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Uptake of solutes by plastic infusion tubing Mathematical solutions

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Summary

The uptake of solutes from aqueous solutions by plastic containers has received considerable attention in recent years. However, the loss of solute from aqueous solutions during flow through plastic tubing has not been as extensively investigated. In this work, the authors present four models to describe the sorption of solute during flow through tubing. These models represent the solution as either a well-stirred compartment or convection flow in a tube, and the plastic as either a well-stirred compartment or a matrix in which diffusion occurs in a radial direction. The time course of outflow solute concentrations observed experimentally after solute infusion into either Tygon or polyvinylchloride tubing was well described by the analytic solutions obtained. The diffusion models appeared to give the more satisfactory fit of the data. However, the data fit showed only small qualitative differences compared to the compartment models. A number of parameters are required to define each model limiting their usefulness. Accordingly, a number of simulations were undertaken to determine the relative effect of each parameter on the outflow concentration profile. As anticipated, the flow rate, the plastic water partition coefficient and the nature of the tubing were important. Extensive loss is most likely at low flow rates when a solute has a high affinity for the infusion tubing.

Introduction

The loss of nitroglycerin during infusion through plastic administration sets has previously been reported (Cossum et al., 1978; Crouthamel et al., 1978). Each component of the administration set (bag, burette, chamber and tubing) has been shown to absorb nitroglycerin (Roberts et al., 1980; Baaske et al., 1985). The effect of flow rate has been demonstrated for other substances such as isosorbide dinitrate, diazepam and chlormethiazole (Hancock and Black, 1980; Baaske and Amann, 1985).

A number of models have been used to describe the uptake of solutes by plastic infusion bags whereas the models available to describe the loss of solutes infused through tubing are limited. The models used for infusion bag kinetics include an equilibrium partition model (Sturek et al., 1978), an open compartment model (Malik et al., 1980), a simple diffusion model (Yuen et al., 1979; Roberts et al., 1980) and complex diffusion models accounting for solute ionisation and aqueous diffusion layers adjacent to the

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plastic (Kowaluk et al., 1986). A comparison of the available models would suggest that the diffusion model is the most appropriate to describe solute uptake (Kowaluk et al., 1986). More recently, we have shown that the initial uptake of solutes in infusion bags may be expressed in terms of a single sorption number and may be predicted, with limited accuracy, from the octanol-water partition coefficient for the solute (Roberts et al., 1991).

Two types of models have been used to describe the time course of drug uptake by administration sets: a convection model and a compartment model. The convection model takes into account the decline in concentration along the tubing length (Kowaluk et al., 1982) but has been limited to a simple first-order irreversible loss of solute (Kowaluk et al., 1982, 1983). The compartment model assumes that the solute is first adsorbed onto the surface of the plastic and then dissolved instantaneously throughout the plastic (Amann and Baaske, 1982). This model assumes that the solution within the tube can be described as being in a well-stirred compartment and does not take into account the observed decrease in the concentration along the tube. More recently, Roberts (1992) has expressed the initial loss of solute from solution infused through tubing by a convection-diffusion model in which the plastic is assumed to act as an infinite sink.

In this study, we have examined mechanistic models for the solute loss during the infusion of solutions through the tubing component of the administration sets. These models are based on the premise that the uptake of drugs is governed by the convection of the fluid in the tubing and the nature of the solute transport in the plastic. In order to simplify the mathematical model, we have assumed that the following steps do not contribute to the overall process: (i) longitudinal diffusion of solute in the flowing solution, (ii) longitudinal diffusion of solute in the plastic and (iii) the laminar flow of the fluid. Four models are considered and are based on the two models used to describe convection down the tube, namely, the well-stirred model (concentration along the tube is assumed constant) (Amann and Baaske, 1982) and a plug flow of fluid down the tube with no longitudinal diffusion (Kowaluk et al., 1982, 1983; Roberts, 1992) combined with two models to describe uptake into the plastic – a compartment model and a diffusion model. Each of these models has been expressed in cylindrical co-ordinates and is used to compare experimental data with model predictions. We also consider approximations of these models that may render them more useful in a clinical context.

Materials and Methods

Experimental data were generated by running the aqueous solution from a constant level reservoir through a tap into a vertical section of Tygon tubing of internal and external diameters 0.79 and 1.1 cm, respectively, cut to the required length. Constant level was maintained by the use of an inverted flask containing solute in the neck of the reservoir container.

Flow rate was controlled by the use of tapered glass capillaries inserted into the distal end of the tubing.

Effluent was collected into individual tubes in a fraction collector and all times indicated in this work are the mid-points of the time intervals used. All chemicals used were of Laboratory Reagent quality.

Effluent concentrations were determined using ultraviolet spectrophotometry at the previously determined wavelength of maximum absorption. All compounds used obeyed Beer's law.

Theory

Each of the models being used in this work is represented schematically in Fig. 1. We now consider the mathematical formulation of each model.

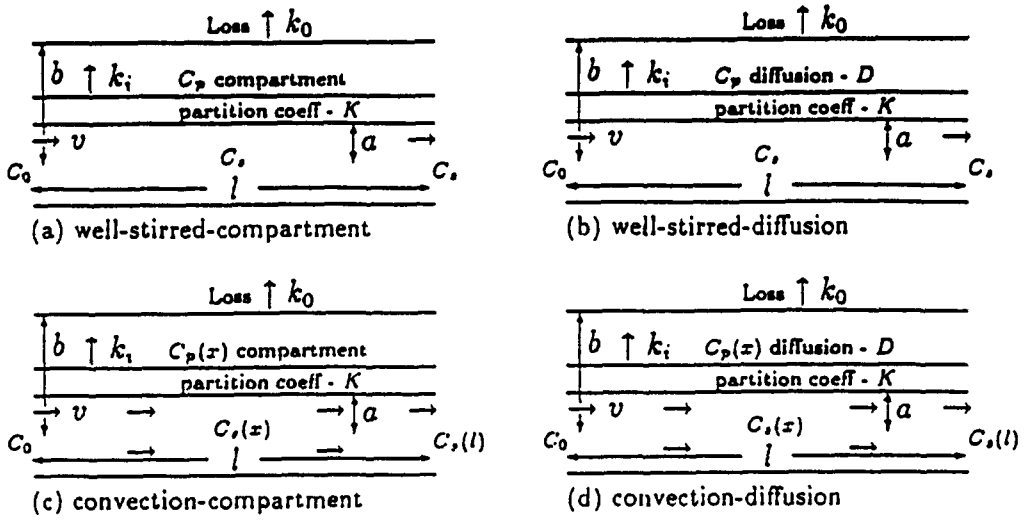

Fig 1 Schematic diagram of the four models considered. (a) well-stirred-compartment, (b) well-stirred-diffusion, (c) convection-compartment, (d) convection-diffusion

Well-stirred-compartment model

In the convection of fluid through a well-stirred compartment the concentration, at time t, $C_s = C_s(t)$ of the solute in the solution in the tube (compartment) is independent of distance along the tube (compartment). The solute concentration in the solution leaving the tube is also equal to that in the tube. Loss occurs through the tubing walls by a transfer of solute from the solution to the plastic with an apparent coefficient, $K = C_{surf}/C_s$, where C_{surf} is the concentration on the surface of the plastic. The concentration in the plastic, $C_p(t)$, is also taken to be constant with respect to distance along the tube. The equations governing the rates of change of C_s and C_p are then given by:

$$l\pi a^2 \frac{dC_s}{dt} = \pi a^2 v(C_0 - C_s) - 2\pi a k_i l(KC_s - C_p), \tag{1}$$

$$\pi(b^2 - a^2)\frac{dC_p}{dt} = 2\pi a k_i(KC_s - C_p) - 2\pi b k_o C_p, \tag{2}$$

where v is the rate of the flow, a and b denote the inner and outer radii of the tube, l is the length of the tube and k_i and k_o represent the rates of transfer across the inner and outer surfaces of the tube. The initial conditions are given by $C_s(0) = C_0$, $C_p(0) = 0$. Eqns 1 and 2 may be written in the form

$$\frac{dC_s}{dt} = \alpha_1 C_s + \beta_1 C_p + QC_0, \tag{3}$$

$$\frac{dC_p}{dt} = \alpha_2 C_s + \beta_2 C_p \tag{4}$$

where $Q = v/l$, $\alpha_1 = -Q - 2k_1K/a$, $\alpha_2 = 2k_1aK/(b^2 - a^2)$, $\beta_1 = 2k_1/a$ and $\beta_2 = -2k_1a - 2bk_0/(b^2 - a^2)$. Solving Eqn 4 for C_p in terms of C_s we obtain

$$C_p = \alpha_2 \int_0^t C_s \exp[\beta_2(t-\tau)]\, d\tau. \tag{5}$$

Substituting into Eqn 3 gives

$$\frac{dC_s}{dt} = \alpha_1 C_s + \beta_1 \alpha_2 \int_0^t C_s \exp[\beta_2(t-\tau)]\, d\tau + QC_0 \tag{6}$$

Taking Laplace transforms of Eqn 6 we have

$$\bar{C}_s = C_0 \frac{s-\beta_2}{(s-\rho_1)(s-\rho_2)} + QC_0 \frac{s-\beta_2}{s(s-\rho_1)(s-\rho_2)} \tag{7}$$

where ρ_1 and ρ_2 are the roots of the quadratic equation

$$\rho^2 - (\alpha_1 + \beta_2)\rho + \beta_2\alpha_1 - \beta_1\alpha_2 = 0. \tag{8}$$

Inverting the Laplace transform gives

$$C_s = C_0(A + (B_1 + B_2)\exp[\rho_1 t] + (C_1 + C_2)\exp[\rho_2 t]) \tag{9}$$

where

$$A = \frac{-\beta_2 Q}{\rho_1\rho_2} \qquad B_1 = \frac{\rho_1 - \beta_2}{\rho_1 - \rho_2} \qquad B_2 = \frac{\rho_1 - \beta_2 Q}{\rho_1 - \rho_2\rho_1} \qquad C_1 = \frac{\rho_2 - \beta_2}{\rho_2 - \rho_1} \qquad C_2 = \frac{\rho_2 - \beta_2 Q}{\rho_2 - \rho_1\rho_2} \tag{10}$$

It should be noted that this result does not agree with the report by Amann and Baaske (1982). Their Eqns 2 and 6 are inconsistent, making their final equation, Eqn 15, invalid.

Well-stirred-diffusion model

In this case the solute is again well-stirred throughout the tube so that the concentration, C_s, satisfies Eqn 3. In the tubing the solute diffuses radially in the plastic after diffusion across an aqueous layer adjacent to the plastic. The plastic component of the tube can be represented as a circular cylinder, $a \le r \le b$. The concentration of the solute, $C_p(r,t)$, at any radial distance, r, at a given time, t, is defined by:

$$\frac{\partial C_p}{\partial t} = D\frac{1}{r}\frac{\partial}{\partial r}\left(\frac{r\partial C_p}{\partial r}\right) \tag{11}$$

The initial and boundary conditions are given by

$$\begin{aligned} &C_p(r,0) = 0, && a \le r \le b \\ &\frac{\partial C_p}{\partial r} = -k_1(KC_s - C_p), && r = a \\ &\frac{\partial C_p}{\partial r} = -k_o C_p, && r = b \end{aligned} \tag{12}$$

If we assume that the diffusion within the plastic along the tube is negligible with respect to the radial diffusion, then each cross-section may be considered as the cross-section of an infinitely long cylinder. The solution of Eqn 11 is then given by (Luikov, 1968):

$$C_p(r,t) = \frac{2}{a^2}\sum_{n=1}^{\infty} \frac{\mu_n^2 U_0\left(\mu_n \frac{r}{a}\right) \exp\left[-\mu_n^2 \frac{Dt}{a^2}\right]}{\left[\frac{b}{a}\right]^2 U_0^2\left(\mu_n \frac{b}{a}\right)\left(\mu_n^2 + \left[\frac{k_o}{k_1}\right]^2 Bi_1^2\right) - \frac{4}{\pi^2 Bi_1^2}\left[\mu_n^2 + Bi_1^2\right]} \frac{-2D}{\pi}\int_0^t KC_s(\tau)$$

$$\times \exp\left[\mu_n^2 \frac{D\tau}{a^2}\right] d\tau \tag{13}$$

where

$$Bi_1 = k_1 a,$$

$$U_0\left(\mu_n \frac{r}{a}\right) = \left(Y_0(\mu_n) + \frac{\mu_n}{Bi_1} Y_1(\mu_n)\right) J_0\left(\mu_n \frac{r}{a}\right) - \left(J_0(\mu_n) + \frac{\mu_n}{Bi_1} J_1(\mu_n)\right) Y_0\left(\mu_n \frac{r}{a}\right), \ \mu_n$$

are the roots of the equation

$$U_0\left(\mu_n \frac{b}{a}\right) = \frac{k_1}{k_o}\frac{\mu_n}{Bi_1} U_1\left(\mu_n \frac{b}{a}\right)$$

and J and Y are Bessel functions of the first and second kind. Substituting Eqn 13 with $r = a$ into Eqn 3 we find

$$\frac{dC_s}{dt} = \alpha_1 C_s + QC_0 + \beta_1 C_p(a,t) \tag{14}$$

In abbreviated form we may write

$$C_p(a,t) = \sum_{n=1}^{\infty} \gamma_n \int_0^t C_s \exp\left(-\mu_n^2 \frac{D(t-\tau)}{a^2}\right) d\tau \tag{15}$$

We now observe that since μ_n^2 is increasing with n the major contribution will come from $n = 1$. In this case we find, on taking Laplace transforms of this equation, that $\bar{C}_s$ satisfies an equation similar to Eqn 7 but with α_2 replaced by γ_1 and β_2 replaced by $(-\mu_n^2 D/a^2)$.

Convection-compartment model

In this case account is taken of flow of the solute along the tube. The concentration will depend on position along the tube so that

$$C_s = C_s(x,t) \quad \text{and} \quad C_p = C_p(x,t) \quad \text{for} \quad 0 \le x \le l$$

We assume that the solute in the solution is uniform over each cross-section and that there is no diffusion along the tube. The equations are now

$$\pi a^2 \frac{\partial C_s}{\partial t} + \pi a^2 v \frac{\partial C_s}{\partial x} = -2\pi a k_1 (KC_s - C_p) \tag{16}$$

$$\pi (b^2 - a^2) \frac{\partial C_p}{\partial t} = 2\pi a k_1 (KC_s - C_p) - 2\pi b k_0 C_p. \tag{17}$$

The initial and boundary conditions are given by

$$C_p(x,0) = 0,\ 0 \le x \le l \qquad C_s(x,0) = C_0,\ 0 \le x \le l \qquad C_s(0,t) = C_0,\ 0 \le t.$$

Using the earlier notation, Eqns 16 and 17 may be simplified by expressing them in the form

$$\frac{\partial C_s}{\partial t} + v \frac{\partial C_s}{\partial x} = \alpha_1' C_s + \beta_1 C_p, \tag{18}$$

$$\frac{\partial C_p}{\partial t} = \alpha_2 C_s + \beta_2 C_p \tag{19}$$

where $\alpha_1' = \alpha_1 + Q$ and α_1, β_1, α_2 and β_2 are as defined in Eqns 3 and 4. Using Eqn 5 and substituting into Eqn 16 we obtain

$$\frac{\partial C_s}{\partial t} + v \frac{\partial C_s}{\partial x} = \alpha_1' C_s + \beta_1 \alpha_2 \int_0^t C_s(x,\tau) \exp(\beta_2 (t - \tau)\, d\tau. \tag{20}$$

Taking Laplace transforms gives

$$v \frac{\partial \bar{C}_s}{\partial x} + \left(s - \alpha_1' - \frac{\beta_1 \alpha_2}{s - \beta_2} \right) \bar{C}_s = C_0. \tag{21}$$

Integrating Eqn 21 with the initial condition $\bar{C}_s(0) = C_0/s$ now yields

$$\bar{C}_s = \frac{C_0 (s - \beta_2)}{(s - \rho_1')(s - \rho_2')} + C_0 \left(\frac{1}{s} - \frac{s - \beta_2}{(s - \rho_1')(s - \rho_2')} \right) \exp\left(\frac{-x}{v} \left(s - \alpha_1' - \frac{\beta_1 \alpha_2}{s - \beta_2} \right) \right) \tag{22}$$

where ρ_1' and ρ_2' are the roots of the equation

$$\rho^2 - (\alpha_1' + \beta_2)\rho + \beta_2 \alpha_1' - \beta_1 \alpha_2 = 0 \tag{23}$$

On taking inverse Laplace transforms, Eqn 22 gives

$$\frac{C_s}{C_0} = B_1' \exp(\rho_1' t) + C_1' \exp(\rho_2' t) + \exp\left(\alpha_1' \frac{x}{v}\right)\left\{ H\left(t - \frac{x}{v}\right)\left\{1 - B_1' \exp\left\{\rho_1'\left(t - \frac{x}{v}\right) - C_1' \exp\left\{\rho_2'\left(t - \frac{x}{v}\right)\right\}\right\}\right.\right.$$

$$+ \exp\left(\alpha_1' \frac{x}{v}\right) \int_0^t \left\{ H\left(u - \frac{x}{v}\right)\left\{1 - B_1' \exp\left\{\rho_1'\left(u - \frac{x}{v}\right) - C_1' \exp\left\{\rho_2'\left(u - \frac{x}{v}\right)\right\}\right\} \exp(\beta_2(t-u))\right.\right.$$

$$\times \left(\frac{\beta_1 \alpha_2 x}{v(t-u)}\right)^{1/2} I_1\left\{2\left(\frac{\beta_1 \alpha_2 x (t-u)}{v}\right)^{1/2}\right\} du \tag{24}$$

where B_1', C_1' are the corresponding values to B_1, C_1 in Eqn 10, H represents the Heaviside-step function and I is the modified Bessel function of the first kind.

Convection-diffusion model

Here, the governing equations are those specified under Well-stirred-diffusion model for C_s and under Convection-compartment model for C_p except that $C_p = C_p(x,r,t)$ depends on the variable x. The corresponding solution for C_p is given by Eqn 13 with account being taken that C_s is also a function of x. Hence, C_s satisfies the equation

$$\frac{\partial C_s}{\partial t} + v \frac{\partial C_s}{\partial x} = \alpha_1' C_s + \sum_{n=1}^{\infty} \gamma_n \int_0^t C_s(x,\tau) \exp\left(-\mu_n^2 \frac{D(t-\tau)}{a^2}\right) d\tau. \tag{25}$$

If we again assume that the major contribution comes from $n = 1$ in Eqn 25, solving that equation gives a solution for the Laplace transform similar to Eqn 22. Following the section Well-stirred-diffusion model, we finally obtain a solution of the same form as Eqn 24.

Approximation of early time

Cossum et al. (1978) have suggested that the diffusion kinetics of solutes may be considerably simplified if the duration is limited to early times when the diffusion process has penetrated the plastic only a small distance. The plastic is then treated as an infinite sink and the boundary condition at $r = b$ in Eqn 12 is replaced by

$$C_p \to 0 \text{ as } r \to \infty \tag{26}$$

Using standard techniques (see Kowaluk et al., 1985), the Laplace transform of C_p from Eqn 11 is given by

$$\bar{C}_p = \frac{K k_1 \bar{C}_s K_0\left(\left(\frac{s}{D}\right)^{1/2} r\right)}{\left(\frac{s}{D}\right)^{1/2} K_1\left(\left(\frac{s}{D}\right)^{1/2} a\right) + k_1 K_0\left(\left(\frac{s}{D}\right)^{1/2} a\right)} \tag{27}$$

Substituting into Eqn 1 gives the corresponding Laplace transform of C_s in the form

$$\bar{C}_s = \frac{C_0}{s}\left(1 - \frac{\dfrac{2k_1K}{a}\left(\dfrac{s}{D}\right)^{1/2} K_1\left(\left(\dfrac{s}{D}\right)^{1/2} a\right)}{\left(s+Q+\dfrac{2k_1K}{a}\right)\left(\dfrac{s}{D}\right)^{1/2} K_1\left(\left(\dfrac{s}{D}\right)^{1/2} a\right) + (s+Q)k_1K_0\left(\left(\dfrac{s}{D}\right)^{1/2} a\right)}\right) \tag{28}$$

Inverting the Laplace transform gives C_s in terms of a real integral:

$$C_s = C_0\left(1 - \frac{8k_1^2K}{(\pi a)^2}\int_0^\infty \frac{\exp[-Du^2t](Q-Du^2)\,\mathrm{d}u}{G+H}\right) \tag{29}$$

where

$$G = \left(\left(-Du^2+Q+\frac{2k_1K}{a}\right)uJ_1(ua) + (-Du^2+Q)k_1J_0(ua)\right)^2 \tag{30}$$

$$H = \left(\left(-Du^2+Q+\frac{2k_1K}{a}\right)uY_1(ua) + (-Du^2+Q)k_1Y_0(ua)\right)^2 \tag{31}$$

Of particular interest is the approximation for small time t which may be obtained by examining the expansion of C_s for large values of s. We have

$$\bar{C}_s = \frac{C_0}{s}\left(1 - \frac{2k_1K}{a}\frac{1}{s} + \frac{2k_1^2KD^{1/2}}{a}\frac{1}{s^{3/2}} + \cdots\right) \tag{32}$$

Inverting gives the required approximation for small t as

$$\frac{C_s}{C_0} = 1 - \frac{2k_1K}{a}t + \frac{2k_1^2KD^{1/2}}{a}\frac{1}{3\sqrt{\pi}}t^{3/2} + \cdots \tag{33}$$

Alternative boundary conditions

In the above cases the contact between the solution and the plastic has not been considered perfect, so that the boundary condition at $r = a$ has been taken to be one expressing transfer. If, however, the contact is taken as perfect, then up to a partition coefficient $C_p = KC_s$, the boundary conditions are given by

$$C_p = KC_s, \quad r = a \tag{34}$$

Eqn 1 is replaced by

$$\frac{\mathrm{d}C_s}{\mathrm{d}t} = Q(C_0 - C_s) + \frac{2k_1}{a}\frac{\partial C_p}{\partial r}, \quad r = a \tag{35}$$

Again taking the simplification of small times (Eqn 26) the Laplace transform of C_s is found to be

$$\bar{C}_s = C_0\left(1 - \frac{s+Q}{s}\frac{K_0\left(\left(\frac{s}{D}\right)^{1/2}a\right)}{\frac{2k_1}{aK}\left(\frac{s}{D}\right)^{1/2}K_0\left(\left(\frac{s}{D}\right)^{1/2}a\right) - (s+Q)K_1\left(\left(\frac{s}{D}\right)^{1/2}a\right)}\right) \tag{36}$$

Inverting the Laplace transform gives C_s in terms of a real integral similar to that in the previous section

$$C_s = C_0\left(1 - \frac{4k_1^2K}{(\pi a)^2}\int_0^\infty \frac{\exp[-Du^2t](Q-Du^2)\,du}{u(G+H)}\right) \tag{37}$$

where

$$G = \left(\frac{2k_t}{aK}\right)uJ_1(ua) - \left(-Du^2+Q\right)J_0(ua))^2 \tag{38}$$

$$H = \left(\frac{2k_1}{aK}\right)uY_1(ua) - \left(-Du^2+Q\right)Y_0(ua))^2 \tag{39}$$

Of special interest is the approximation for small values of t. From Eqn 36 we have

$$\bar{C}_s = \frac{C_0}{s}\left(1 - \frac{\frac{2k_1}{K}}{aD^{1/2}}\frac{1}{s^{1/2}} + \frac{\frac{k_1}{K}\left(\frac{4k_t}{K} - D\right)}{\alpha^2 D}\frac{1}{s} + \cdots\right) \tag{40}$$

Inverting gives the required approximation for small t as

$$\frac{C_s}{C_0} = 1 - \frac{\frac{2k_1}{K}}{aD^{1/2}}\frac{2t^{1/2}}{\sqrt{\pi}} + \frac{\frac{k_t}{K}\left(\frac{4k_t}{K} - D\right)}{a^2 D}t + \cdots \tag{41}$$

Data Analysis

Numerical and graphical analyses of the equations were conducted on a Macintosh SE/30 using the system Mathematica (Wolfram, 1988).

In all studies a fixed input concentration was assumed, and the availability $F = C_{out}/C_0$ was plotted as a function of time, t (in min), for each of the models.

The well-stirred-compartment model and the convection-compartment model are given respectively by Eqns 9 and 24. The well-stirred-diffusion model is given by an equation of the same form as Eqn 9 where only the first term, the most significant, of the series in Eqn 15 is used: in essence, in Eqn 9, α_2 is replaced by γ_1 and β_2 is replaced by $(-\mu_n^2 D/a^2)$.

Similarly, the convection-diffusion model is given by an equation similar to Eqn 24 with again, α_2 replaced by γ_1 and β_2 replaced by $(-\mu_n^2 D/a^2)$.

The analytical solutions of the various models were compared with experimental data for several drugs *. The data were obtained using Tygon plastic tubing. The internal diameter, a, and the external diameter, b, of the tubing were 0.79 and 1.1 cm, respectively. Different lengths of tubing and flow rates were used to generate the experimental data and those corresponding to a tubing length $l = 40$ cm were selected. Given that there were a large number of parameters in each equation, the fit of the data was obtained empirically by an adjustment of parameters using a subdivision process.

For each of the simulations, which examine the effects of the various parameters on the output, a fixed length infusion tubing set of 175 cm was assumed with an internal radius $a = 0.15$ cm and external radius $b = 0.2$ cm, except in the case where a comparison of the effect of changes in tubing radii was considered.

Results and Discussion

Comparison with experimental data

A major limitation with experimental data available in the literature is that much of it has been developed with either a burette-plastic bag present, or with uncertain initial conditions. We have therefore used the data mentioned in the preceding section. The data is presented in Figs 2–4, where it is compared with the analytic solutions. With the appropriate adjustment of parameters the data set and the analytic solutions are in good agreement. The main difference between the models is the cusp shape for the convection models compared with the smooth turning point in the well-stirred models. It is clear that the choice of model cannot be differentiated using the available data.

The parameters in the well-stirred-compartment model and the convection-compartment model which had to be determined were k_1, k_0 and K. The small time approximation of Eqn 33 gives a guide to the relationship between k_1 and K which proved to be useful: the product $k_1 K$ is an approximation to the slope of the graph obtained from the data of the ratio C_s/C_0 as a function of time. The alternative boundary conditions do not appear as useful since the theoretical slope is initially indeterminate. It should, however, produce some information on the value of the diffusion coefficient D.

The values of k_1 and K were obtained using an empirical subdivision process which compared the numerical output with the experimental data. The process was considerably simplified by relying on the relationship that the product $k_1 K$ is a specific value as referred to in the previous paragraph. Instead of a two parameter subdivision one proved sufficient. As expected any loss to the atmosphere takes some time to become significant and the parameter k_0 was estimated from the 'tails' of the curves.

The diffusion models contain the extra parameter D. In this situation it was found that, taking a normalised value of $D = 1$, the theoretical results from Eqns 15 and 24 are of the same form as their compartment counterparts when only one term of the series involved is taken. The additional terms provide corrections to these cases but for the drugs considered the comparisons indicate these are small.

Simulations

Figs 5–9 show the results of simulation for a variety of conditions. In Fig. 5 the flow rate has been varied between 0.1 and 50 ml per min for each of the four models. The parameters fixed in the simulation were the partition coefficient $k = 10$, $k_1 = 0.00033$ (compartment) $= 0.00015$ (diffusion), $k_0 = 0$ (no loss to the atmosphere). In the diffusion models, v was assumed to equal 0.5 units. It is

* Experiments conducted when one of us (A.E.P.) was on sabbatical leave at the University of Tennessee, Centre for Health Sciences, Memphis, TN

observed that with low rate the availability falls rapidly with time consistent with the transient time of the solute within the tube. At a time corresponding to the normal transient time of solution in the tube (volume of the solution in the tube divided by the flow) the outflow concentration either increased or remained constant. At the slower flow rates the outflow concentration is relatively constant as if the plastic were acting as an infinite sink. With an increasing flow rate increases of concentrations of the solute are observed in the outflow due to the saturation of some of the surface sites in the plastic tubing. The appearance of these profiles is similar to that described by Roberts et al. (1980). At the low flow rates a relatively constant outflow concentration is observed, which is similar to much of the data shown by Kowaluk et al. (1982). In the latter work, Kowaluk et al. assumed that the uptake for many solutes could be described by an apparent first-order loss across an interface into a sink.

An important determinant of the loss of solutes from the solution into plastics is the affinity of the solute for the plastic material. Fig. 6 shows the effect of varying the partition coefficient (K) between the values of 0.1 and 50 and the availability for a fixed flow rate of 1 ml/min. It is observed that with a low partition coefficient the loss of solute into the tubing is minimal. A number of authors have previously shown that the rate of permeation of various chemicals from aqueous solutions into plastic materials can be directly related to their partition coefficients. Much of this early work was conducted with polyethylene (Sercota et al., 1962; Nasim et al., 1972; Jordan and Polack, 1972; Polack et al., 1979; Roberts et al., 1979). More recently, the importance of the partition coefficient has been used for the uptake of solutes into polyvinyl chloride. (Illum and Bungaard, 1982; Atkinson and Duffal, 1991; Roberts, 1992).

Fig. 7 illustrates the role of atmospheric loss on outflow concentration of solutes with a partition coefficient of 10 (solid line) and 30 (dashed line). The dimensionless rate constants for atmospheric loss chosen were 0, 0.00001 and 0.0001. Substantive loss to the atmosphere results in a constant outflow

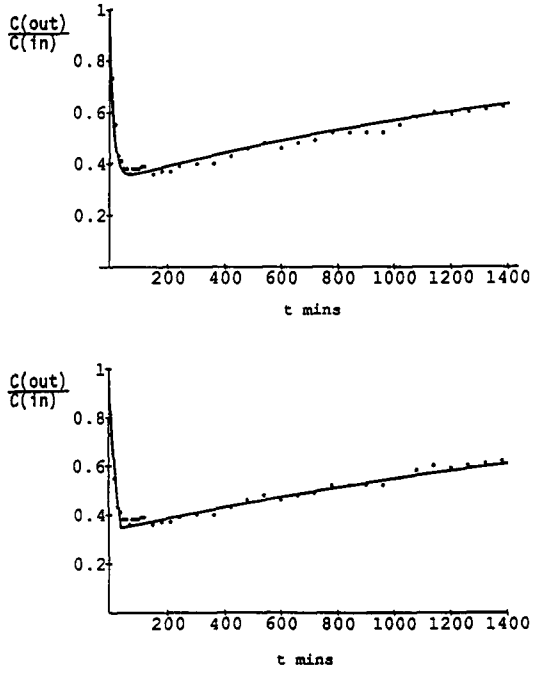

Fig 2. Drug uptake as a function of time. (a) Dimethylaniline: well-stirred-compartment and well-stirred-diffusion models. $d = 36$, $K = 0.000267$, $k_0 = 0\ 00001$, $l = 40$ cm, $a = 0.395$ cm, $b = 0.55$ cm, $v = 0.959$ cm/min. (b) Dimethylaniline: convection-compartment and convection-diffusion models $d = 38$, $K = 0.000135$, $k_0 = 0.00001$, $l = 40$ cm, $a = 0\ 395$ cm, $b = 0.55$ cm, $v = 0.959$ cm/min.

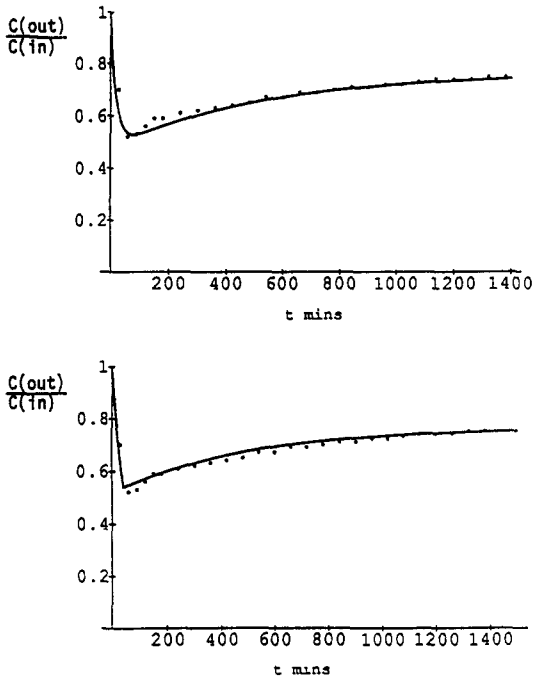

Fig. 3 Drug uptake as a function of time. (a) 4-Methylacetophenone. well-stirred-compartment and well-stirred-diffusion models $d = 36$, $K = 0.000267$, $k_0 = 0\ 00001$, $l = 40$ cm, $a = 0\ 395$ cm, $b = 0.55$ cm, $v = 0\ 979$ cm/min. (b) 4-Methylacetophenone convection-compartment and convection-diffusion models $d = 13\ 5$, $K = 0.00023$, $k_0 = 0\ 000012$, $l = 40$ cm, $a = 0\ 395$ cm, $b = 0.55$ cm, $v = 0\ 979$ cm/min.

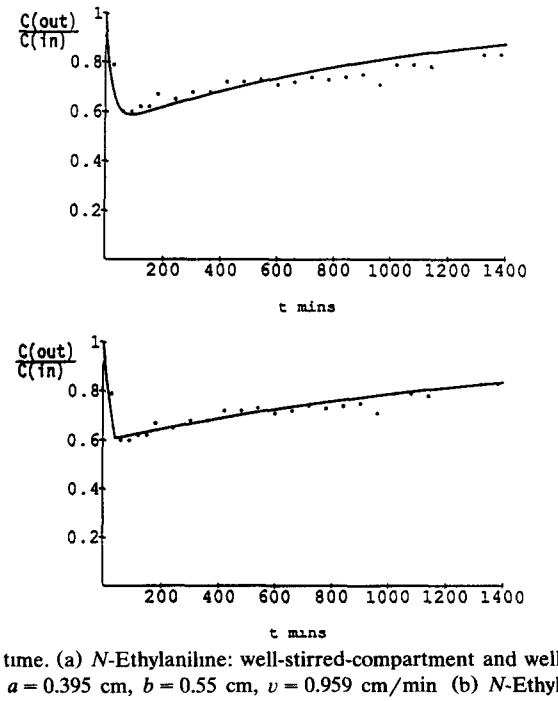

Fig. 4. Drug uptake as a function of time. (a) *N*-Ethylaniline: well-stirred-compartment and well-stirred-diffusion models. $d = 12$, $K = 0.00033$, $k_0 = 0.0000$, $l = 40$ cm, $a = 0.395$ cm, $b = 0.55$ cm, $v = 0.959$ cm/min (b) *N*-Ethylaniline: convection-compartment and convection-diffusion models. $d = 15$, $K = 0.00016$, $k_0 = 0.0000$, $l = 40$ cm, $a = 0.395$ cm, $b = 0.55$ cm, $v = 0.959$ cm/min.

concentration with time. Such behaviour is consistent with the tubing acting as an interfacial barrier between the solution and the outside atmosphere. We have previously examined the importance of atmospheric loss in terms of both the organic nitrates (Roberts et al., 1983) and clomethiazole (Kowaluk et al., 1984). In each of these instances, the affinity for the polyvinyl chloride tubing was more important than for loss into the atmosphere.

An important parameter determining the likely outflow concentration-time profiles is the diffusivity of the solute within the plastic. In Fig. 8, the effect of varying dimensionless diffusivities is shown using values of 0.05, 0.5 and 5 for a solute with a constant partition coefficient of 10 and no loss to the atmosphere ($k_0 = 0$). The higher the diffusivities the more rapidly the drug moves into the plastic and the more rapidly does the plastic become saturated. Hence, the output concentration returns to the input value more quickly.

Fig. 9 shows the importance of the dimensions of the system. Using solutes with partition coefficients of 10 (continuous line) and 30 (dashed line) and no loss to the atmosphere ($k_0 = 0$), the outflow concentrations observed with time on the doubling of the internal and external radius of the tubing are illustrated in Fig. 6. It is observed that with larger tubing radius, but with the same thickness and same flow speeds v the outflow concentrations are larger. Kowaluk et al. (1982) showed that the availability was directly related to the radius and that a lower availability was observed as the radius was increased for any given flow rate. They showed a linear relationship between the logarithm of the availability and the internal radius of the tubing. The present results are not inconsistent, since Kowaluk et al. used a

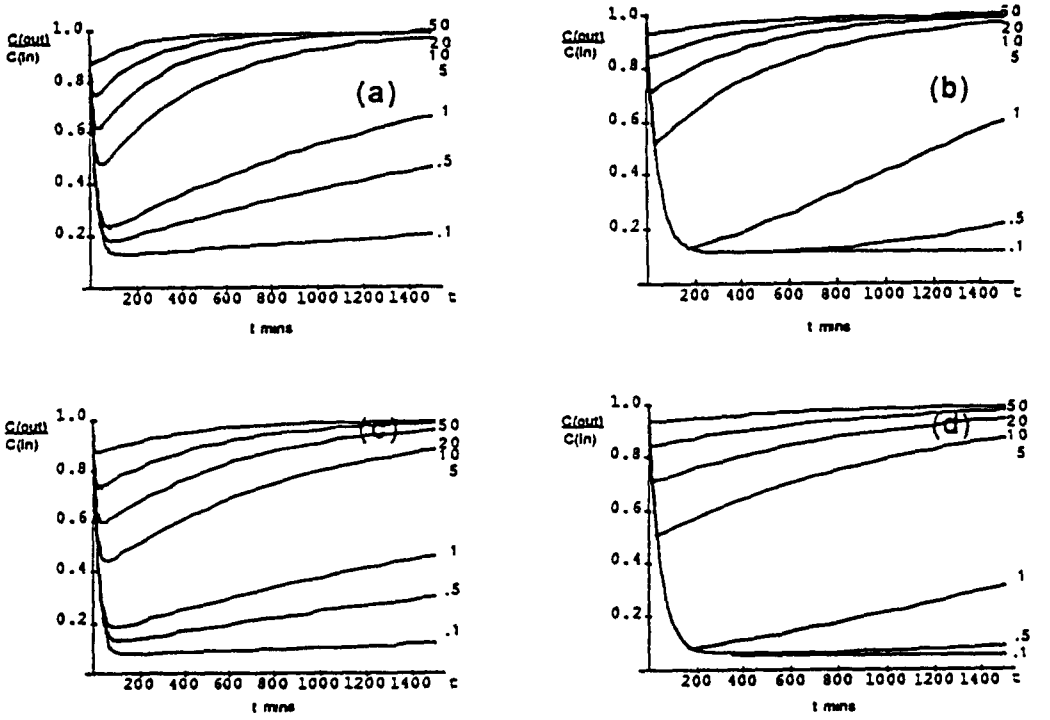

Fig. 5. Effect of flow speed, v, on availability. (a) Well-stirred-compartment model, (b) convection-compartment model, (c) well-stirred-diffusion model, (d) convection-diffusion model. $K = 10$, $k_1 = 0.00033$ (compartment), $k_1 = 0.00015$ (diffusion), $k_0 = 0.00$, $D = 0.5$, $l = 175$ cm, $a = 0.15$ cm, $b = 0.2$ cm

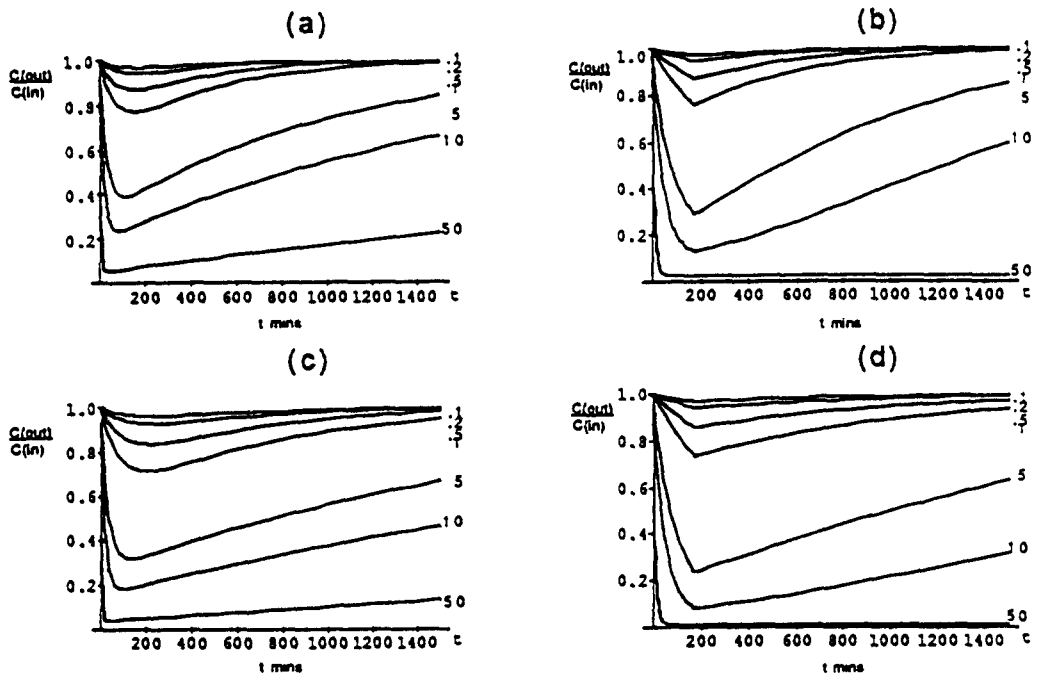

Fig. 6 Effect of partition coefficient, K, on availability (a) Well-stirred-compartment model, (b) convection-compartment model, (c) well-stirred-diffusion model, (d) convection-diffusion model $k_1 = 0.00033$ (compartment), $k_1 = 0.00015$ (diffusion), $k_0 = 0.00$, $D = 0.5$, $l = 175$ cm, $a = 0.15$ cm, $b = 0.2$ cm, $v = 1$ cm/min

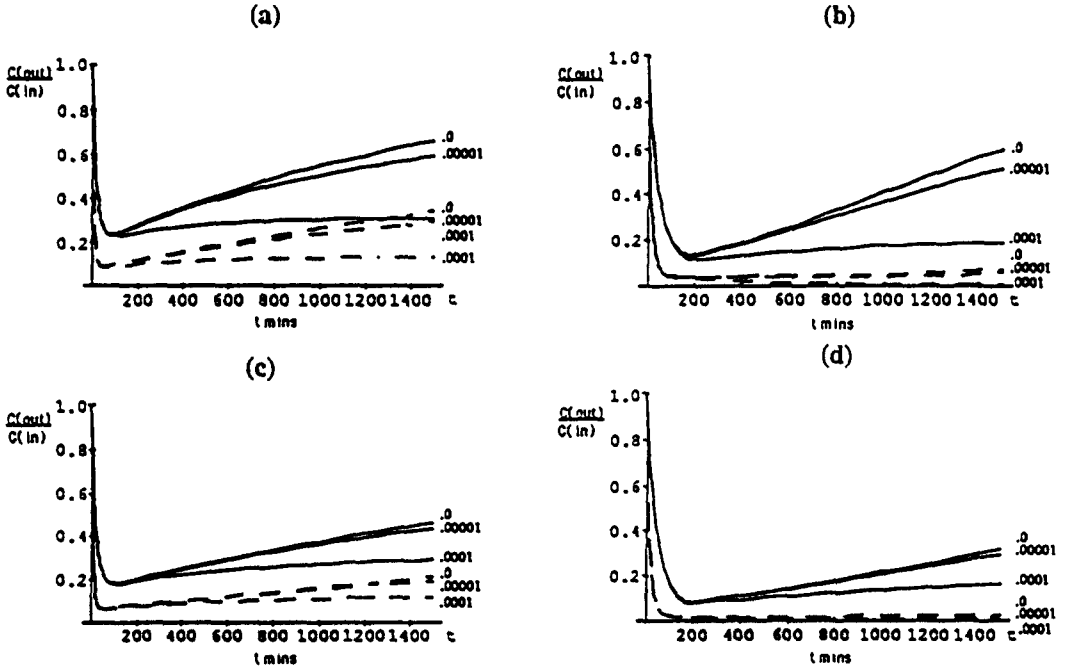

Fig. 7 Effect of loss, k_0, to atmosphere on availability (a) Well-stirred-compartment model, (b) convection-compartment model $K = 10$ (———), $K = 30$ (— — —), $k_1 = 0.00033$ (compartment), $k_1 = 0.00015$ (diffusion), $D = 0.5$, $l = 175$ cm, $a = 0.15$ cm, $b = 0.2$ cm, $v = 1$ cm/min

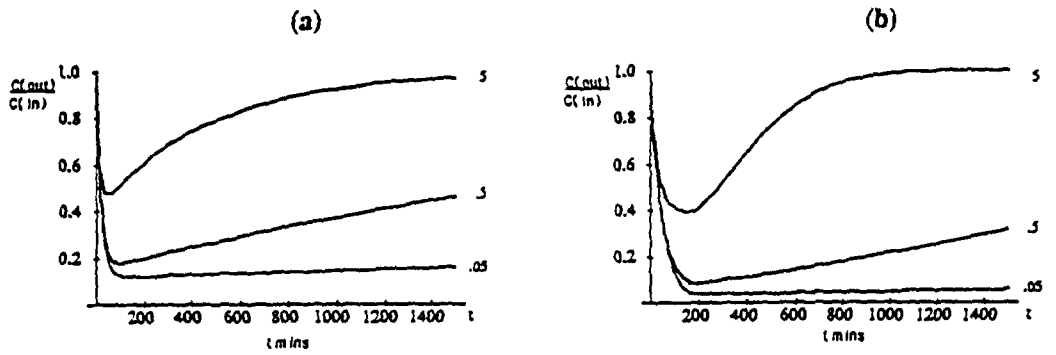

Fig. 8. Effect of diffusion coefficient, D, on availability. (a) Well-stirred-diffusion model, (b) convection-diffusion model $K = 10$, $k_1 = 0.00015$ (diffusion), $k_0 = 0.00$, $l = 175$ cm, $a = 0.15$ cm, $b = 0.2$ cm, $v = 1$ cm/min

fixed volumetric flow rate which depends on the inner radius of the tube and they did not take the thickness of the plastic tube into account.

One of the major outcomes expressed in Figs 5–9 is that the choice of model does not greatly affect the shapes of profiles for outflow concentration vs time with variation of parameters such as flow rate, partition coefficient, loss to the atmosphere and tubing radius. The main qualitative difference between the models is that the minimum of the well-stirred-compartment model is smooth, whereas that of the convection models is cusp-like. In addition, the diffusion model exhibits a more rapid rise after the

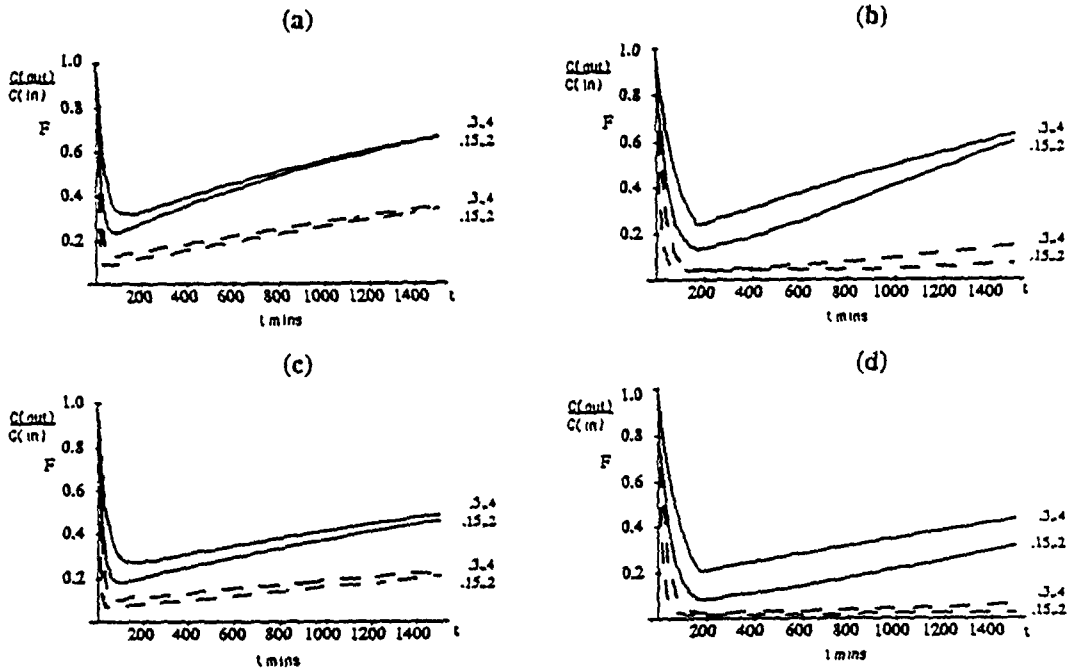

Fig 9 Effect of tubing radii, a and b, on availability. (a) Well-stirred-compartment model, (b) convection-compartment model, (c) well-stirred-diffusion model, (d) convection-diffusion model. $d = 10$ (———), $d = 30$ (— — —), $k_1 = 0.00033$ (compartment), $k_1 = 0.00015$ (diffusion), $k_0 = 0.00$, $D = 0.5$, $l = 175$ cm, $a = 0.15$ cm, $b = 0.2$ cm and $a = 0.3$ cm, $b = 0.4$ cm, $v = 1$ cm/min

minimum is reached than does the well-stirred model consistent with saturation of sites close to the surface to which the solution is in contact.

However, the empirically obtained values of the parameters differ for each model. If these values can be obtained experimentally then a determination of which model is the most appropriate would be made on quantitative grounds.

Conclusion

Analytic solutions have been obtained for four models of the uptake of solutes during flow through plastic tubing, the well-stirred compartment, well-stirred diffusion, convection compartment and convection diffusion models. As indicated by Figs 2–4, good agreement has been obtained with the experimental data. The convection model appears to be the most satisfactory with the cusp or sharp turning point being of special significance.

The theoretical values do not appear to be affected a great deal when diffusivity, with $D = 1$ is taken into account, but further analysis should be made for other values of D.

The enable the models to be useful as predictors of drug loss it is necessary to have predetermined values of the various parameters. The qualitative information illustrated in Figs 5–9 should assist in estimating how these parameters may be obtained from known data and other well-established physical and chemical properties of the drugs involved. Once this is done then which of the models best describes the process can be determined.

Glossary

Symbol	Meaning
t	time
C_s	concentration in solute
C_p	concentration in plastic
C_{surf}	concentration on surface of plastic
K	apparent coefficient
v	rate of flow
a	inner radius of plastic tube
b	outer radius of plastic tube
k_i	rate of transfer across inner surface
k_o	rate of transfer across outer surface
Q	flow rate
$\alpha_1,\alpha_2,\beta_1,\beta_2$	defined constants
τ, u	dummy variables of integration
A_1,B_1,B_2,C_1,C_2	integration constants
$\bar{C}$	Laplace transform of C
s	Laplace variable
r	radial distance from centre of tube
x	distance along tube
D	diffusion coefficient in plastic
J,Y,I	Bessel functions
C',α', etc.	constants of corresponding model
H	Heaviside's function

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