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Effect of pH on drug release between sodium salicylate–Eudragit compound and gastric liquid: modelling of the process

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Summary

The effect of the pH of synthetic gastric liquid on drug release has been studied by soaking sheets made of sodium salicylate previously dispersed in a polymer matrix. Eudragit RS plays the role of polymer and binder. The liquid enters the polymer and dissolves the drug, and then the drug is released into the liquid. Both these transfers are controlled by diffusion under transient conditions, and diffusivity is concentration-dependent. The value of the pH of the synthetic gastric liquid was found to be of great importance for the diffusivities and the amount of matter transferred at equilibrium. The model described was used verify the rate of matter transferred for various values of pH ranging from 1.2 to 7. A law accurately described variation of diffusivity with the pH of the liquid. Profiles of concentration of drug and liquid were calculated for various pH values.

Introduction

There are two ways to improve the care of the sick: the development of better drugs, and a more effective use of existing drugs. Developments in drug delivery will be possible by the simultaneous development of the two fields of knowledge — pharmacokinetics and the technology of more effective drug delivery. The development of therapeutic systems that release a controlled amount of drug over a defined time represents a significant pathway for optimizing drug effects through galenic measures. Therapeutic systems offer especially important advantages over traditional dosage forms in diseases requiring a constant drug level over prolonged durations of therapy: such dosage forms can decrease the total daily drug dosage and allow for the reduction of side-effects; uniform drug levels are achieved and the therapy is optimized.

Several polymeric controlled release devices have been developed (Heilman, 1984; Heller, 1984; Feijen, 1984); namely, (i) reservoir devices where active agents form a core enveloped by an inert barrier allowing diffusion; (ii) devices with the active agent bound to the polymer backbone; and (iii) devices where the active agent is previously dispersed in a polymeric matrix (Heller, 1984; Focher et al., 1984; Fessi et al., 1982; Touitou and Donbrow, 1982).

As the present paper was especially concerned with this last device, it is of interest to examine the various theories which were previously put forward to describe the dissolution process with

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drug–polymer compounds. Very often these theories were built on diffusive effects explaining the square-root law of time dependence with the amount of drug transferred, at least for the beginning of the process (Nicklasson et al., 1985; Gurny et al., 1982; Teillaud and Pourcelot-Toubeau, 1984; Brossard et al., 1983; Touitou and Donbrow, 1982; Peppas, 1985; Peppas and Segot-Chicq, 1985; Tojo and Chien, 1984; Higuchi, 1961; Higuchi, 1963; Crank, 1975). Some workers assumed that pseudo-steady-state conditions would exist during the extraction process, and that a sharp linear concentration front for the drug and the liquid was formed between the extracted part and the untouched portion. Of course, the process was described by moving boundary conditions. Under pseudo-steady-state conditions, the total amount of drug release per unit time is then given by Fick's first law (Higuchi, 1961; Higuchi, 1963; Lee, 1980; Higuchi et al., 1983). Following these assumptions, by differentiating Fick's first law, several studies were done when no swelling takes place. Other studies were done in the same way in order to find solution when the liquid is responsible for a swelling of the polymer (Peppas, 1984; Peppas et al., 1980). In a few studies, some attempts were made in order to find solutions expressed in the same form as for the kinetics of a single reaction with a reaction order (Peppas, 1985; Peppas and Franson, 1983). These above studies, as well as the result obtained with the dissolution in hexane of Red Sudan previously dispersed in polystyrene (Hopfenberg and Hsu, 1978), laid the way for further works looking for drug–polymer matrix able to give drug transfers following a zero-order kinetic with a constant rate of drug release (Peppas, 1984; Teillaud and Pourcelot-Roubeau, 1984; Peppas and Segot-Chicq, 1985). In all these above studies, only the drug transfer was considered and the diffusivity was assumed to be constant. However, other studies reported some results on simultaneous transfer of the liquid into, and plasticizer out of a plasticizer PVC when the plasticized PVC was contacted with different kinds of liquids (Messadi and Vergnaud, 1981; Messadi et al., 1983). In a previous paper (Droin et al., 1985), concerned with sodium salicylate embedded in Eudragit playing the role of matrix, both transfers were shown as follows: the liquid penetrates the matrix and dissolves the drug, which then diffuses out into the exterior liquid. The same results were obtained by using the same drug and Carbopol as polymer matrix, with in addition a large swelling of the polymer followed by a disintegration of the compound (Malley et al., in press). In both these studies, modelling of the process was achieved by using diffusivities for the two transfers.

The main purpose of this present paper is to show that both transfers of the liquid and drug can be studied when diffusivities are concentration-dependent, for various values of pH of synthetic gastric liquid. Sheets composed of sodium salicylate and Eudragit RS were produced by pressing powder mixtures of these components, Eudragit RS playing the role of binder. Eudragit was proved to exhibit mechanical properties of interest such as hardness and stability, and it can be used in human studies because it is not absorbed in the body and passes through unchanged (Hecht et al., 1966). Diffusivities for both transfers were determined by using the method with "short tests" described previously for the matter transfers taking place between plasticized PVC and various liquids (Taverdet and Vergnaud, 1984). The dependence of diffusivities on the concentrations of drugs was measured by using several samples of various concentrations of drug ranging from 15 to 50 (weight %) (Droin et al., 1985; Taverdet and Vergnaud, 1984).

Modelling of the process for various values of the pH of gastric liquid was another purpose in this study. Models taking into account the simultaneous diffusion of the liquid into, and the previously dispersed additive out of the polymer matrix, were successfully applied to the case at hand (Taverdet and Vergnaud, 1984; Taverdet and Vergnaud, 1986). This model, based on an explicit numerical method with finite differences, described both these matters transferred by diffusion under transient conditions. It used some data obtained from experiments, as the dependence laws of diffusivities with drug and liquid concentrations and amounts of liquid and drug transferred at equilibrium.

Theoretical

Assumptions

The following assumptions are made.

(i) A thin sheet of drug–polymer matrix is used so that only one-dimensional diffusion is considered.

(ii) Matters are transferred under transient conditions, and the diffusivities are determined as a function of the concentration by using short tests and Eqn. 2.

(iii) The concentration of the drug and liquid on both sheet faces reaches the value at equilibrium as soon as the sheet is soaked into the liquid. These values at equilibrium are obtained by using long tests. So the drug concentration on sheet faces is not zero, as it is often assumed in order to find an analytical solution of the equation of diffusion (Crank, 1975; Vergnaud, 1983).

Mathematical treatment

With the above conditions, the equation of diffusion through a sheet:

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left(D \cdot \frac{\partial C}{\partial x}\right) \tag{1}$$

cannot obtain an analytical solution.

At the beginning of the process and for a short time, the concentration throughout the sheet may be considered as constant, so that the amount of matter transferred M_i after the time $i\Delta t$ can be expressed as a function of the quantity M_∞ obtained at equilibrium

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

D being the diffusivity obtained with the initial concentration of drug and liquid, at time 0 when the sample is soaked into the liquid, and L is the thickness of the sheet.

Eqn. 1 cannot be solved with the boundary conditions expressed by the third assumption, and concentration-dependent diffusivities.

Numerical analysis and modelling

The problem was solved by using a numerical explicit method with finite differences.

As shown in Fig. 1, the cross-section of the sheet is divided into n equal slices of finite thickness Δx by concentration-reference planes (n = space; i = time). The balance written on the plane n enables one to obtain the following equation for the drug and the liquid:

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

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

The dimensionless numbers M^d and M^s are expressed as a function of the diffusivities and the increments of space and time

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

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

The general expressions for the diffusivities are

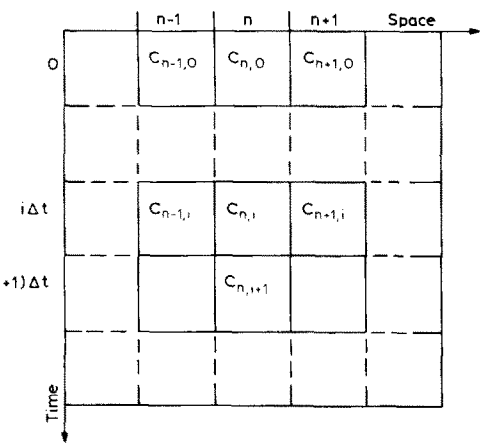

Fig. 1. Diagram for concentration–time references.

as follows:

$$D^l_{n,i} = \exp\left(- \frac{A_l}{C^d_{n,i} + C^l_{n,i} \cdot a_l} - B_l \right) \quad (5)$$

$$D^d_{n,i} = \exp\left(- \frac{A_d}{C^d_{n,i} + C^l_{n,i} \cdot a_d} - B_d \right) \quad (5')$$

In all these expressions, $C^l_{n,i}$ and $C^d_{n,i}$ are the concentration at the plane n and time $i\Delta t$ for the liquid and the drug, respectively.

The third assumption enables one to write the following conditions, for $i > 0$.

$$i > 0 \qquad C^l_{0,i} = C^l \qquad \text{at equilibrium} \quad (6)$$

$$i > 0 \qquad C^d_{0,i} = C^d \qquad \text{at equilibrium} \quad (6')$$

The amount of matter transferred at time $i\Delta t$ is obtained by summing the concentrations of all the planes through the sheet thickness determined at this time.

$$M_i = \frac{1}{n}\left[C_{0,i} + \sum_{1}^{n-1} C_{n,i} \right] \quad (7)$$

Experimental

Drug–polymer matrix

Eudragit RS (copolymer of dimethylamino-ethylacrylate and ethylmethacrylate with PM = 150,000 Röhm Pharma) was used as polymer matrix and sodium salicylate for the drug. These materials in powder form were mixed with great care, and then 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 of 1.9 cm in diameter and 0.024 cm in the thickness were cut from the sheets.

Measurements of matter transfers

The tablet of about 250 mg previously inserted in a basket of fiber glass, was soaked into synthetic gastric liquid (100 ml) maintained at a constant temperature (37°C) and at a controlled rate of stirring.

Samples of liquid were taken at regular times for analysis and the tablet was weighed. The amount of drug released from the tablet was measured by using a double-beam UV-spectrophotometer calibrated at 300 nm (Beckman DB-G).

Various compositions were prepared for the liquid in order to have several pH values.

Results

As this paper is especially concerned with the effect of the value of pH of synthetic gastric liquid on matter transferred between this liquid and a galenic form, we have experimented with several tablets of the same composition (Eudragit 75–sodium salicylate 25, those percentages being expressed in weight %) in the same operational conditions but with various values of pH for the liquid. The values chosen for the pH of liquid ranged from 1.9 to 7.4.

Experimental results for matter transfers

The amount of liquid transferred into the galenic form is plotted against time in Fig. 2 for various pHs within the 1.9–7.4 range. As shown in these curves, the behavior of the liquid is quite

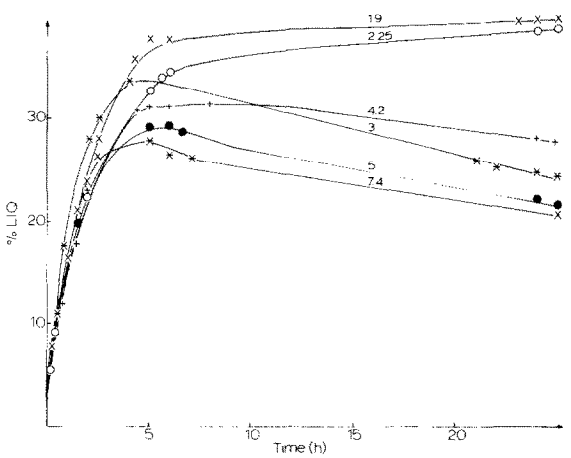

Fig. 2. Amount of liquid transferred into the matrix as a function of time, for various pH. Eudragit–sodium salicylate (75 : 25).

different according to the pH value. For instance, the amount of liquid transferred increases regularly with time for the lower values of the pH (1.9–2.25). But for the higher pH values the amount of liquid transferred increased with the time, and then decreased passing through a maximum. The value of this maximum varied with the pH of the liquid. On the whole, it is seen that the higher the pH, the lower the maximum for the amount of the liquid transferred.

As shown in Fig. 3, the amount of drug transferred from the galenic form into the liquid increased regularly with time, for the various values chosen for the pH of the liquid. The value of the pH had an effect on the drug transfer; the higher the pH, the larger the amount of the drug transferred.

In order to obtain the values of diffusivity for the liquid and drug, the amounts of liquid (Fig. 4) and drug (Fig. 5) transferred were expressed as a function of the square-root of time, respectively. Straight lines can be plotted in all cases, demonstrating a diffusional process.

By using the data shown in Figs. 4 and 5, it is easy to calculate the values of diffusivity with the help of Eqn. 2, if the values of the amount transferred at equilibrium are available. If there is no special problem for determining the amount of drug at equilibrium, it is not the same for the liquid. We are able to account for the variation of the liquid with time when it passes through a maximum, as was proved in a previous paper (Taverdet and Vergnaud, 1986). In the present study, two different values can be chosen for the value of the amount of liquid transferred at equilibrium: (i) the value obtained for a long time, by considering the decrease in the amount of liquid with the time, when a maximum occurs; and (ii) the maximum value of the liquid transferred.

As the solution given in the previous method (Taverdet and Vergnaud, 1986) is rather complex, and the effect of the liquid is very important on the drug transfer especially for the first 6 h, we

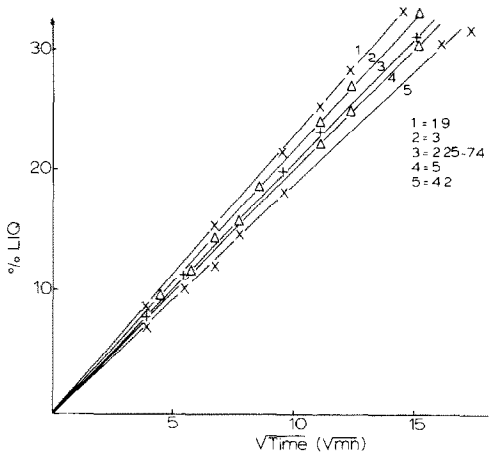

Fig. 4. Amount of liquid transferred as a function of $(\text{time})^{0.5}$, for various pHs.

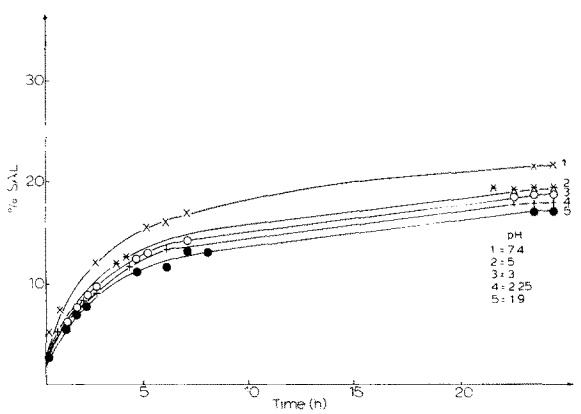

Fig. 3. Amount of drug transferred into the liquid as a function of time, for various pHs. Eudragit–sodium salicylate (75 : 25).

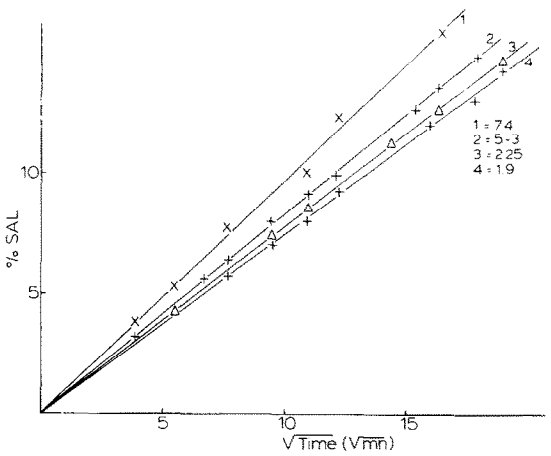

Fig. 5. Amount of drug transferred as a function of $(\text{time})^{0.5}$, for various pHs.

have chosen to use a more simple method which gave us good results (Manoussaki et al., 1985).

Variation of diffusivities with the pH of liquid

The values obtained for diffusivities in various cases are shown in Table 1 for the liquid and drug.

The variation of the diffusivity of the drug with the pH of the liquid has been shown in Fig. 6 by plotting pH · log D as a function of pH. The straight line obtained allows one to fit the following equation for this variation:

$$D_{drug} = 2.5 \times 10^{-7} \cdot \exp - \frac{0.3}{pH} \ (cm^2/s) \qquad (8)$$

As shown in a previous paper (Droin et al., 1985), the diffusivity for the drug transfer does not depend on the concentration of drug or liquid in the polymer matrix.

The diffusivity of the liquid transfer through the polymer has been found to increase with the pH of the liquid as shown in Fig. 7. The dependence of the pH of the liquid is of great importance for pHs lower than 3, and slightly sensitive for higher pHs. By taking into account the effect of both these factors, the concentration and pH, the following expression was found to express the variation of the diffusivity

$$D_{liquid} = 1.48 \times 10^{-6} \times (\exp 0.129 \ pH) \times \left(\exp - \frac{40.1}{C_s + C_1}\right) (cm^2/s) \qquad (9)$$

TABLE 1

DIFFUSIVITIES (10^8 cm^2/s) AND M_∞ WITH pH

pH	D_{liquid}	D_{drug}	$M_{\infty liquid}$	$M_{\infty drug}$
1.2	37.5	15.2	48	13
1.9	37.9	21.2	40.3	18
2.25	38	22	39.3	18.2
3	55.8	22.5	34	19.4
4.2	99.8	22.8	32	20
5	104	23.1	29.5	20.4
7.4	131	23.6	28	21.8

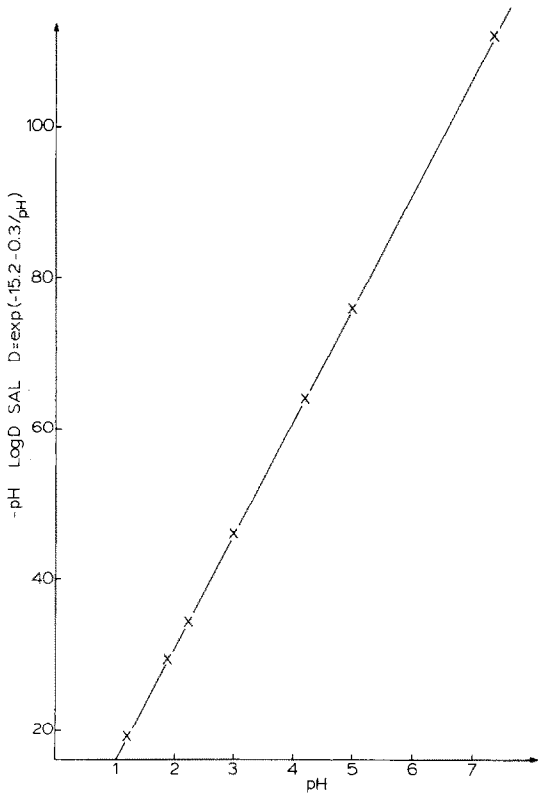

Fig. 6. pH·log D for drug as a function of pH of liquid.

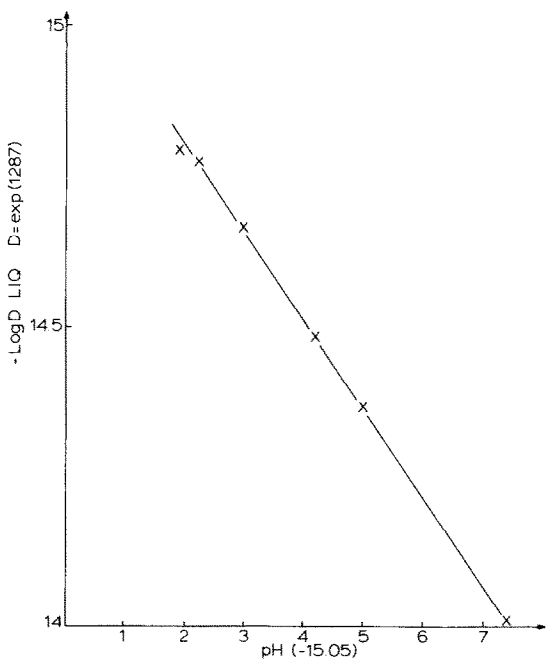

Fig. 7. Diffusivity for liquid as a function of its pH.

Another result of interest is concerned with the amount of matter transferred at equilibrium, and its variation with pH. As shown in Fig. 8, the increase in pH from 1.8 to 7 was responsible for an increase in the amount of drug transferred at equilibrium and a decrease in the corresponding amount of liquid.

Modelling of the process

Modelling of the process has been obtained by using the above numerical analysis in the case of experiments with a constant value for the pH. As shown in Fig. 3 for the drug, and in Fig. 9 for the liquid, the theoretical results are in good agreement with the experimental ones for various values. In every case, the pH of the synthetic liquid gastric was kept constant during the experiment.

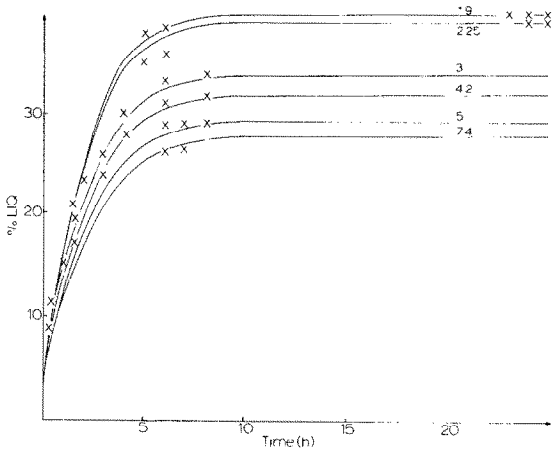

Fig. 9. Amount of liquid transferred as a function of time, for various pHs. ×, experimental; ———, calculated.

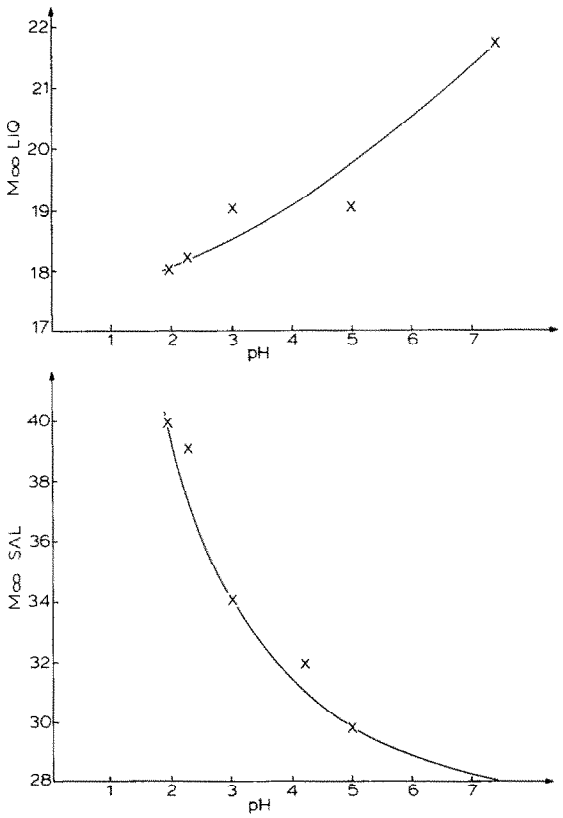

Fig. 8. Amounts of drug and liquid at equilibrium as a function of the pH of liquid.

Conclusions

Galenic forms obtained by distributing the drug (sodium salicylate) in a polymer matrix such as Eudragit were able to give a retarded drug release in synthetic gastric liquid for about 7 h. Simultaneous transfers of the liquid into and the drug out of the polymer matrix were observed. They are controlled by diffusion under transient conditions with concentration-dependent diffusivity for the liquid. So, parameters such as the pH of the liquid are of interest as well as the concentration of the drug in the polymer.

The effect of the pH of the liquid on the rate of both these transfers was specifically studied. Not only the diffusivities, but also the amount of matter transferred at equilibrium was found to vary with the pH. So, the diffusivity for the drug and liquid increased as the pH was increased, but the effect of the pH is more significant for the liquid than for the drug. The effect of the pH on the amount of matter transferred at equilibrium is quite different for the drug and the liquid. While this amount increased with the pH in case of the drug, in contrast is decreased for the liquid.

Models of both these transfers has been ob-

tained with good results by taking into account all these experimental results; in case of constant pH, these values were chosen within a large range (1.8–6). These results pave the way to further modelling experiments for more complicated processes obtained with the pH varying with time according to various laws.

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