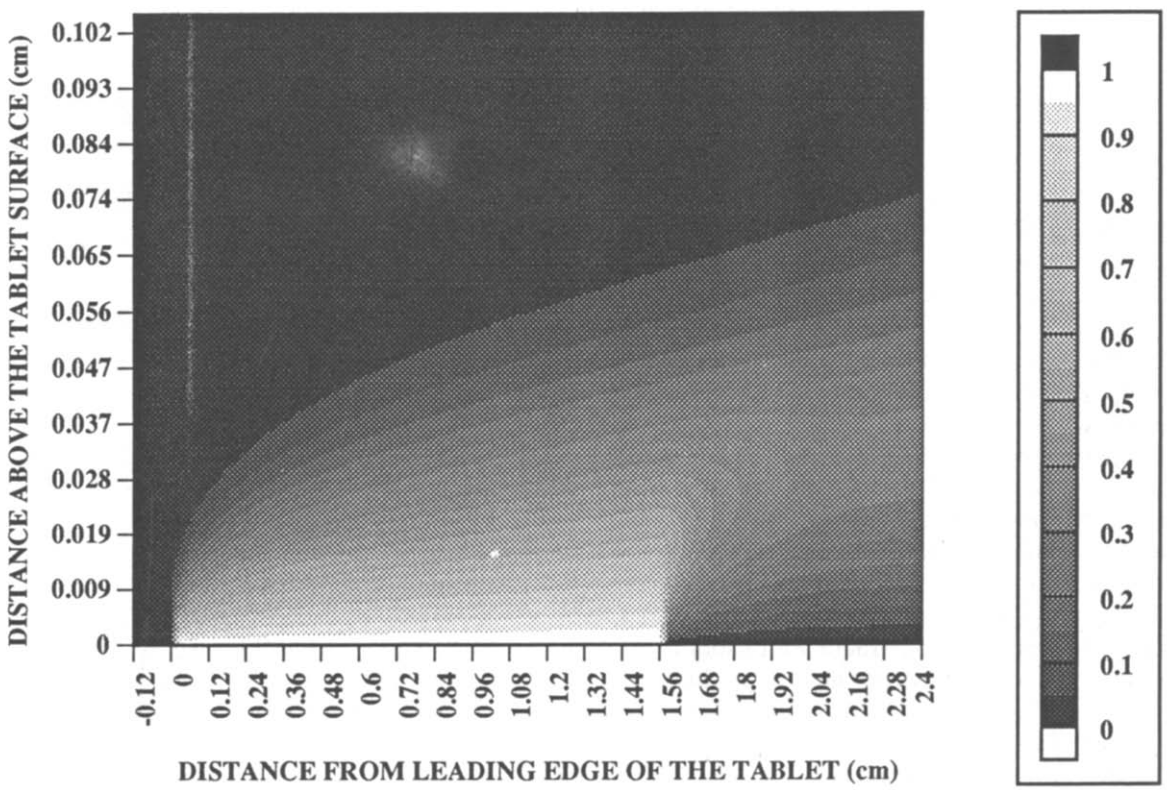

Fig. 4. Concentration profile of benzoic acid at 3.48 ml/min near the tablet surface. The length of the tablet is 1.57 cm. The concentrations were normalized with respect to the saturated solubility of the acid (C/C_o) and the shading in the contour plot represents the normalized concentrations ranging from saturated solubility (1) to sink conditions (0).

TABLE 3

Effect of space step sizes on predicted dissolution rate ($\times 10^7$ mol / min) of benzocaine at a flow rate of 13.33 ml / min and a time step size of 0.01 s

Δx (cm)	Δy (cm)			
	0.001	0.0008	0.0007	0.0006
0.010	1.140	1.138	1.137	1.135
0.005	1.127	1.128	1.141	1.138
0.004	1.128	1.127	1.142	1.140
0.003	1.130	1.129	1.140	1.140

Levich boundary layer thickness was valid and therefore a reasonable assumption for the numerical routine. The concentration profile also shows the effects of both diffusion and convection in the region near the tablet surface. Concentration gradients beyond the tablet surface and downstream indicates that material is carried over due to convection and diffuses out towards both top and bottom surfaces of the device.

This numerical approach has some limitations in specifying the space step sizes. For each time step, there exists a maximum space step size beyond which the routine becomes unstable. For a time step size of 0.01 s, the maximum stable x-step is on the order of 0.01 cm and corresponding value for the y-step is on the order of 0.001 cm. Decreasing the step sizes generally does not change the dissolution rate prediction in this routine (Table 3). The above step sizes were used in all our runs (Table 2). The routine can be made more efficient by using an implicit finite difference approximation instead of an explicit form and the problem with the space step dimensions avoided or minimized.

Conclusions

A convective-diffusion model for laminar flow hydrodynamics in a rectangular channel for dissolution of neutral compounds was solved by a numerical approach and using the actual parabolic velocity profile characteristic of laminar flow. The model predicted the dissolution rates of benzocaine, benzoic acid and naproxen within 10% of the experimental values and was comparable to an analytical solution which assumed a linear velocity profile.

The numerical model is an enhancement of earlier work in that it allows study of fluid flow patterns and the resultant concentration profiles in the region above the tablet. It does not require the linear velocity assumption of Shah and Nelson. Knowledge of concentration and flow enables one to visualize the essential transport mechanisms involved in dissolution, thus enhancing our appreciation of this important mass transport process. The model can be expanded to include the presence of chemical reactions, such as acid-base reactions, within the profile. The earlier analytical model with the linear velocity profile cannot be readily used to accomodate such interactions.

The flow and boundary layer characteristics in the experimental device were analyzed theoretically and the presence of laminar flow confirmed.

Acknowledgments

The authors wish to thank Dr Ashok Shah for various fruitful discussions and the Upjohn Company, Kalamazoo, MI, for providing use of his laminar dissolution apparatus. This work was supported by the Center for Drug Delivery Research, a member of the Higuchi Biosciences Center, a Kansas Technology Enterprise Corporation Center of Excellence; Grant GM-47848 from the National Institutes of Health and a University of Kansas Honors Program Undergraduate Research Award (J.D.R.).

Appendix

Fluid velocity in a rectangular channel is parabolic in both the cross-sectional dimensions. In fully developed flow, there is no y- and z-component of the velocity. The x-component is defined as:

$$V_x(y,z) = V_x(y)V_x(z)$$

$$= V_{max}\left(1 - \frac{y^2}{Y^2}\right)\left(1 - \frac{z^2}{Z^2}\right) \qquad \text{(A1)}$$

To simplify the numerical solution, the velocity is averaged over the width of the tablet in the z-direction and then calculated as:

$$V_x(y,z) = \frac{V_{max}\left(1-\frac{y^2}{Y^2}\right)\int_{-w}^{w}\left(1-\frac{z^2}{Z^2}\right)2Y\,dz}{\int_{-w}^{w}2Y\,dz}$$

$$= V_{max}\left(1-\frac{y^2}{Y^2}\right)\left(1-\frac{W^2}{3Z^2}\right) \qquad (A2)$$

where $2W$ is the width of the tablet and V_{max} denotes the maximum fluid velocity at the center of the channel which can be calculated according to (Bird et al., 1975):

$$V_{max} = 1.5 \times V_{avg} = 1.5\left(\frac{Q}{4YZ}\right) \qquad (A3)$$

where Q represents the volumetric flow rate and Y and Z are half height and width of the channel, respectively (Fig. 3).

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