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MODELLING OF CONTROLLED DRUG-RELEASE IN CASE OF CARBOPOL-SODIUM SALICYLATE MATRIX IN GASTRIC LIQUID

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ABSTRACT

Sodium salicylate in various concentrations in Carbopol matrix, a polymer of acrylic acid, has been tested in synthetic gastric liquid for determining matter transfers controlled by transient diffusion. The liquid enters the polymer with a large swelling as a result, dissolves the drug which is then extracted from the matrix. Concentration-dependent diffusivities are found for these transfers. Modelling of these transfers using an explicit numerical method with finite differences is described. Profiles of concentrations of both materials throughout the matrix are determined. By integrating these results, matters transferred as a function of time have been calculated, giving results in good agreement with experiments.

INTRODUCTION

Optimization of conventional agent delivery to maximize agent availibility with a minimum amount of the drug can be realized by

the repeated application of small increments of the total dose. Obviously continuous applications of drugs by conventional drug delivery systems are impractical. However, the method becomes practical and highly promising when is considered a new type of dosage form consisting of a protected supply of drug form which the drug is automatically released at a controlled rate over a long period of time. Several polymeric controlled release devices have been developed (1-3);

i : reservoir devices where active agents form a core surrounded by an inert diffusion barrier

ii : devices where the active agent is bound to a polymer backbone

iii : monolithic devices where the agent is dispersed in an inert matrix. Both biodegradable and nondegradable polymers can be used (3-6).

In the last case, several theories have been put forward in order to explain the dissolution process. Very often they are built on a combination of hydrodynamic and diffusive effects (7-10), explaining the square root law of time dependence with the amount of drug transferred. In previous works (11-14) we pointed out that modelling for matter transfers through plasticized PVC-liquid interface could be of interest, allowing some additional knowledge on the profiles of concentration of matters developed throughout the polymeric matrix. It was shown that two matter transfers take place simultaneously : the liquid penetrates the matrix and dissolves the additives which then diffuses out into the exterior liquid.

The purpose of this paper is to work on tablets containing different concentration of sodium salicylate dispersed in Carbopol 934 as polymeric matrix. Carbopol has shown promise in pharmaceutic tableting where it controls release of the medicament (15). Tablets having Carbopol 934 as binder exhibit several advantages : hardness, palatibility, strength, stability. Moreover, the Carbopol residue is not absorbed in the body and passes through unchanged. For the purpose of derivation, thin sheets of material are considered, and

soaked into synthetic gastric liquid. Both transfers of liquid into, and drug out of the slab are studied, and diffusivities are determined from the square root time dependence with amounts of both matters transferred. The method previously described has with very good result been applied to the determination of dissolution rates from disintegrating discs of sodium salicylate. Carbopol in synthetic gastric liquid. To get insight into the mechanism, our mathematical model has been applied to the study of the drug release kinetics into the liquid. This model is also of interest, allowing to enhance the range of applicability for the results obtained.

EXPERIMENTAL

Sodium salicylate and Carbopol 934 P (FB Goodrich) have been used as drug and polymer matrix, respectively. Carbopol is a polymer of acrylic acid, and Carbopol 934 P is a material of high purity with a molecular weight around 3.000,000. Both of these materials in powder form have been mixed in a mortar. Sheets were obtained from a steel mold operated by a press at 120°C under a pressure of 180 bars, after a 6 min. heating. Several tablets (2 cm. in diameter, and 0.016 cm. $\pm$ 0.002 for the thickness) have been cut from the sheets.

Experiments have been conducted in closed flashs using a controlled rate of stirring, because the stirring of liquid was shown to be of interest (16). The tablet (250 mg) located in fiber glass basket, is soaked in synthetic gastric liquid (100 ml) at 37°C. The liquid (pH = I.2) has the following composition : 80 ml HCl 1 N, 2 g. Na Cl for 1000 ml of aqueous solution.

Sample of liquid is taken at interval for analysis of sodium salicylate and the tablet is weighed for determining the amount of liquid in polymer matrix. The amount of sodium salicylate released from the polymer device is measured by using UV-spectrophotometry (DB-G Beckman) at 300 nm.

For calculation, 9 slices are considered with an increment of space of about 0.02 cm. and increment of time of 180 s. The modulus for the liquid and drug is higher than 3, so that convergence is easily obtained in calculations. The profiles of concentration developed through polymer sheet are calculated for the liquid and drug, as well as the amount of both these materials transferred through the liquid-polymer interface.

METHOD OF CALCULATION

Two simultaneous diffusions take place : the liquid penetrates the polymer, dissolves the drug which then diffuses out into the liquid. Both transfers are assumed to be governed by Fickian laws of transient diffusion. Some other assumptions are made :

- One-dimensional diffusion is considered through the thin sheet of material.
- Both transfers are controlled by transient diffusion with concentration-dependent diffusivities.
- The concentration at equilibrium is obtained for the liquid and drug on sheet faces as soon as the sheet is soaked into the liquid.

Classical equation of diffusion with the above-mentioned conditions cannot be solved (17).

However for short times, because the amount of substance M_t at time t is small and the local concentrations within the sheet may be assumed to be constant, the amount M_t is expressed as a function of the quantity M_∞ transferred at equilibrium by the single equation :

$$(1) \qquad \frac{M_t}{M_\infty} = \frac{4}{L} \left(\frac{D \cdot t}{\pi} \right)^{0.5}$$

where D is the diffusivity of the substance and L the thickness of the sheet.

The problem has been solved by using an explicit numerical method with finite difference. Fig. 1 shows a cross section of the sheet of thickness L, having a uniform cross-sectional area ; the solid is divided into a number of equal finite slices of thickness Δx by concentration-reference planes. The matter balance written on the plane n allow one to obtain the concentration for the liquid and drug as follows :

Liquid in polymer matrix

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

with the unidimensional modulus M as a funtion of increments of space Δx and time Δt

$$(3) \quad M^{l}_{n,i} = \frac{(\Delta x)^2}{\Delta t} \cdot \frac{1}{D^{l}_{n,i}}$$

and

$$(4) \quad D^{l}_{n,i} = \exp \left(- \frac{13.8}{V^{s} + \beta . V^{l}} - 14.74 \right)$$

V^{s} and V^{l} being the volume fraction of drug and liquid transferred.

Drug in Polymer Matrix

We have also for the drug

$$(5) \quad C^{s}_{n,i+1} = \frac{1}{M^{s}} \left[C^{s}_{n+1,i} - (M^{s}_{n,i} - 2) C^{s}_{n,i} + C^{s}_{n-1,i} \right]$$

with

$$(6) \quad M^{s}_{n,i} = \frac{(\Delta x)^2}{\Delta t} \cdot \frac{1}{D^{s}_{n,i}}$$

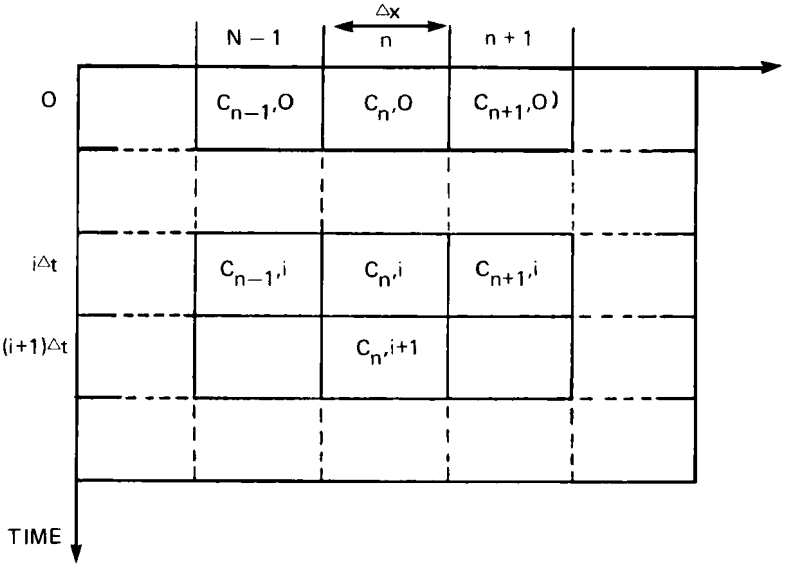

Fig. 1 : Diagram for concentration-time references.

and

$$(7) \qquad D^{s}_{n,i} = D_o \left(1 + \frac{V^{l}}{V_l + V_s}\right)$$

V_l and V_s being the volume of liquid and drug in volume unit of polymer matrix.

Amount of matter transferred

The amount of matter transferred between the liquid and sheet up to time t are obtained by summing the above-mentioned concentrations with respect to space :

$$(8) \qquad M_i = \frac{1}{N}\left[C_{o,i} + \sum_{n=1}^{N-1} C_{n,i}\right]$$

$C_{o,i}$ being the concentration of material on sheet faces.

RESULTS AND DISCUSSION

After soaking in synthetic gastric liquid, polymer tablets containing sodium salicylate swell progressively maintaining their shape for times lower than about 1 hr, and then become gelatinous and undergo attrition. The higher the initial concentration of polymer in the tablet, the higher the swelling. These results are illustrated in Fig. 7 and Fig. 6 showing that the amount of liquid transferred in polymer matrix is largely higher than that of drug transferred into the liquid.

Fig. 2 shows that the amount of drug transferred into the gastric liquid is linearly proportional to the square root of time, with an increase in the shope of these curves at about 2 hr.

In the same way, Fig. 3 proves the square root of time dependence of matrix formulations with the amount of liquid which has entered the polymer. The values of the slopes of these straight lines obtained in Fig. 2 and Fig. 3, as well as the values of the amount of matter transferred at equilibrium shown in Fig. 6 and Fig. 7 allow the calculation of diffusivity for tne liquid and drug, by using eq. 1.

The values of diffusivity for the liquid in the logarithm form is found to be proportional to (drug concentration in polymer matrix)$^{-1}$ in Fig.4 for various drug concentrations throughout 15-20 % range. The diffusivity for the drug does not follow the same law, and it can be expressed by eq. 7 as a function of the volumes of liquid and drug located per unit volume of polymer matrix. Values for diffusivities at the beginning of the process as well as amounts of matters transferred at equilibrium are cited in Table 1 for samples of various compositions. The diffusivity for the liquid can be expressed as a function of concentrations of drug and liquid in the polymer matrix by eq. 4, where these concentrations depend on the time and position in the matrix. The best results obtained for the simulation are obtained when the value given for the coefficient in eq. 4 is 1, showing in this case that liquid and drug play the same role for calculation.

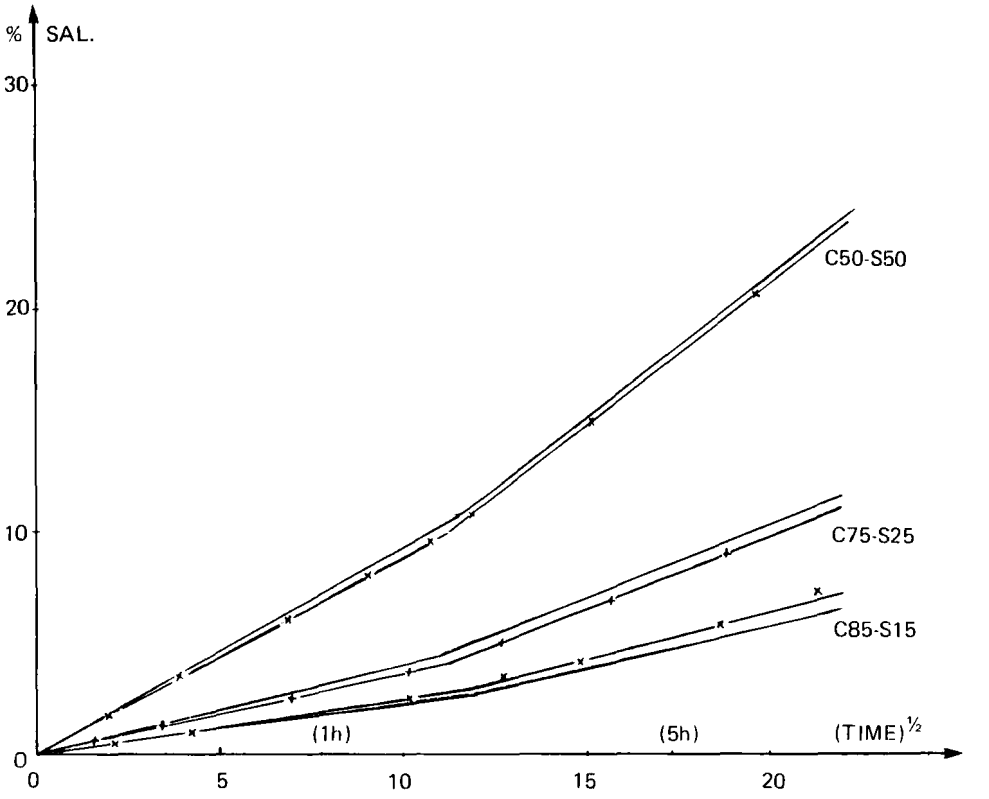

Fig. 2 : Amount of Na Sal. transferred vs. square root of time, for various matrix compositions.

Mathematical simulations undertaken simultaneously for the drug and liquid by using the model and above-mentioned equations allow directly the determination of the profiles of concentration of the drug and liquid developed throughout polymer matrix at various times. Some profiles are illustrated in Fig. 5 while the initial concentration of the drug in the matrix is 25 %. It is not easy to verify by experiments these theoretical results, as proved in a previous paper concerned with plasticizer PVC contacted with benzylic alcohol (11).

However, the validity of mathematical simulations undertaken by using the above-described model can be appreciated by comparing

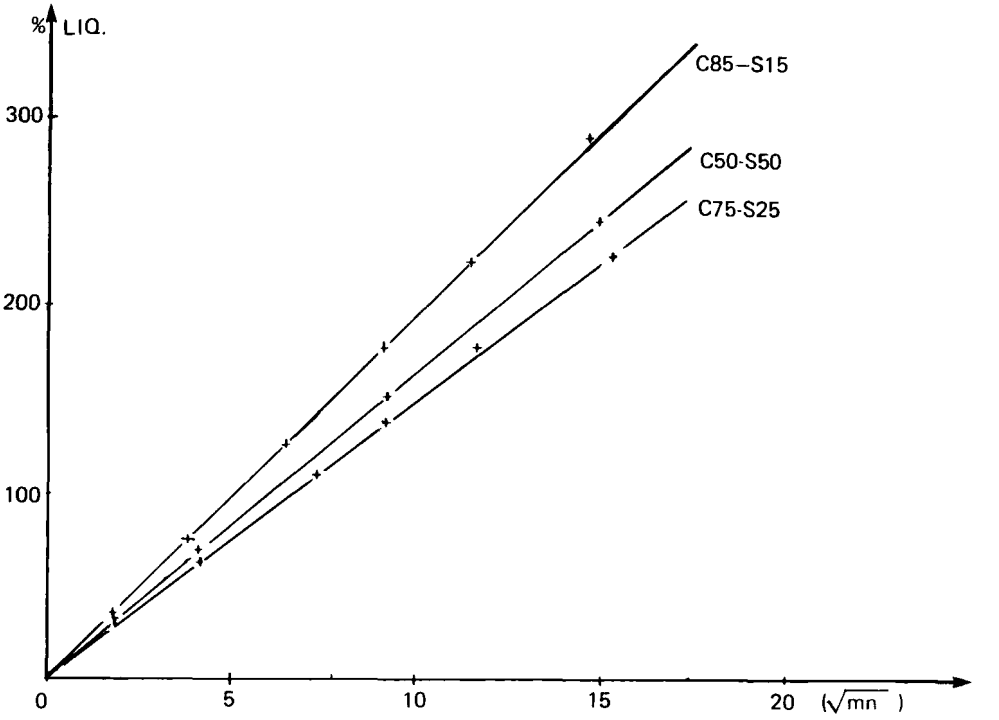

Fig. 3 : Amount of liquid transferred vs. square root of time, for various matrix compositions.

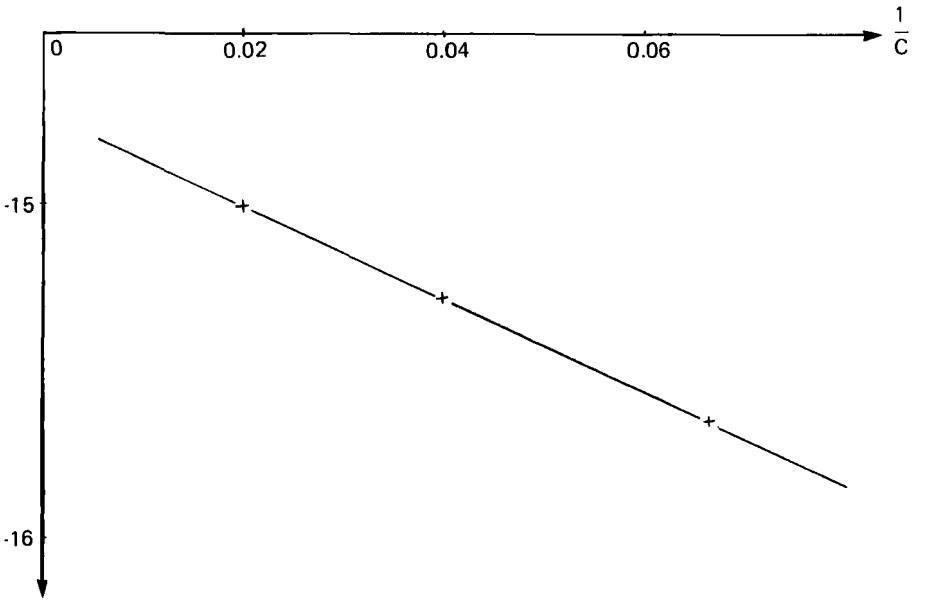

Fig. 4 : Log. of Diffusivity for liquid as a function of (Na Salicylate conc. in matrix)$^{-1}$.

TABLE 1 : Diffusivities and amounts transferred at equilibrium.

Compound	$D^{l}.10^{8}$ (cm^2/s)	M^{l}_{∞} (%)	$D^{s}.10^{8}$ (cm^2/s)	M^{s}_{∞} (%)
Car50-Sal50	16	235	3,3	38
Car75-Sal25	23	315	3,6	19
Car85-Sal15	30	500	6,7	7,5

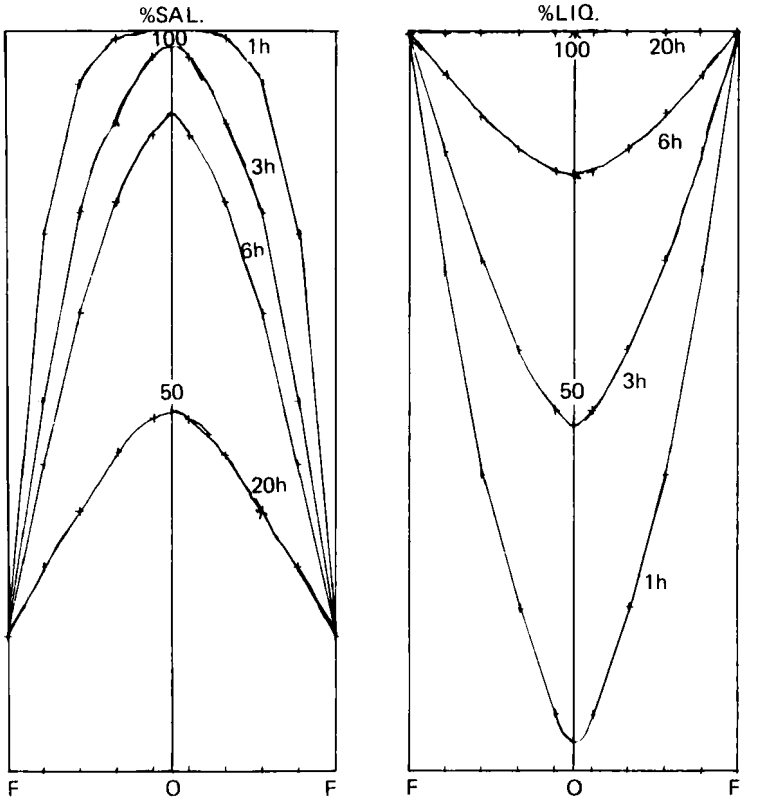

Fig. 5 : Profiles of concentration developed though the matrix sheet. Left : Na Salicylate - Right : liquid.

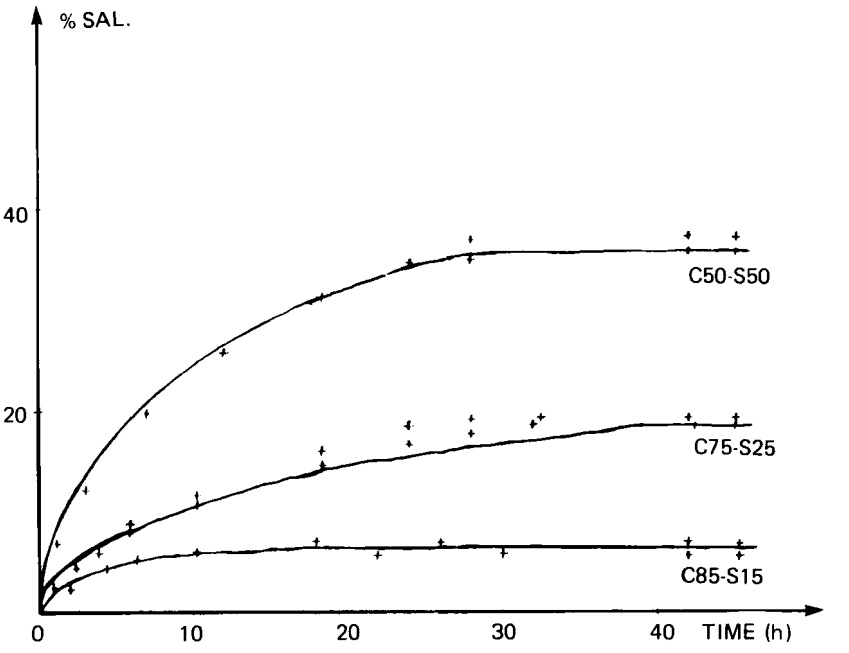

Fig.6 : Amount of Na Sal. transferred as a function of time.
_____ : calculated + : experimental.

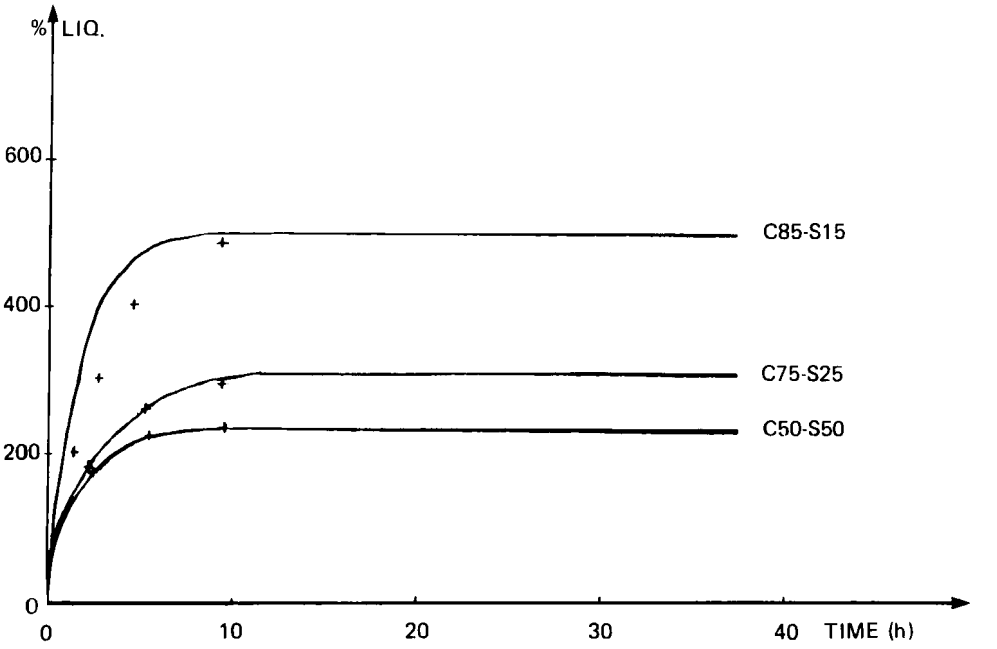

Fig. 7 : Amount of liquid transferred as a function of time.
_____ : calculated + : experimental.

the calculated values with the experimental ones for matters transferred through the liquid-matrix interface. Fig. 6 and Fig. 7 bear out the good agreement between theoretical and experimental amounts of matter transferred at different times and for various concentrations of drug in polymeric matrix.

CONCLUSIONS

These studies carried out with thin sheets of various concentrations of sodium salicylate pressed into Carbopol matrix in synthetic gastric liquid have got insight into the phenomenon of matter transfers. Both transfers of liquid and drug take place with a swelling of the matrix and drug release in the liquid as the result. These matter transfers are controlled by transient diffusion with concentration-dependent diffusivities.

In order to enhance these studies and obtain results able to give industrial applications for controlled-drug release, a model describing these phenomena has been described. This model gives calculated results in good agreement with experiments. So it is able to predict by calculation the rate of matter transferred in other various cases with different shapes and sizes of the matrix.

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