A STUDY OF MULTI-DIMENSIONAL DRUG DIFFUSION IN MATRICES AND MEMBRANES

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SUMMARY

The existence of both linear and radial non-steady state drug diffusion within rotationally-symmetric matrices and membranes held in a diffusion cell has been investigated. The error involved in the calculation of diffusivities from experimental release and permeation data using solutions to the linear form of Fick's Second Law could thereby be determined as a function of system geometry. For the case of drug release from a matrix, the use of a linear model underestimates the diffusivity, even for thin matrices (radius : height = 200). For drug permeation through a membrane, diffusivity will be overestimated with a linear model, the error also being strongly dependent on the value for partition coefficient.

I. INTRODUCTION

The release of a drug from a rectangular matrix or its permeation through a plane membrane are two common diffusional problems of great importance in the field of controlled release. The kinetics of either process can be investigated experimentally by using a diffusion cell. Although numerous designs are available for such cells,[1] they have in common the manner in which the matrix or membrane is affixed within the cell. As illustrated schematically in Figure 1a, the matrix or membrane is held taught

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within the cell, between either a backing plate for a matrix or a donor chamber for a membrane, and an acceptor chamber. The results of such experiments are expressed as release or permeation profiles of drug mass in the acceptor medium, $m_a(t)$, *versus* time, t. The diffusivity of the drug within either matrix, D_m, or membrane, D_s, can be calculated from a profile by using the appropriate solution to Fick's Second Law. If the drug is initially homogeneously distributed within the matrix or donor solution and membrane, the simplification is made that only linear diffusion of drug in the x-dimension occurs. The two diffusional models illustrated in Figure 1b can then be employed, for which analytical solutions to the linear form of Fick's Second Law for both sink[2a,3] and non-sink[2b,4] boundary conditions are known.

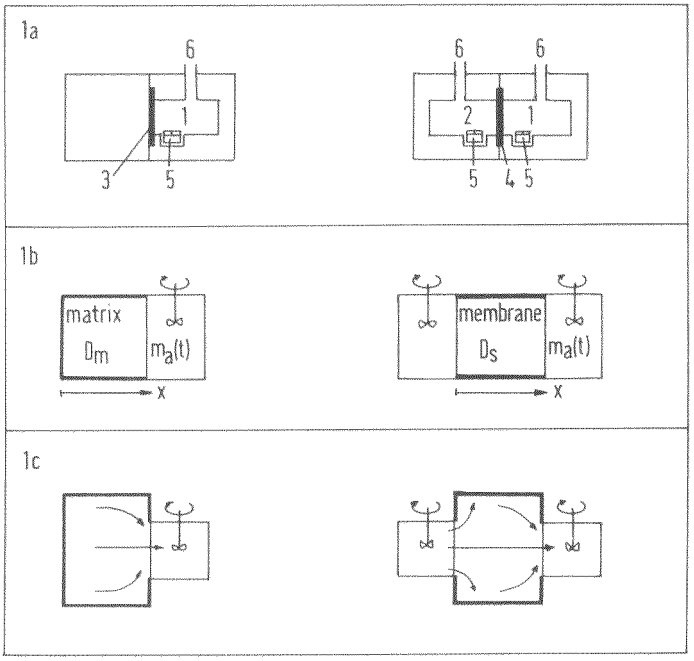

Figure 1. Schematic illustrations of drug release from a matrix (left) and drug permeation through a membrane (right). *a) Cross sections through a diffusion cell (1, acceptor chamber; 2, donor chamber; 3, matrix; 4, membrane; 5, stirrer; 6, sampling port). b) Linear diffusional models for the two processes (x, space coordinate; D_m, drug diffusivity in matrix; D_s, drug diffusivity in membrane; $m_a(t)$, drug mass in acceptor medium. c) Illustration of radial and linear drug diffusion within matrix and membrane.*

As part of a study of the transdermal application of the drug clenbuterol, we wished to make measurements of drug release and permeation using matrices and membranes of substantial thickness (up to 4 mm). A closer examination of

the geometry of the diffusion cell shows that in these cases the assumption of linear diffusion may be far from exact. Thus, Figure 1a shows how the matrix or membrane is larger in size than the area available within the cell for release or permeation. The edge region of the matrix or membrane necessary for fixation within the cell is not in contact with the opening of the donor or acceptor chambers. A true representation of the two models is given in Figure 1c for radially-symmetric bodies. It is clear that not only linear diffusion in the x-dimension occurs. Within the matrix, radial diffusion out of the edge region into its centre also takes place. Within the membrane, radial diffusion into the edge region occurs adjacent to the donor, and out of the edge region adjacent to the acceptor. The existence of both linear and radial diffusion within thick matrices or membranes is not taken into account by the linear models of Figure 1b. The use of solutions to the linear form of Fick's Second Law to calculate diffusivities from release or permeation data must, therefore, be subject to an error. The error arising in steady state flux has been shown some years ago by Barrer[5] to be negligible for permeation through very thin membranes. His steady state analysis does not, however, consider the error in calculated diffusivity, nor does it take into account the influence of partitioning. Additionally, it is uncertain at what matrix or membrane thickness the errors becomes large enough that they can no longer be ignored.

We have conducted an examination of the influence of matrix and membrane geometry on the size of the error. A numerical solution to a multi-dimensional form of Fick's Second Law for non-sink diffusion through matrices and membranes held in a diffusion cell is first derived. With the help of this model it is possible to predict the influence of system geometry on experimental release and permeation data. It is also used to evaluate results obtained from two series of experiments, namely, drug release from a thin polyacrylate matrix and drug permeation through a thick silicone membrane. The contrast between thick and thin bodies can thus clearly be made. Additionally, multi-dimensional diffusion can be made visible to the eye by examining the uptake of a dyestuff into a gel-matrix using digital image processing.

II. THEORY

The most general formulation of the problem to be solved is that of the non-steady state diffusion of dissolved drug with a single diffusivity, D, through the isotropic cylinder of finite length illustrated in Figure 2. The selection of suitable initial and non-sink boundary conditions allows the representation of either a matrix or a membrane held perpendicularly within a diffusion cell. Solution of this non-steady state problem is very involved. For the related case under sink boundary conditions, a formidable analytical solution is available.[6] The non-sink problem is, however, too ponderous to

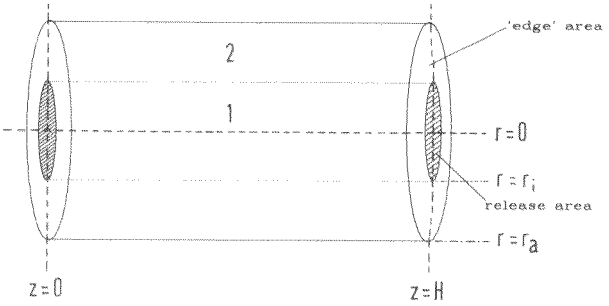

Figure 2. Geometric model applicable to non-steady state diffusion within a composite cylinder. *(1, inner layer of cylinder; 2, outer layer of cylinder; H, length of cylinder; r_a, total radius; r_i, radius of inner layer).*

be considered analytically, and must be tackled using numerical techniques. We solved the problem using Crank and Nicolson's implicit finite-difference method.[7,8] As the system is radially symmetric about the axis r=0 (see Figure 2), the drug concentration within the cylinder, c(r,z,t), is independent of angle, θ, and can be represented by the applicable form of Fick's Second Law[2c]:

$$\frac{\partial c(r,z,t)}{\partial t} = \frac{1}{r}\left[\frac{\partial}{\partial r}\left(rD\,\frac{\partial c(r,z,t)}{\partial r}\right) + \frac{\partial}{\partial z}\left(rD\,\frac{\partial c(r,z,t)}{\partial z}\right)\right] \quad , \; t>0 \ldots . (1)$$

The outer circumference of the cylinder represents the edge region and is insulated:

$$\frac{\partial c(r_a,z,t)}{\partial r} = 0 \qquad t>0 \qquad \ldots . (2)$$

For the case of release from a matrix, the cylinder can be represented by the finite difference grid illustrated in Figure 3a. By rotating the grid around its symmetry axis, the resulting body has the form of a cylindrical matrix. The grid points describe circles around the axis and delineate the points where the same drug concentration exists. Only those points marked with a cross lie within the release area of the face of the matrix, which is limited by an inner radius r_i. r_a is the total radius of the matrix. The drug is initially homogeneously dispersed within the matrix:

$$c(r,z,0) = c_o, \qquad 0 \le z \le H, \; 0 \le r \le r_a \qquad \ldots . (3)$$

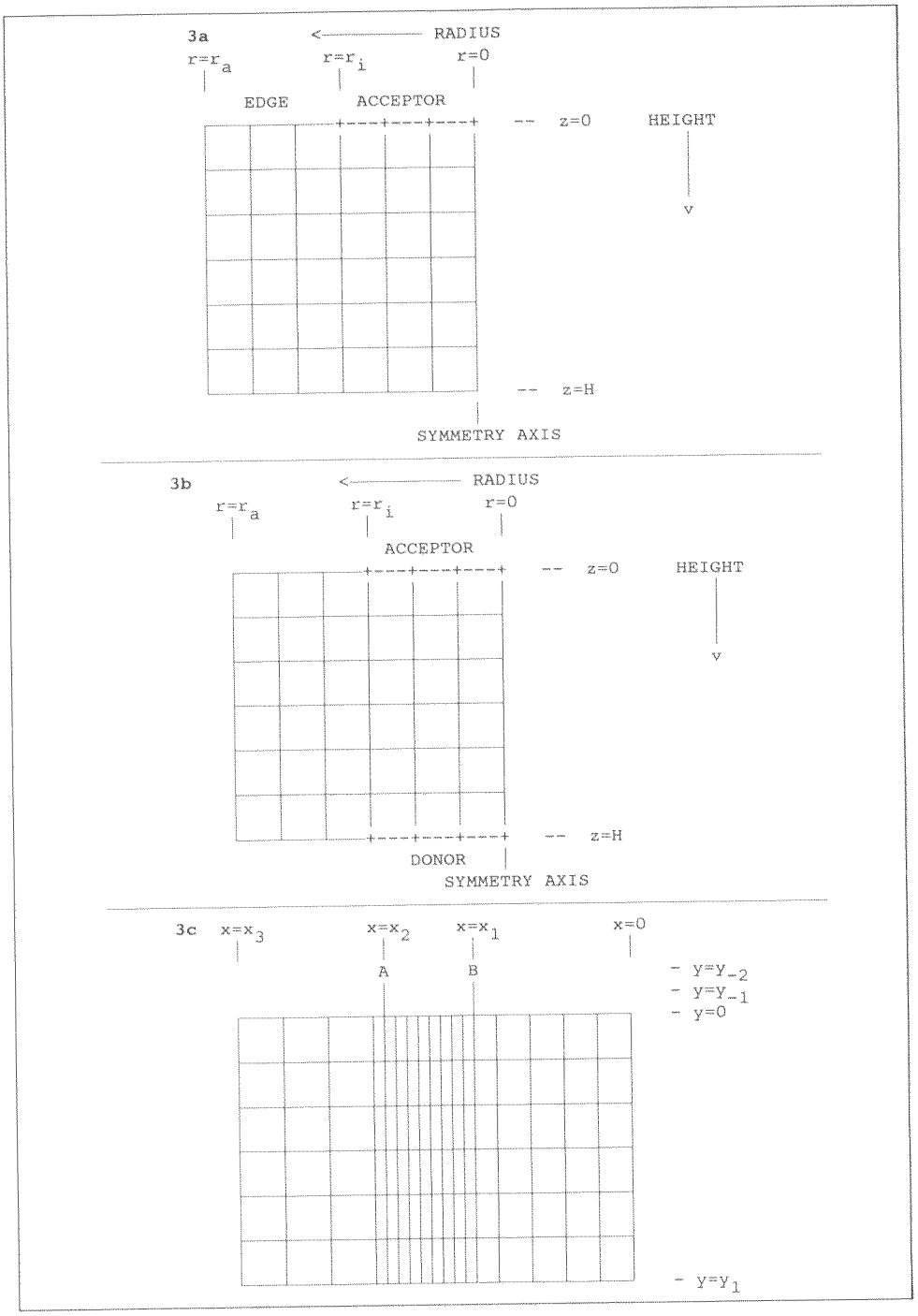

Figure 3. Finite difference grids. *a) Drug release from a matrix. b) Drug permeation through a membrane. c) Uptake into a gel-matrix.*

The whole area of the face at z = H is insulated:

$$\frac{\partial c(r,H,t)}{\partial z} = 0, \qquad 0 \le r \le r_a \qquad .....(4)$$

Drug release into a non-sink occurs through the inner layer (crosses) of the face at z = 0, the outer layer representing the edge region and being, therefore, insulated:

$$\frac{\partial c(r,0,t)}{\partial z} = 0, \; r_i \le r \le r_a; \qquad \frac{dm_a(t)}{dt} = -D_m \frac{\partial c(r,0,t)}{\partial z}, \; 0 \le r \le r_i \qquad ....(5)$$

$$K\, c_a(t) = c(r,0,t), \qquad 0 \le r \le r_i \qquad ....(6)$$

where K is the drug's partition coefficient between matrix and acceptor medium.

For the case of permeation through a membrane, the finite difference grid shown in Figure 3b is used. At z = H uptake of drug from the donor into the membrane occurs at the points marked with a cross ($z = H, 0 \le r \le r_i$). The complete model is described by rotating the grid around the symmetry axis. The drug is initially contained within a perfectly-stirred medium adjacent to the membrane's face at z = 0, the membrane being drug free:

$$c_d(0) = c_o; \quad c(r,z,0) = 0, \quad 0 \le z \le H, \; 0 \le r \le r_a \qquad ....(7)$$

Uptake of drug from the donor medium occurs through the inner layer (crosses) of the face at z = H, with the outer layer representing the edge region and being insulated:

$$\frac{\partial c(r,H,t)}{\partial z} = 0, \quad r_i \le r \le r_a; \qquad \frac{dm_d(t)}{dt} = -D_s \frac{\partial c(r,H,t)}{\partial z}, \; 0 \le r \le r_i \qquad ....(8)$$

$$K\, c_a(t) = c(r,0,t), \qquad 0 \le r \le r_i \qquad ....(9)$$

where K is the drug's partition coefficient between membrane and donor/acceptor medium. The non-sink release of drug through the inner layer (crosses) of the face at z = 0 is described, as for the matrix, by Equations 5 and 6.

III. MATERIALS AND METHODS

3.1 Solution of models and simulation of theoretical behaviour

The finite difference representations of the initial and boundary conditions were first derived. For drug release from a matrix, the resulting forms of Equations 1-6 form a linear system of multi-diagonal matrices that was programmed in Pascal on an Epson PC (80 386 processor with 80 387 coprocessor). For drug permeation through a membrane, the finite difference forms of Equations 1, 2 and 5-9 were similarly programmed. Solution by Gauss's elimination method yielded both the theoretical drug concentration profile within matrix or membrane, c(r,z,t), and the theoretical release or permeation profile, $m_a(t)$.

3.2 Measurement of drug release from a thin polyacrylate matrix

The model was used to evaluate some results obtained for the release of the basic drug clenbuterol (MWt = 277, pK_a = 9.5; Boehringer Ingelheim, Germany) from matrices prepared from purified[9] Eudragit NE30D (Röhm Pharma, Darmstadt, Germany). The 50 μm-thick matrices were prepared by solvent casting.[10] The release rate into pH 8 phosphate buffer was undertaken using the glass diffusional cell illustrated schematically in Figure 1a and operated as described before.[11] Two solutions to Fick's Second Law were then fitted to the experimentally-determined release profile, $m_a(t)_{exp}$: the numerical solution for the linear release model[11] illustrated in Figure 1b; and the numerical solution to the multi-dimensional release model illustrated in Figures 2 and 3a. An improved simplex method was used for the fit[12], which yielded the best value for D_m.

3.3 Measurement of drug permeation through a thick silicone membrane

An evaluation of the experimental permeation of clenbuterol through a thick poly(dimethyl)siloxane membrane was also undertaken with the model. The membrane was prepared by vulcanising dimethyl dichlorosilane with 3% Hardner T (Wacker Chemie, Munich, Germany) at 70°C for 12 h in a 4 mm deep, circular teflon mold. The diffusional cell illustrated in Figure 1a was used as described before[11], with Miglyol 840 (Dynamit Nobel, Witten, Germany) as a donor and acceptor medium to ensure high drug solubility. The linear[11] (Figure 1b) and multi-dimensional (Figure 3b) models were then fitted to the experimentally-determined permeation profile, $m_a(t)_{exp}$, yielding the best values in this case for both D_s and K.

3.4 Measurement of uptake into a thick agarose gel matrix

With this experiment, the edge effect could be made visible to the naked eye. A plexiglas diffusion cell was used, which had a geometry equivalent to that of matrix and acceptor illustrated in Figure 1c. It allowed examination of the two-dimensional uptake of a dyestuff from a donor medium into a solid gel. The gel was prepared from a 5% seaplaque agarose sol (FMC Corporation, Rockland, USA) that had been allowed to set within the diffusion cell. 2 ml of a 1% w/w aqueous methylene blue (Merck, Darmstadt, Germany) solution were then carefully filled into the neck of the cell at room temperature. The dyestuff diffused into the gel to produce a visible, two-dimensional profile of blue colour-intensity. Digitalized photographs of the cell were taken at regular intervals up to 56 h with a ccd camera (WVCD 110E, Panasonic, Tokyo, Japan) connected to a IBM-AT containing an 8 bit digitial image processing card (MVP-AT, Matrox Ltd., Canada). A resolution of 512 x 512 picture points with shades on a scale of 0 to 255 was used, the latter being subsequently converted into concentration profiles, c(r,z,t), with the help of calibration gels of known dyestuff concentration.

To calculate diffusivity, the applicable multi-dimensional numerical solution to Fick's Second Law was fitted to each concentration profile. A complication arose here in the design of a two-dimensional finite difference grid to fit the contours of the diffusion cell. For a constant step size in space, delta x, the edge points A and B at the neck of the cell and also the side walls of the cell did not necessarily coincide with grid points. To account for this, the grid was deformed as illustrated in Figure 3c. Delta x is now not constant across the grid from $x = 0$ to $x = x_3$. The isolated grid points A and B take into account the concave shape of the gel surface. The origin of the coordinate system is the upper right corner of the cell at the point (0|0). Problems arise at those grid points where delta x changes. At a specific grid point (e.g. $x_1|0$), the two neighbouring points on the x axis are now not equally distanced. The usual finite difference form of Equation 1 (i.e. the Crank-Nicolson formula) cannot be applied at that point. A solution to this problem was taken from Crank[2d] by using a Lagrange interpolation. The resulting set of equations was solved by an improved Gauss algorithm to step over zero elements. As before, the fit of this theoretical solution to the experimental c(z,r,t) values yielded the best values for D and K.

IV. RESULTS AND DISCUSSION

4.1 Drug release from a matrix

Fig 4a shows the theoretical concentration-distance profile within a cylindrical thick matrix whose radius equals its height (i.e. r:h = 1). The