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# Model for matter transfers between sodium salicylate–Eudragit matrix and gastric liquid

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**Summary**

Drug release in synthetic gastric liquid has been studied by using sheets made of sodium salicylate and Eudragit, this component playing the role of a polymer matrix. A double transfer has been observed as follows: the liquid entered the matrix, dissolved the drug which then diffused out into the gastric liquid. Both these transfers have been found to obey Fickian laws of transient diffusion, with a constant diffusivity for the drug and a concentration-dependent diffusivity for the liquid. A model, using an explicit method with finite differences has been described, taking into account both transfers of material (drug and liquid), as well as the values of matter transferred at equilibrium. The model has been verified on tablets containing various concentrations of sodium salicylate in the polymer ranging from 15 to 50 (weight %), and calculated values were in substantial agreement with experiments.

## Introduction

The release rate of a drug, in order for it to be compatible with the surrounding environment and especially the behaviour of the patient, must be controlled.

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Recently, efforts have been directed to the development of methods for the administration of drugs, which are more effective and safer than conventional methods (Heilman, 1984). Controlled release techniques can generally be divided into three categories based on the mechanism that controls the release of the active agent from the delivery device. These mechanisms are diffusion, osmosis and polymer erosion, but sometimes the drug release is controlled by more than one mechanism (Feijen, 1984). Special attention was directed to finding a way for regulating the amount of drug released by means of monolithic devices where the agent is dispersed in an inert matrix. Both biodegradable and non-degradable polymers can be utilized for the polymeric drug delivery system (Heller, 1984; Focher et al., 1984; Fessi et al., 1982; Touitou and Donbrow, 1982).

Several theories have been put forward in an attempt to model the details of the dissolution process of the drug from an inert matrix system. Invariably they are built on a combination of diffusive and hydrodynamic effects (Nicklasson et al., 1985). In all cases, experimental data have been studied only for short periods (Gurny et al., 1982; Touitou and Donbrow, 1982; Teillaud and Pourcelot-Roubeau, 1984; Brossard et al., 1983), so that the diffusion process can be expressed as square-root law of time dependence with the amount of drug transferred (Crank, 1975). Moreover, the diffusivity is assumed to be non-concentration-dependent, and only the drug transfer is considered. Other works report some results on the simultaneous transfer of the liquid into, and plasticizer out of a plasticized PVC when this PVC was contacted with different kinds of liquids (Messadi and Vergnaud, 1981; Messadi et al., 1983).

One purpose of this present work is to show that both transfers simultaneously take place as follows: the liquid penetrates the matrix and dissolves the drug, which than diffuses out into the exterior liquid. For the study a polymeric matrix sheet is considered in which sodium salicylate was imbedded. These sheets were produced by pressing powder mixtures by using Eudragit RS as the tablet binder. Eudragit RS is a high molecular weight polymer, and tablets having Eudragit RS as the binder exhibit some advantages as hardness, palatability, strength and stability. Moreover the Eudragit residue is not absorbed in the body and passes through unchanged (Hecht et al., 1966). Tablets containing various concentrations of sodium salicylate in the polymer matrix swelled without disintegration or attrition. The release rate of the drug from the whole tablet was shown to conform with the Fick's diffusion equations.

The other purpose of this paper is to get insight into the process of hydrolysis and matter transfers by developing a mathematical model able to describe all the facts. Previous works (Vergnaud, 1983; Taverdet and Vergnaud, 1984; Taverdet and Vergnaud, 1985) pointed out that modelling liquid transfers by using a numerically explicit method with finite differences and data concerned with diffusivities and amounts of liquids transferred at equilibrium, was of interest. No drastic assumption was necessary for the method, so that matter transfers were studied for both liquids simultaneously, and the diffusivities were found to be concentration-dependent. In the present work, the mathematical model has been applied to the study of the diffusion of sodium salicylate from Eudragit matrix into synthetic gastric fluid at pH 1.2. The model has been developed and verified on tablets containing various

concentrations of sodium salicylate in the polymer ranging from 15 to 50 (weight %) by considering not only the transfer of the drug but also that of the liquid into the polymer.

## Theoretical aspects

A simultaneous diffusion takes place according to the following process: the liquid penetrates the polymer and dissolves the drug which then diffuses out into the liquid. Both transfers are stated to be governed by Fickian laws of diffusion.

*Mathematical treatment*

(1) A thin plane sheet of material is considered with a one-dimensional diffusion.

(2) Transient diffusion has a concentration-dependent diffusivity for the liquid, and a constant one for the drug, as was found from experiments.

(3) The concentration of liquid and drug on sheet faces reaches the value at equilibrium as soon as the sheet was soaked into the liquid. The drug concentration on sheet faces is not zero as is often assumed in order to get an analytical solution (Crank, 1975).

The equation of diffusion with a concentration-dependent diffusivity

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left[D \cdot \frac{\partial c}{\partial x}\right] \tag{1}$$

and the above-mentioned conditions cannot be solved.

However, for very short times, the amount of substance transferred $M_i$ at time $i\Delta t$ is small, and the local concentrations throughout the sheet may be considered as constant. This small amount $M_i$ is expressed as a function of the quantity after infinite time $M_\infty$ by the single equation:

$$\frac{M_i}{M_\infty} = \frac{4}{l}\left(\frac{D \cdot i\Delta t}{\pi}\right)^{0.5} \tag{2}$$

where D is the diffusivity and l the sheet thickness.

*Numerical analysis for transfer modelling*

The problem must be solved by using a numerically explicit method with finite differences, available for micro-computers.

In the cross-section of the sheet shown in Fig. 1, the thickness is divided into n equal finite slices of thickness $\Delta x$ by concentration-reference planes (n, i). A matter balance written on the plane n enables one to obtain for the liquid and drug within the polymer matrix.

*Liquid in polymer matrix*:

$$C^1_{n,i+1} = \frac{1}{M^e}\left[C^1_{n-1,i} + (M^1_{n,i} - 2)C^1_{n,i} + C^1_{n+1,i}\right] \tag{3}$$

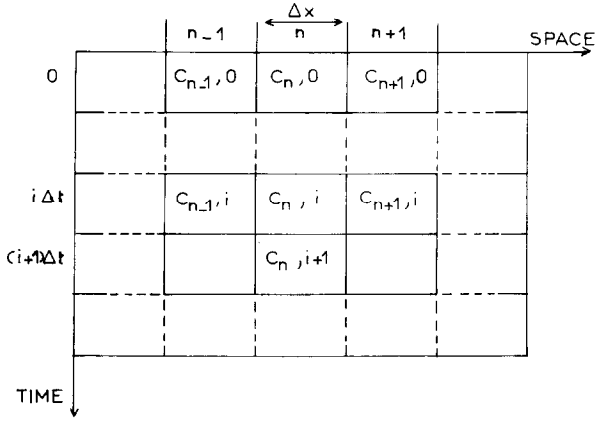


Fig. 1. Diagram space–time for calculation of material (liquid, drug) concentration. Explicit method with finite differences.

with the unidimensional number M and the increment of space and time $\Delta x$ and $\Delta t$.

$$M^1_{n,i} = \frac{(\Delta x)^2}{\Delta t} \cdot \frac{I}{D^1_{n,i}} \tag{4}$$

and

$$D^1_{n,i} = \exp\left( - \frac{A_1}{C^P_{n,i} + C^1_{n,i} \cdot a_1} - B_1 \right) \tag{5}$$

$C^1_{n,i+1}$ being the concentration of the liquid in polymer matrix at the plane n and time $(i + 1)\Delta t$.

*Drug in polymer matrix*:

In the same way, we have for the drug:

$$C^s_{n,i+1} = \frac{1}{M_s}\left[C^s_{n+1,i} + (M^s_{n,i} - 2) \cdot C^s_{n,i} + C^s_{n-1,i}\right], \tag{3'}$$

with

$$M^s_{n,i} = \frac{(\Delta x)^2}{\Delta t} \cdot \frac{1}{D^s_{n,i}} \tag{4'}$$

and

$$D^s_{n,i} = \exp\left( - \frac{A_s}{C^s_{n,i} + C^s_{n,i} \cdot a_s} - B_s \right) \tag{5'}$$

$C^s_{n,i+1}$ being the concentration of the drug in polymer matrix at the plane n and time $(i + 1)\Delta t$.

*Liquid and drug on sheet faces*:

On sheet faces, the concentrations for the liquid and drug are those obtained at equilibrium as soon as the material is soaked into the liquid.

$$t > 0 \qquad C^l_{o,i} = C^l_{equilibrium} \tag{6}$$

$$t > 0 \qquad C^s_{o,i} = C^s_{equilibrium} \tag{6'}$$

The amount of each matter transferred at time t between the liquid and sheet are obtained by integrating the above-mentioned concentrations with respect to time.

$$M_i = \frac{1}{n}\left[C_{o,i} + \sum_{n=1}^{n-1} C_{n,i}\right] \tag{7}$$

## Experimental

*Materials*

Sodium salicylate and Eudragit RS PM (copolymer of dimethylaminoethylacrylate and ethylmethacrylate PM = 150,000 (Röhm Pharma)) were used as the drug and polymer matrix, respectively. Both of these materials in powder form were mixed in a mortar. Sheets were pressed in a steel mold operated by a press at 120°C for 30 s under a pressure of 180 bars, after a 6-min heating. Tablets (1.5 cm in diameter 0.024 cm thick) were cut from the sheets. Cohesion after compression is excellent, Eudragit being an effective tablet binder.

*Determination of matter transfers*

Experiments were conducted in a closed flask using a controlled rate of stirring. The tablet (500 mg) inserted in a basket made of fiber glass, was soaked in synthetic gastric liquid (100 ml) at 37°C. The composition of the liquid is as follows: for 1 000 ml of aqueous solution, 80 ml HCl 1 N, 2 g NaCl, pH = 1.2.

Sample of liquid was taken at regular intervals for analysis and the tablet was weighed. The amount of sodium salicylate released from the polymer device was determined using a double-beam UV-spectrophotometer (Beckman DB-G) calibrated at 300 nm.

*Calculations*

The profiles of concentration of both liquid and drug developed through the polymer sheet were calculated by using the above-described model and data concerned with diffusivity and amount transferred at equilibrium.

The number of slices was 9, with an increment of space ranging from 0.0214 to

0.244 cm and increment of time of 120 s. In all cases, modulus for the liquid and drug is always higher than 3, in order to obtain convergence for calculation.

## Results

*Experimental results*

Fig. 2 shows the amount of sodium salicylate transferred into the synthetic gastric liquid as a function of $(\text{time})^{0.5}$, for various concentrations of sodium salicylate in polymer matrix; the higher the concentration of the drug, the higher the rate of transfer for the drug into the liquid. The values at equilibrium are obtained for times of about 15–20 h as shown in Table 1. The amount of drug transferred up to this time is directly proportional to $(\text{time})^{0.5}$, and diffusivities obtained from the slope of these straight lines were about constant and do not depend on the drug concentration.

The amount of liquid transferred into the polymer sheet is shown in Fig. 3 as a function of $(\text{time})^{0.5}$, for various concentrations of sodium salicylate in polymer matrix. Straight lines are obtained by plotting the amount of liquid transferred against $(\text{time})^{0.5}$.

The diffusivities in the logarithm form for the liquid are shown in Fig. 4 to be proportional to $(\text{drug concentration in polymer})^{-1}$, while diffusivities for drug were about constant.

The diffusivities and amount of materials transferred at equilibrium are cited in Table 1 for the various samples. The equation for diffusivity of liquid is:

$$D_l = \exp\left( - \frac{40.4}{C^s + C^l} - 13.3 \right)$$

where the concentration of drug and liquid depend on the time and position in the matrix.

The best results for stimulation were obtained when the value of coefficient $a_1$ shown in Eqn. 5 is 1.

*Modelling and simulation*

In Eqns. 1, 4 and 4′, the thickness l of the sheet was assumed to remain constant

TABLE 1

DIFFUSIVITIES AND $M_\infty$ FOR VARIOUS COMPOSITIONS

| Eudragit–drug | $Ms_\infty$ | $Ds \times 10^{-8}$ (cm$^2$/s) | $Ml_\infty$ | $Dl \times 10^{-8}$ (cm$^2$/s) |
|---|---|---|---|---|
| 50–50 | 20.5 | 16.5 | 48 | 70.5 |
| 75–25 | 12.5 | 16.5 | 37 | 37.5 |
| 85–15 | 4 | 16.5 | 29.5 | 11 |

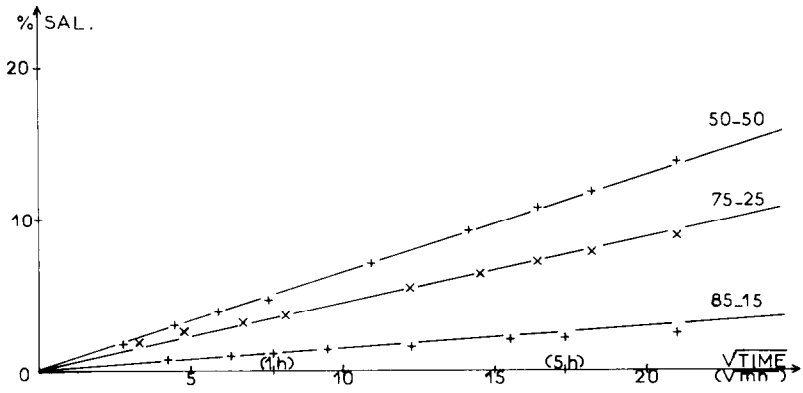


Fig. 2. Sodium salicylate transferred (weight % of initial sample) as a function of $(\text{time})^{0.5}$, for various initial concentrations of sodium salicylate. 37°C.

as diffusion proceeds. However, a swelling takes place as the rate of liquid transferred is higher than that for the drug. But these equations can still be used provided a frame of reference fixed with respect to the matrix itself is considered. Then the thickness of the sheet, measured in these units, is constant and equal to the thickness of the original unswollen sheet.

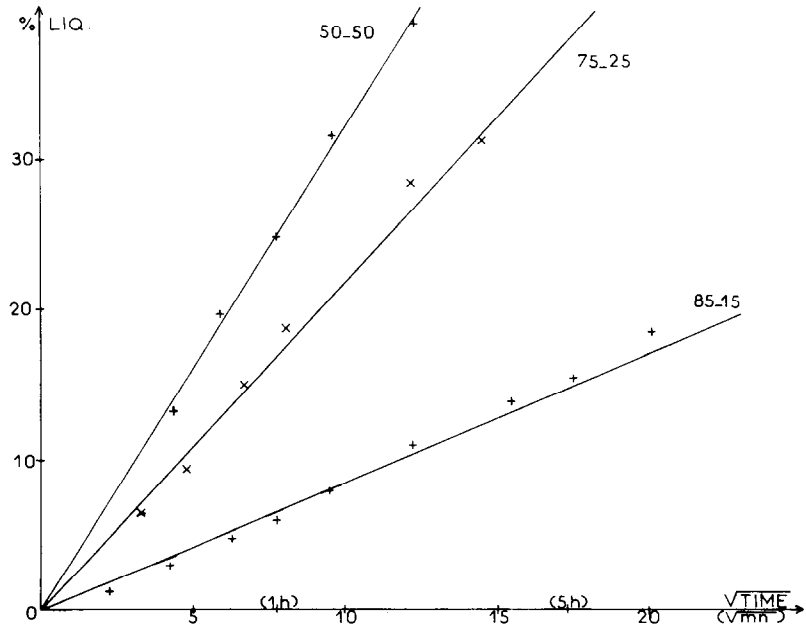


Fig. 3. Gastric liquid transferred (weight % of initial sample) as a function of $(\text{time})^{0.5}$, for various initial concentrations of sodium salicylate. 37°C.

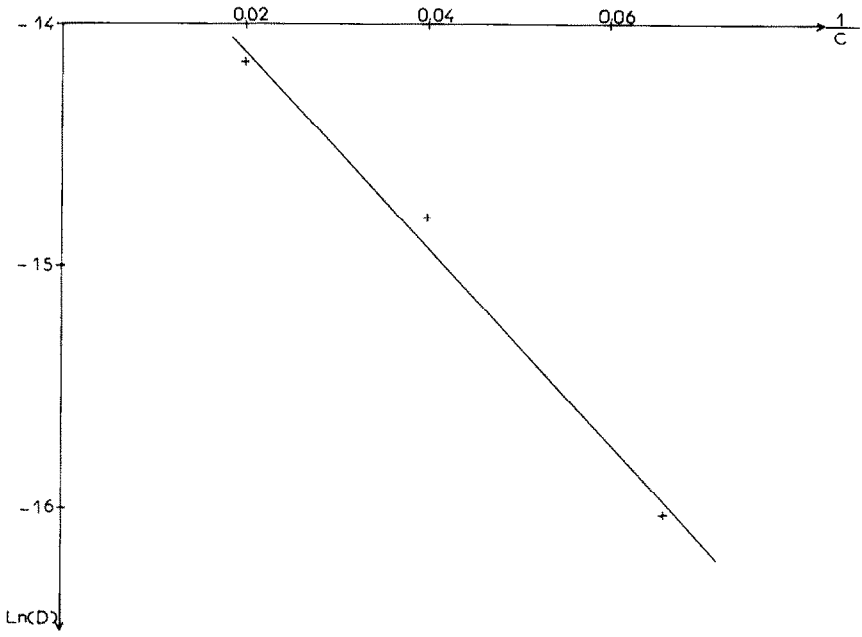


Fig. 4. Log D (for the liquid) as a function of (initial concentration of sodium salicylate)$^{-1}$. 37°C.

Figs. 5 and 6 illustrate the validity of the model for the sodium salicylate and liquid transferred, respectively. A good agreement was obtained not only for acid salicylate transfer throughout the process, but also for liquid transfer. Perhaps a slight difference can be appreciated in Fig. 6 for the liquid transfer obtained when the initial concentration of the drug is 15% in the matrix.

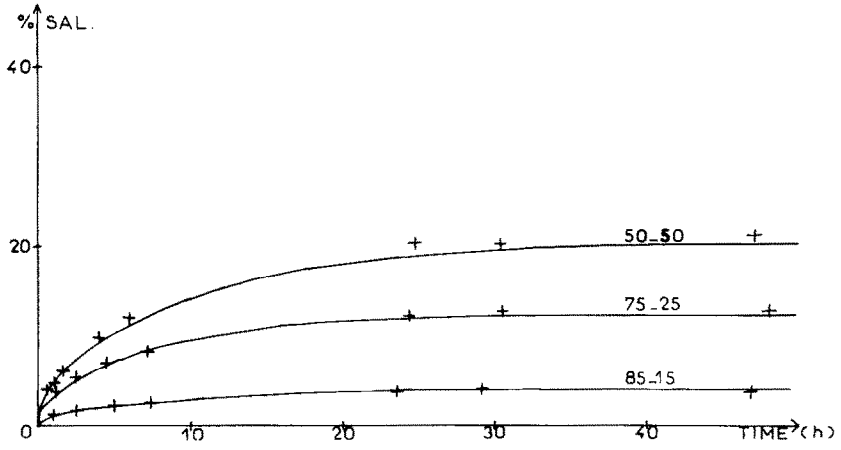


Fig. 5. Validity of the model for transfer of sodium salicylate. 37°C. ———, calculated; +, experimental.

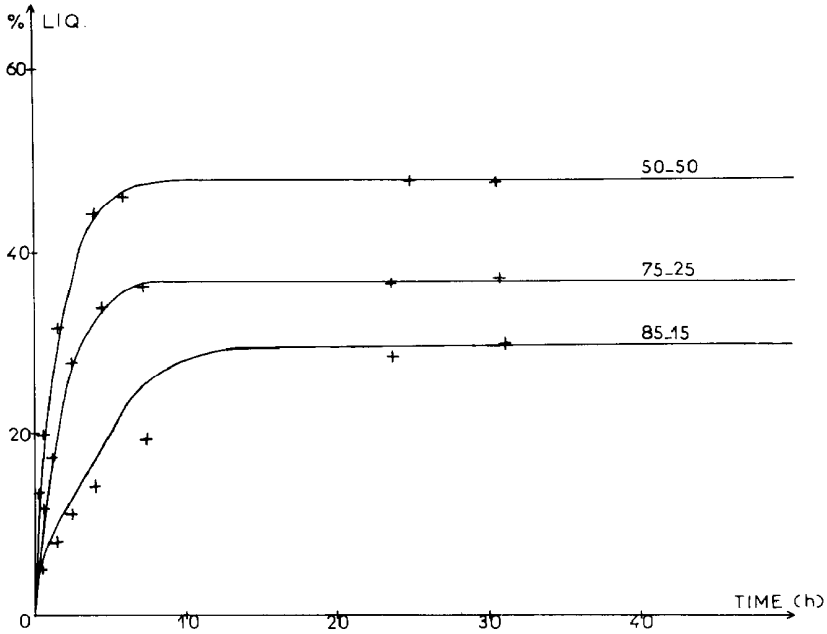


Fig. 6. Validity of the model for transfer of liquid. 37°C. ———, calculated; +, experimental.

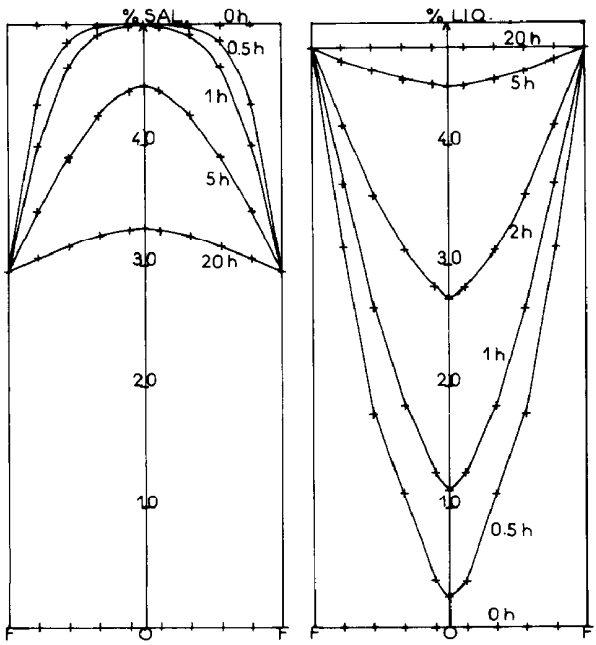


Fig. 7. Profiles of concentration of liquid and sodium salicylate throughout the sheet thickness (calculated). Initial concentration of sodium salicylate: 50–37°C; 0.022 cm thick.

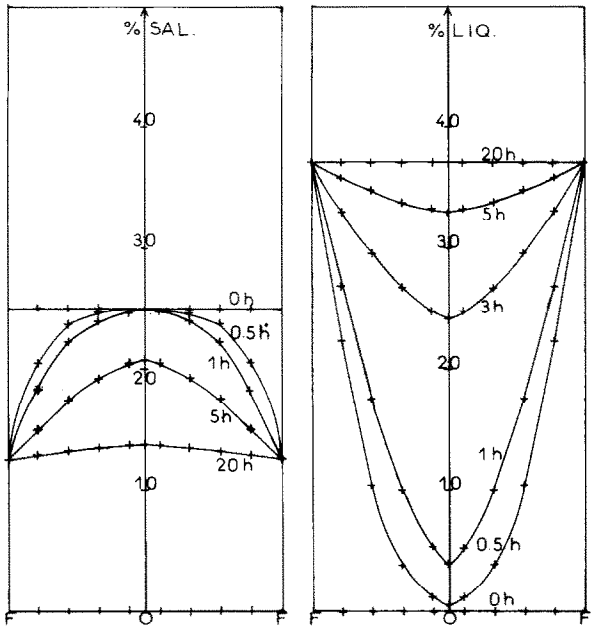


Fig. 8. Profiles of concentrations of liquid and sodium salicylate throughout the sheet thickness (calculated). Initial concentration of sodium salicylate: 25–37°C; 0.022 cm thick.

The profiles of concentration of liquid and sodium salicylate can be seen, as they were developed through the sheet thickness as a function of time, for various concentrations of sodium salicylate in the matrix: Fig. 7 for 50% and Fig. 8 for 25%.

## Conclusion

The drug release mechanism has been elucidated when sodium salicylate–Eudragit mixtures with various concentrations were soaked into synthetic gastric liquid. Simultaneous diffusion of the liquid into, and the previously dispersed drug out of the polymer sheet were observed. Moreover, the polymer matrix swelled without disintegration or attrition during the process. Both transfers were explained by transient diffusion, and diffusivity was found to be constant for the drug, and concentration-dependent for the liquid.

A model using a numerically explicit method with finite differences previously described for studying simultaneous transfers between liquid and plasticized PVC has, with very good results, been applied to the determination of transfer rate of both materials in this case. The diffusivity for the liquid was found to depend on the total concentration of liquid and drug in polymer matrix. The model is able to take into account various laws for diffusivity and amounts of materials transferred at equilibrium, and it can be used for various sizes and shapes of the controlled-release drug device.

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