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# Group theoretic approach for solving the problem of diffusion of a drug through a thin membrane

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**Abstract**

The transformation group theoretic approach is applied to study the diffusion process of a drug through a skin-like membrane which tends to partially absorb the drug. Two cases are considered for the diffusion coefficient. The application of one parameter group reduces the number of independent variables by one, and consequently the partial differential equation governing the diffusion process with the boundary and initial conditions is transformed into an ordinary differential equation with the corresponding conditions. The obtained differential equation is solved numerically using the shooting method, and the results are illustrated graphically and in tables. © 2002 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

The diffusion through membranes is one of the interesting types of diffusion studies that is of great importance in the pharmaceutical sciences. Several experiments may be made to study the process. One such experiment which clearly exhibits this behaviour is that of non-stationary diffusion of a drug from a donor cell through a thin membrane to a receiver cell. This type of experiment was used in several works by Hoogervorst et al. [6] and Spacek and Kubin [7].

To explain the process, consider two cells of the same volume, the donor and the receiver cells, separated by a thin membrane. A high concentration of a drug in a saline solution is placed in the donor cell and the receiver cell contains only a saline solution. Initially, the membrane is free from the drug, the two cells are stirred continually, and the drug starts to diffuse through

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the membrane. The concentration of drug in the receiver cell and also in the membrane begins to increase.

This experiment was carried out and the proposed mathematical model was solved numerically by Spoelstra and Van Wyk [8] using the finite-difference method only to evaluate the values of the parameters of the model and to define the concentration in the donor and the receiver cells.

In this work, the mathematical model is solved using the group transformation method applied by Abd-el-Malek and El-Mansi [1], Boutros et al. [2], Gaggioli and Moran [4] and Hansen [5], to define the concentration of drug in the membrane in addition to that in the donor and the receiver cells.

In the group transformation, the number of independent variables are reduced by one and thus the partial differential equation in two variables is transformed to an ordinary differential equation. The resulting differential equation is then solved numerically using the shooting method presented by Cheney and Kincaid [3].

## 2. Mathematical formulation

Mathematical models for diffusion, based on Fick's laws, do not apply to the following cases: membranes of hairless mouse skin, human skin and several synthetic membranes (see Spoelstra and Van Wyk [8]).

The applied model is based on the following assumptions: the rate of absorption at any point in the membrane is proportional to the concentration of the drug at the point, the $x$-axis of the coordinate system is taken in the direction of the normal on the membrane and no diffusion takes place through the edges of the membrane, the concentration in the membrane is considered as a function of time and of the $x$-coordinate, and the rate of transfer of diffusant in the membrane, per unit area, is proportional to the gradient of the concentration across the membrane.

Let $C(x,t)$ be the *concentration of the drug* at a distance "$x$" from one face of the membrane and at an instant of time "$t$" and $P(x,t)$ be the function which determines the *coefficient of diffusion*. The concentrations of drug in the donor and the receiver cells are $D(t)$ and $R(t)$, respectively.

Consider a membrane of unit thickness and if "$Q$" is the coefficient of partition, "$q$" is the coefficient which determines the rate of absorption of the drug in the membrane. The equation which governs the diffusion process may be written as

$$\frac{\partial C}{\partial t} = P\frac{\partial^2 C}{\partial x^2} + \frac{\partial P}{\partial x}\frac{\partial C}{\partial x} - q\frac{C^2}{t^2}, \quad 0 < x < 1, \ t > 0 \tag{2.1}$$

with the following conditions.

(i) Initial condition:

$$C(x,0) = 0, \quad 0 \leqslant x \leqslant 1. \tag{2.2}$$

(ii) Boundary conditions:

$$\text{(a) } C(0,t) = \phi(t), \quad t > 0,$$

$$\text{(b) } C(1,t) = \psi(t), \quad t > 0, \tag{2.3}$$

where

$$\phi(t)=\frac{\alpha Q}{D(t)-\beta}, \quad \alpha,\beta \text{ are constants}$$

and

$$\psi(t)=aQR^2(t), \quad a \text{ is a constant.}$$

## 3. Solution of the problem

Our method of solution depends on the application of a one-parameter group transformation to the partial differential equation (2.1). Under this transformation the two independent variables will be reduced by one and differential equation (2.1) transforms into an ordinary differential equation.

### 3.1. The group systematic formulation

The procedure is initiated with the group $G$, a class of transformation of one-parameter "$b$" of the form

$$G: \quad \bar{u}=K^u(b)u+S^u(b), \tag{3.1}$$

where $u$ stands for $x,t$; $C$ and $P$ and the $K$'s and $S$'s are real-valued and at least differentiable in the real argument "$b$".

### 3.2. The invariance analysis

To transform the differential equation, transformations of the derivatives of $C$ and $P$ are obtained from $G$ via chain-rule operations

$$\bar{u}_{\bar{i}}=\left(\frac{K^u}{K^i}\right)u_i, \quad \bar{u}_{\bar{i}\bar{j}}=\left(\frac{K^u}{K^iK^j}\right)u_{ij}, \quad i=x,t; \ \ j=x,t \tag{3.2}$$

where $u$ stands for $C$ and $P$.

Eq. (2.1) is said to be invariantly transformed, for some function $H(b)$, whenever

$$\bar{C}_{\bar{t}}-\bar{P}\bar{C}_{\bar{x}\bar{x}}-\bar{P}_{\bar{x}}\bar{C}_{\bar{x}}+\bar{q}\,\frac{\bar{C}^2}{\bar{t}^2}=H(b)\left[C_t-PC_{xx}-P_xC_x+q\frac{C^2}{t^2}\right]. \tag{3.3}$$

Substitution from (3.1) into (3.3) yields

$$\left(\frac{K^C}{K^t}\right)C_t-(K^PP+S^P)\left(\frac{K^C}{(K^x)^2}\right)C_{xx}-\left(\frac{K^PK^C}{(K^x)^2}\right)P_xc_x+\left(\frac{K^CC+S^C}{K^tt+S^t}\right)^2q$$

$$=H(b)\left[C_t-PC_{xx}-P_xC_x+q\frac{C^2}{t^2}\right]+R(b), \tag{3.4}$$

where

$$R(b) = -\left[\frac{K^C S^P}{(K^x)^2}\right] + 2q\left[\frac{K^C S^C C}{(K^t t)^2 + 2K^t S^t t + (S^t)^2}\right] + \left[\frac{q(S^C)^2}{(K^t t)^2 + 2K^t S^t t + (S^t)^2}\right]. \tag{3.5}$$

For conformal invariance, $H(b)$ is taken as a constant. For the remainder $R(b)$ to vanish,

$$S^P = S^C = 0, \tag{3.6}$$

and from (3.4)

$$\left[\frac{K^C}{K^t}\right] = \left[\frac{K^P K^C}{(K^x)^2}\right] = \left[\frac{K^C}{K^t}\right]^2 = H(b), \quad S^t = 0. \tag{3.7}$$

Moreover, initial condition (2.2) and boundary conditions (2.3) are also invariant in form, implying that

$$\frac{K^C}{K^t} = 1, \quad \frac{K^C}{K^t} = \frac{K^P K^C}{(K^x)^2}, \quad K^x = 1, \tag{3.8}$$

giving

$$K^C = K^t, \quad K^P = \frac{1}{K^t}. \tag{3.9}$$

Finally, we get the one-parameter group $G$ which invariantly transforms differential equation (2.1), as well as initial condition (2.2), and boundary conditions (2.3). The group $G$ is of the form

$$G: \begin{cases} \bar{x} = x, \\ \bar{t} = (K^t)t, \\ \bar{C} = (K^t)C, \\ \bar{P} = \left(\dfrac{1}{K^t}\right)P. \end{cases} \tag{3.10}$$

### 3.3. The complete set of absolute invariants

The reduction of the partial differential equation (2.1) into an ordinary differential equation proceeds as follows:

$$g_j(x,t,C,P) = F_j[\eta(x,t)],$$

where $\eta$ is the absolute invariant of the independent variables $x$ and $t$. $C$ and $P$ are the dependent variables and $g_j$ $(j = 1,2)$ represents the invariant groups for both $C$ and $P$.

According to the fundamental theorem of group analysis [4]

$$\sum_{i=1}^{4} (\alpha_i u_i + \beta_i) \frac{\partial g_i}{\partial u_i} = 0, \tag{3.11}$$

where

$$u_i = (x, t, C, P),$$

$$\alpha_i = \frac{\partial K^{u_i}}{\partial b}(b^0) = 0, \quad i = 1, 2, 3, 4$$

$$\beta_i = \frac{\partial S^{u_i}}{\partial b}(b^0) = 0,$$

where $b^0$ is the identity element of the group.

From this we get $\beta_i = 0$, $i = 1, 2, 3, 4$ as $S^x = S^t = S^C = S^P = 0$.

Eq. (3.11) is applied to obtain $\eta(x, t)$. It is written as

$$\alpha_1 x \frac{\partial \eta}{\partial x} + \alpha_2 t \frac{\partial \eta}{\partial t} = 0, \tag{3.12}$$

giving

$$\alpha_2 t \frac{\partial \eta}{\partial t} = 0 \quad \text{since } \alpha_1 = \frac{\partial K^x}{\partial b} = 0$$

from which $\eta = f_1(x)$. Without loss of generality, we can consider the identity function, i.e., $\eta = x$. By a similar analysis the dependent variables $C$ and $P$ are found to be

$$C(x, t) = \Gamma(t) F(\eta) \tag{3.13}$$

and

$$P(x, t) = \omega(t) T(\eta). \tag{3.14}$$

## 4. The reduction to an ordinary differential equation

To obtain a similar representation for the problem, Eq. (2.1) is reduced to an ordinary differential equation. This is carried out by substituting "$C$" and "$P$" and their partial derivatives using (3.13) and (3.14). This is achieved as follows:

$$\frac{\partial C}{\partial t} = F \frac{\mathrm{d}\Gamma}{\mathrm{d}t}, \quad \frac{\partial C}{\partial x} = \Gamma \frac{\mathrm{d}F}{\mathrm{d}\eta}, \quad \frac{\partial^2 C}{\partial x^2} = \Gamma \frac{\mathrm{d}^2 F}{\mathrm{d}\eta^2}, \quad \frac{\partial P}{\partial x} = \omega \frac{\mathrm{d}T}{\mathrm{d}\eta}. \tag{4.1}$$

Upon substituting into Eq. (2.1), we get

$$\frac{\mathrm{d}^2 F}{\mathrm{d}\eta^2} + \left[\frac{1}{T}\frac{\mathrm{d}T}{\mathrm{d}t}\right]\frac{\mathrm{d}F}{\mathrm{d}\eta} - \left[\frac{1}{\omega T \Gamma}\frac{\mathrm{d}\Gamma}{\mathrm{d}t}\right] F - q\left[\frac{\Gamma}{\omega T t^2}\right] F^2 = 0. \tag{4.2}$$

For (4.2) to be reduced to an expression in the single independent invariant $\eta$, it is necessary that the coefficients should be constants or functions of $\eta$ alone. Thus,

$$\frac{1}{T}\frac{\mathrm{d}T}{\mathrm{d}\eta} = E_1(\eta), \tag{4.3a}$$

$$\frac{1}{\omega T \Gamma}\frac{\mathrm{d}\Gamma}{\mathrm{d}t} = E_2(\eta), \tag{4.3b}$$

$$\frac{\Gamma}{\omega T t^2} = E_3(\eta). \tag{4.3c}$$

*Case* 1: Let $T(\eta)=\mathrm{e}^{-\eta}$, $\Gamma(t)=\gamma t$, $\omega=1/t$, where $\gamma$ is a constant; hence,

$$E_1=-1, \quad E_2=\mathrm{e}^{\eta}, \quad E_3=\gamma\mathrm{e}^{\eta}$$

and, consequently, Eq. (4.2) takes the form

$$\frac{\mathrm{d}^2F}{\mathrm{d}\eta^2}-\frac{\mathrm{d}F}{\mathrm{d}\eta}-\mathrm{e}^{\eta}F-\gamma q\mathrm{e}^{\eta}F^2=0 \tag{4.4}$$

with the boundary conditions:

$$F(0)=\alpha Q, \tag{4.5a}$$

$$F(1)=Q. \tag{4.5b}$$

In addition,

$$P(x,t)=\frac{\mathrm{e}^{-x}}{t},$$

$$D(t)=\frac{1}{\gamma t}+\beta,$$

$$R(t)=\sqrt{\frac{\gamma}{a}}t. \tag{4.6}$$

*Case* 2: Let $T(\eta)=\mathrm{e}^{-\eta^2}$, $\Gamma(t)=\gamma t$, $\omega=1/t$, where $\gamma$ is a constant; hence,

$$E_1=-2\eta, \quad E_2=\mathrm{e}^{\eta^2}, \quad E_3=\gamma\mathrm{e}^{\eta^2}$$

and, consequently, Eq. (4.2) takes the form

$$\frac{\mathrm{d}^2F}{\mathrm{d}\eta^2}-2\eta\frac{\mathrm{d}F}{\mathrm{d}\eta}-\mathrm{e}^{\eta^2}F-\gamma q\mathrm{e}^{\eta^2}F^2=0 \tag{4.7}$$

with the boundary conditions:

$$F(0)=\alpha Q, \tag{4.8a}$$

$$F(1)=Q. \tag{4.8b}$$

In addition,

$$P(x,t)=\frac{\mathrm{e}^{-x^2}}{t}. \tag{4.9}$$

## 5. Numerical results

Eqs. (4.4) and (4.7) with the associated boundary conditions are boundary value problems. The most effective method to solve such type of problems is the *shooting method*. Referring to Spoelstra and Van Wyk [8] and to meet the physics of the problem, a suitable choice of the constants and the parameters of the problem is made.

Consider

$$q = 1.16, \quad Q = 81.95, \quad \alpha = 2.0, \quad \beta = 40,000, \quad \gamma = \frac{10^{-6}}{4}, \quad a = \frac{10^{-11}}{32}.$$

The results are given in tables and figures.

## 6. Discussion of results

The model used is illustrated in Fig. 1. The results obtained in Fig. 2 show the decrease of concentration in the donor cell and increase of concentration in receiving cell as expected physically. A detailed study of the concentration and diffusion in the membrane is given as follows:

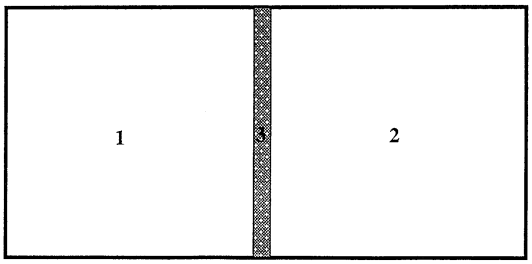


Fig. 1. A physical model of the experiment of the problem: (1) the donor cell; (2) the receiver cell; and (3) a thin membrane.

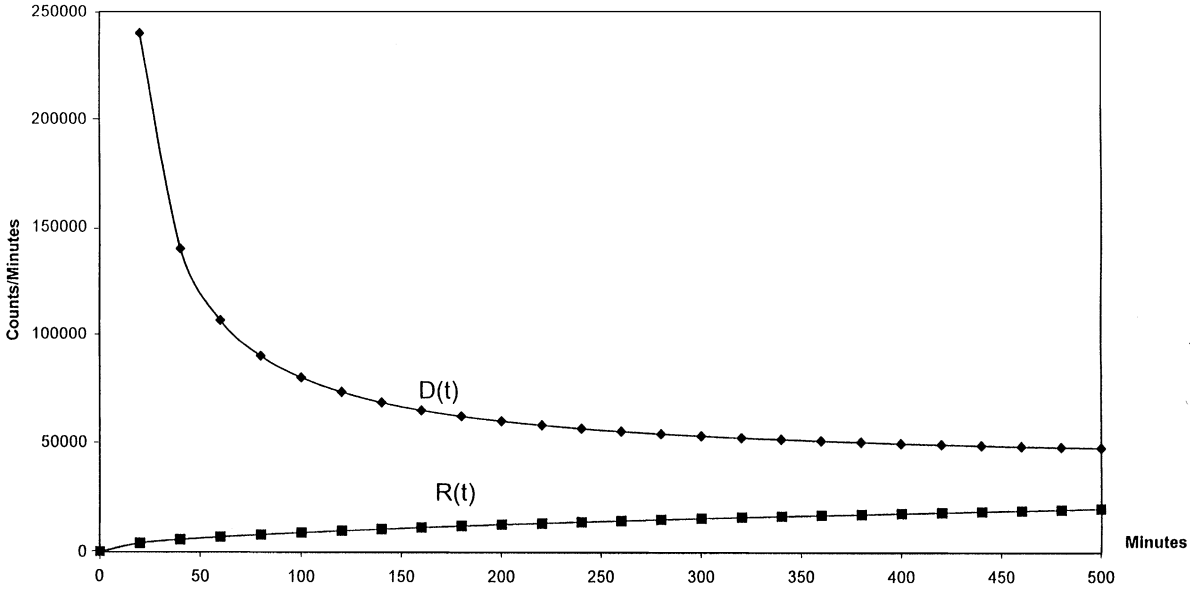


Fig. 2. The concentration of the donor and the receiver cells.

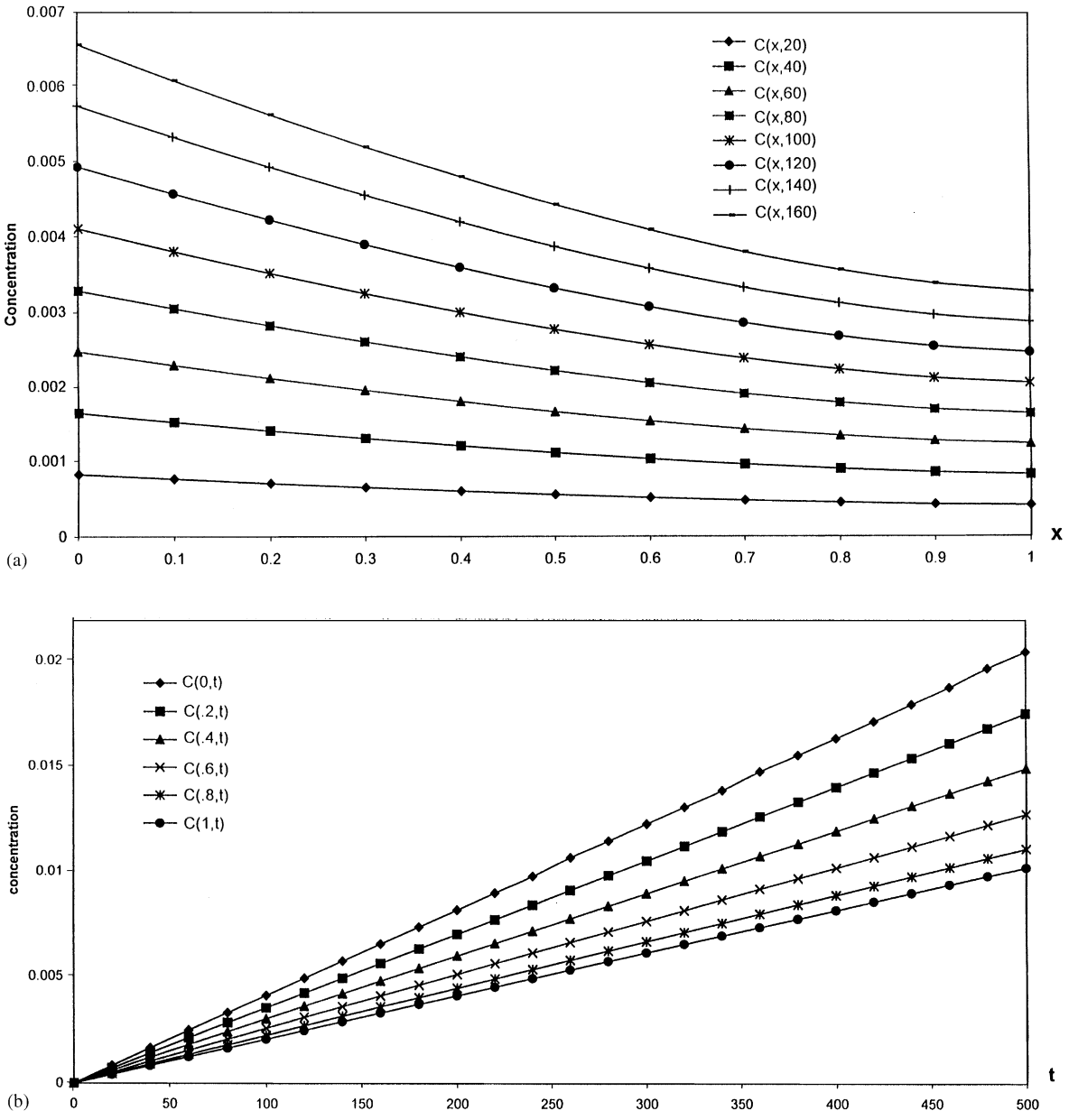


Fig. 3. (a) Curves of the concentration through the membrane at different times for the two cases of $P(x,t)$. (b) Variation of the concentration with time at specific sections of membrane for $P(x,t)=e^{-x}/t$ and (c) $P(x,t)=e^{-x^2}/t$.

(i) In Fig. 3a, the concentration of the drug inside the membrane is given versus $x$. It is found that $C(x,t)$ slowly decreases from the border of the membrane to the other. (ii) In Figs. 3b and c, the concentration $C(x,t)$ is plotted for the two physical cases:

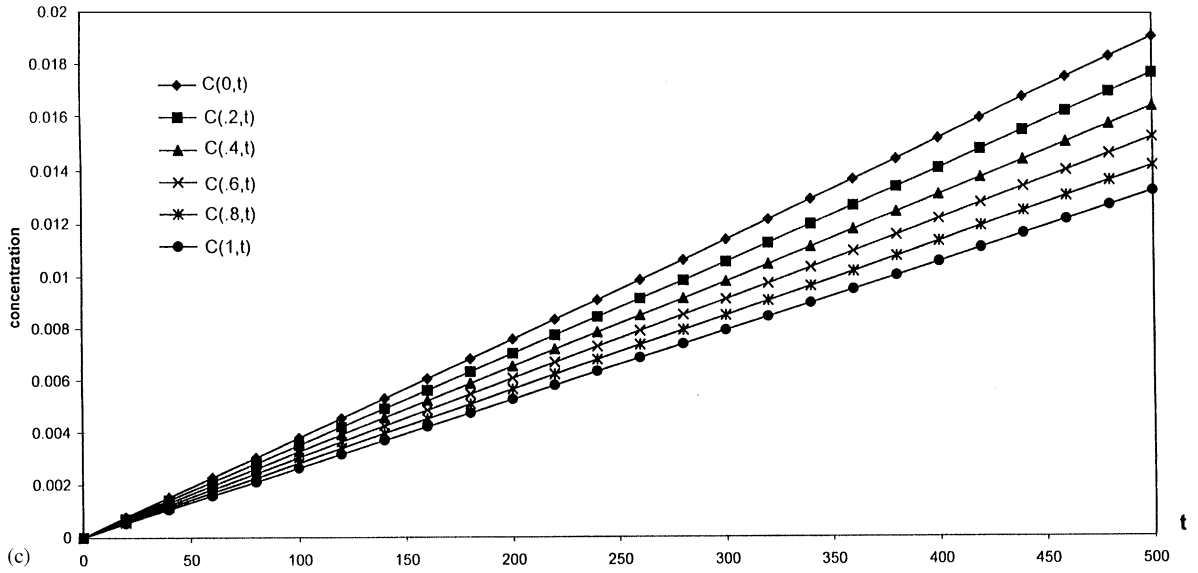


Fig. 3. (*Continued*)

Table 1
Values of concentration in membrane for the two cases at $t = 20$ min

| $X$ | $C(x,20)$ | | R.D.% |
|---|---|---|---|
| | case(1) | case(2) | |
| 0.0 | 0.000820 | 0.000820 | 0.000 |
| 0.1 | 0.000760 | 0.000758 | −0.260 |
| 0.2 | 0.000703 | 0.000703 | 0.000 |
| 0.3 | 0.000650 | 0.000653 | 0.610 |
| 0.4 | 0.000600 | 0.000608 | 1.315 |
| 0.5 | 0.000553 | 0.000566 | 2.330 |
| 0.6 | 0.000512 | 0.000528 | 3.030 |
| 0.7 | 0.000476 | 0.000492 | 3.250 |
| 0.8 | 0.000446 | 0.000461 | 3.180 |
| 0.9 | 0.000424 | 0.000433 | 2.080 |
| 1.0 | 0.000410 | 0.000410 | 0.000 |

$$P(x,t) = \frac{e^{-x}}{t} \quad \text{and} \quad P(x,t) = \frac{e^{-x^2}}{t}.$$

The figures show that the concentration increases with time.

(iii) The relative difference between the concentration in the membrane for the two different cases is tabulated in Tables 1 and 2 for two different times (20 min and 100 min). The small relative variation in concentration for the two cases is explained by the fact that the diffusion coefficient is of small weight in Eq. (2.1).

Table 2
Values of concentration in membrane for the two cases at $t = 100$ min

| $X$ | $C(x, 100)$ | | R.D.% |
|---|---|---|---|
| | case(1) | case(2) | |
| 0.0 | 0.00410 | 0.00410 | 0.000 |
| 0.1 | 0.00380 | 0.00379 | −0.260 |
| 0.2 | 0.00352 | 0.00352 | 0.000 |
| 0.3 | 0.00325 | 0.00327 | 0.610 |
| 0.4 | 0.00300 | 0.00304 | 1.315 |
| 0.5 | 0.00276 | 0.00283 | 2.330 |
| 0.6 | 0.00256 | 0.00264 | 3.030 |
| 0.7 | 0.00238 | 0.00246 | 3.250 |
| 0.8 | 0.00223 | 0.00230 | 3.180 |
| 0.9 | 0.00212 | 0.00216 | 2.080 |
| 1.0 | 0.00205 | 0.00205 | 0.000 |

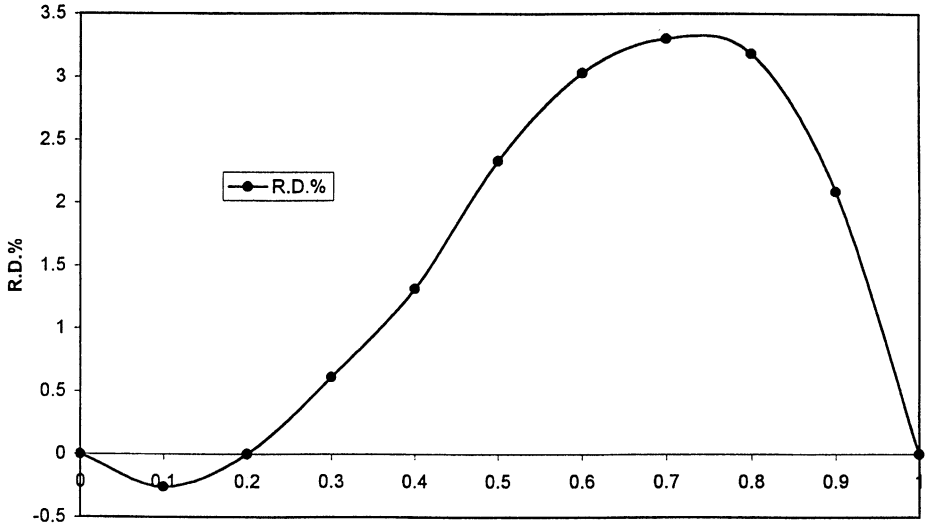


Fig. 4. Relative difference between values of concentration in the two cases through the membrane.

The difference is varying at different sections of the membrane, the greatest relative difference occurs at $x = 0.7$ and gradually decreases to attain a zero value at the two faces of the membrane, as illustrated in Fig. 4.

## 7. Concluding remarks

A highly non-linear partial differential equation, has been solved using the group method, and $C(x, t)$ and $P(x, t)$ have been evaluated analytically using the parameters of an experimental

study [8]. The results obtained map the state of the membrane in a way similar to the one obtained by Spoelstra and van Wyk [8], using a finite-difference method.

The other transformations, like spiral transform and linear transform, do not work for leaving the differential equation as well as the initial and boundary conditions invariant.

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