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Modelling of drug release in gastric liquid from spheric galenic forms with Eudragit matrix

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Summary

Drug release from spheric galenic forms into synthetic gastric liquid was experimentally and theoretically studied, when these galenic forms were made of sodium salicylate dispersed into a biocompatible polymer as Eudragit RS. It was proved that the process followed these steps: the liquid entered the polymer provoking a swelling, dissolved the drug, and then provoked the transfer of the drug out of the galenic form. Both these transfers were found to be controlled by transient diffusion. When the concentration of drug in the polymer matrix was varied within the range of 40–50 wt. %, the diffusivity of the drug was found to depend largely on the concentration of the liquid. The model was successfully tested for various sizes of the galenic form and various concentrations of drug. The effect of the size of the spheric beads appeared to be a parameter of interest for controlling the kinetics of release of drug.

Introduction

On the basis of Ehrlich's key-lock theory, the formula of "drug equals therapy" arose. In fact, this statement ignores the principle that a bioactive substance becomes an effective drug only when properly formulated (Heilmann, 1984). The enormous efforts of the industry to synthesize new agents have contrasted with the relatively modest efforts to utilize the available technology to improve the drug administration. Zaffaroni (1970) recognized this need and developed the concept of programmed or rate-controlled drug administration. Thus, in place of conventional dosage forms responsible for a high drug concentration–time peak, these systems, rationalizing the delivery of therapeutic agents, could not only enhance the therapeutic regimens of many existing agents, but could also permit treatment with pharmacologically active substances that would not be useful in conventional dosage forms because of their toxicity or short half-lives. In this case, the important specification is not the total dose given but the rate and duration of drug administration. The techniques able to control the drug release have been generally classified into 3 categories based on the mechanism followed by the release of the

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drug from the device (Heilman, 1984; Heller, 1984; Feijen, 1984). These mechanisms are diffusion osmosis and polymer erosion; they cannot always be considered separately, because the drug-release may be controlled by more than one mechanism.

Particular attention has been given to regulating the drug release by means of monolithic devices where the active agent has been previously dispersed in a polymeric matrix (Heller, 1984; Focher et al., 1984; Fessi et al., 1982; Touitou and Donbrow, 1982). Various theories have been put forward in order to describe the process of the release of the drug. Generally, they have been built by combining diffusive and convective effects (Nicklasson et al., 1985), or by considering the diffusive effects corresponding with the square-root law of time dependence with the amount of drug released, this law being especially valuable for the beginning of the process when the concentration of the drug in the liquid is low enough (Touitou et al., 1982; Teillaud and Pourcelot-Roubeau, 1984; Brossard et al., 1983; Peppas and Sergot-Chicq, 1985; Peppas, 1985; Tojo and Chien, 1984; Higuchi, 1961; Higuchi, 1963; Crank, 1975; Gurny et al., 1982). Most if not all the studies have been conducted by considering only the drug transfer with a constant diffusivity for the drug. However, some works have reported results on the simultaneous transfer of the liquid into, and plasticizer out in case of plasticized PVC contacting various kinds of liquids (Messadi and Vergnaud, 1981; Messadi et al., 1983; Vergnaud, 1983). In this way it has been shown that both transfers take place simultaneously when a drug–polymer device is contacted with synthetic gastric liquid: the liquid penetrates the polymer matrix, dissolves the drug which may then diffuse out into the exterior liquid (Droin et al., 1985). Thin sheets of Eudragit (Droin et al., 1985) and of Carbopol (Malley et al., 1987) have been used for these studies, with sodium salicylate as the drug.

A purpose of this paper has been to describe and study the behavior of galenic forms, spherical in shape, prepared by dispersing the drug (sodium salicylate) in the polymer matrix (Eudragit RS) and compressing the mixture. The choice of spheric beads has been made for two reasons at least:

(i) from the theoretical point of view, these forms are easy to study because of their (theoretical) symmetry.
(ii) Because of the interesting effect of the size of these beads per unit of weight on the rate of drug release, as shown in the present paper, industrial applications could be enhanced by encapsulating several beads of various sizes and concentrations of drug in the same sample.

Another purpose of the paper has been to gain a fuller insight into the process of matter transfers and hydrolysis by developing a mathematical model able to account for all the facts and describe the effects of all parameters. Previous works (Droin et al., 1985; Taverdet and Vergnaud, 1984; Taverdet and Vergnaud, 1986) have shown the interest of models based on numerical methods with finite differences in case of thin sheets for the sample. In the present work these models have been applied to the case of spheric beads.

Theory

Before describing the model based on numerical analysis calculation, we have made some assumptions in order to clarify the process and mathematical problems.

Assumptions

The following assumptions have been made on the sample and on the process:

i The samples considered are spherical in shape.
ii The drug is properly dispersed in the polymer matrix.
iii Two transfers take place in the sample: the one concerned with the liquid which enters the polymer, dissolves the drug, allowing the other transfer of the drug out of the sample.
iv Both these transfers are controlled by transient diffusion, and are connected with one another.
v The diffusivities of these transfers are concentration-dependent, these laws being determined by experiments with short tests.
vi As soon as the galenic form has been soaked into the gastric liquid, the concentration of the liquid and drug have attained their values at equilibrium, Ceq, on the surface of the galenic form.

vii The polymer swells (especially at the beginning of the process) and the dimension of the galenic forms increases. A frame of reference fixed with respect to the original galenic form is taken for numerical analysis and calculation (Crank, 1975; Khatir et al., 1986).

Mathematical treatment (See the List of Symbols)

In case of a spherical sample, the matter transfers controlled by transient diffusion and following the Fick's laws with concentration-dependent diffusivities, have been written as follows for each of the matter (drug or liquid).

$$J = D \cdot \frac{\partial C}{\partial x} \tag{1}$$

$$\frac{\partial C}{\partial t} = \frac{I}{r^2} \cdot \frac{\partial}{\partial r}\left[D \cdot r^2 \cdot \frac{\partial C}{\partial r}\right] \tag{2}$$

Following the vith assumption, initial and boundary conditions have been written as follows:

$$t = 0 \quad r < R \quad C = C_{init} \text{ sample} \tag{3}$$

$$t > 0 \quad r = R \quad C = C_{\infty} \tag{4}$$

Analytical solutions of Eqns. 1 and 2 have been found (Nicklasson et al. 1985) in the case of a single matter transfer with constant diffusivity, when the equilibrium is attained on the surface of the sample as soon as the sample is contacted with the liquid.

$$\frac{M_{\infty} - M_t}{M_{\infty}} = \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{I}{n^2} \cdot \exp - \frac{n^2 \cdot \pi^2 \cdot D \cdot t}{R^2} \tag{5}$$

For very short tests, Eqn. 5 has been reduced to the simple following equation:

$$\frac{M_t}{M_{\infty}} \cdot \frac{6}{R} \cdot \left(\frac{D \cdot t}{\pi}\right)^{0.5} \tag{6}$$

Eqn. 6 has been very useful for determining the value of diffusivity when the matter has been transferred for a short time. Under these conditions, the concentration of the matter in the matrix can be considered as constant, and the value of the diffusivity is obtained for this constant concentration in the matrix.

Numerical analysis

No analytical solution can be found in the present case described with the above assumptions, especially because of the two simultaneous matter transfers having moreover concentration-dependent diffusivities.

The problem has been solved by using an explicit numerical method with finite differences.

By considering the spheres with the following radius, $r + \Delta r$, r, $r - \Delta r$, taken in the sample, and by assuming that the concentration of the drug and liquid varied linearly within each interval Δr during the short increment of time Δt (Fig. 1), the matter balance has been written as follows:

Within the sample.

$$CN(j) = C(j) + \frac{\Delta t}{2(\Delta r)^2 \cdot \left(j^2 + \frac{I}{I2}\right)} \cdot [G(j+I) - G(j)] \tag{7}$$

The function $G(j)$ has been expressed by:

$$G(j) = \left(j - \frac{I}{2}\right)^2 \cdot [D(j) + D(j-I)] \cdot [C(j) - C(j-I)] \tag{8}$$

and j has been an integer between 1 and n, defining the values of the radius of the concentric

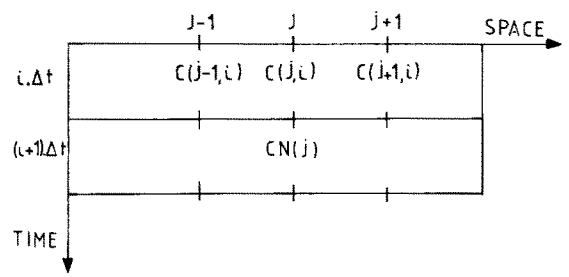

Fig. 1. Scheme for the variation of concentration of matter (drug or liquid) with the space and time (explicit method with finite differences).

spheres considered.

$$r = j \cdot \Delta r \text{ and } R = n \cdot \Delta r \tag{9}$$

Middle of the sample. Because of indetermination of Eqn. 7 in the case of the middle of the sample ($r = 0$), the matter balance has been rewritten for the sphere of radius $\Delta r/2$ located at the middle of the sample.

$$CN(O) = C(O) = 12\frac{\Delta t}{(\Delta r)^2} \cdot G(I) \tag{10}$$

Surface of the sample. Following the vith assumption, the concentration of the drug and liquid have attained their equilibrium on the surface of the galenic form, as soon as this galenic form has been soaked into the gastric liquid.

Amount of drug remaining in the sample. The amount of drug remaining in the sample at time t has been easily obtained by integrating the concentration of drug within the spherical sample:

$$M_t = \int_0^R 4\pi r^2 \cdot C(r, t) \cdot dr \tag{11}$$

By using the finite differences, this expression has been rewritten as follows:

$$M_t = 4\pi(\Delta r)^3 \cdot \left[\frac{C(O)}{24} + \sum_{j=1}^{n-2} j^2 \cdot C(j) + \tfrac{9}{8}(n-1)^2 \cdot C(n-1) + \tfrac{3}{8} \cdot n^2 \cdot C(n)\right] \tag{12}$$

In Eqn. 12, the following contributions to the total amount of drug remaining in the sample can be seen: the small central sphere of radius $\Delta r/2$, the part of the sample located between the spheres of radius $\Delta r/2$ and $R - \Delta r/2$, and the last part between the spheres of radius $R - \Delta r/2$ and R.

Experiments

The materials used in the work as well as the method of preparation of the spherical drug–polymer devices, is described.

Materials

- Na salicylated (COPER) in powder from has been chosen for the drug.
- Copolymer of dimethylaminoethylacrylate and ethylmethacrylate of MN = 150 000 (Eudragit RS. from Röhm Pharma) has been used for the polymer matrix.

These two materials and powder form have been mixed intensively by pressing and mixing them in a mortar. This mixture has been transformed into a homogeneous thick paste, after pulverisation with a small amount of ethanol which is a solvent for Eudragit. Spherical beads of various sizes have been obtained by pressing the paste in a mold, and then drying until complete evaporation of the ethanol (2 days).

Several spheres with the same size (radius 0.43 cm) and various compositions have been prepared and tested in the same way. The percentage of drug in these samples has been as follows: 25 — 40— 50 — 60 — 75 wt. %.

Other spheres with the same composition (50 wt. % of drug) and various sizes (diameters 0.36 — 0.62 — 0.87 cm) have also been prepared and tested.

Determination of parameters of matter transfers

Experiments have been conducted in a closed flask with a quickly rotating bar magnet. The sphere (400–500 mg), inserted in fiber glass basket, are soaked in synthetic gastric liquid (100 ml) at 37 °C, with the following compositions for 1000 ml of aqueous solution:

pH = 1.2: 80 ml HCl 1 N, 2 g NaCl;
pH = 4.7: 6 g acetic acid, 8.2 g sodium acetate;
pH = 7.2: 2.74 g NaH_2PO_4, 10.8 g Na_2HPO_4

At intervals, samples of liquid were taken for analysis and the spheres were weighed. The amount of sodium salicylate released from the polymeric device has been determined using a double-beam UV-spectrophotometer (Beckman DB-G) calibrated at 300 nm.

Calculations

The profiles of concentration of the drug and liquid developed through the spherical device has

been calculated with the help of the model (Eqns. 7 and 10), with the data concerning diffusivities obtained from a short test and with the amount of matter transferred at equilibrium. By integrating the above results, the kinetics of both these matter transfers has also been possible (Eqn. 12).

The number of concentric spheres was 20 and the increment of time 120 s.

Results

Experimental results

The experimental results for the amounts of liquid and drug transferred as a function of time have been shown in various cases: Fig. 2 for drug (50)–polymer (50) spheres of radius 0.435 cm; Fig. 3 for drug (40)–polymer (60) spheres of radius 0.435 cm; Fig. 4 for drug (50)–polymer (50) spheres of radius 0.31 cm. In all these cases, the composition is expressed in wt. %. As shown in these figures, the rate of transfer of liquid is higher than that of drug.

Figs. 5 and 6 illustrate the variation of the drug and the liquid, as a function of the square root of time, for various concentrations of the drug in spheric galenic forms. These curves are of interest for determining the diffusivities associated with the matter transfers, the diffusivity being proportional to the slope of the curves. Two facts have been worth noticing. (i) On the one hand, straight lines have been obtained in Fig. 5 for the liquid, for the various concentrations in drug in galenic forms, and all these straight lines through the origin of the axes. On the other hand, the slopes of the curves (Figs. 2–4) expressing the kinetics of liquid transfer have been found to tend to infinity at the beginning of the transfer, when the galenic forms have been soaked into the liquid. (ii) In contrast with the liquid, the slopes of the curves showing in Fig. 6 the variation of the amount of drug transferred as a function of $(\text{time})^{0.5}$ are not constant at the beginning of the process. Starting with a zero value as soon as the galenic form has been contacted with the liquid, the slope has been found to increase progressively with time and then

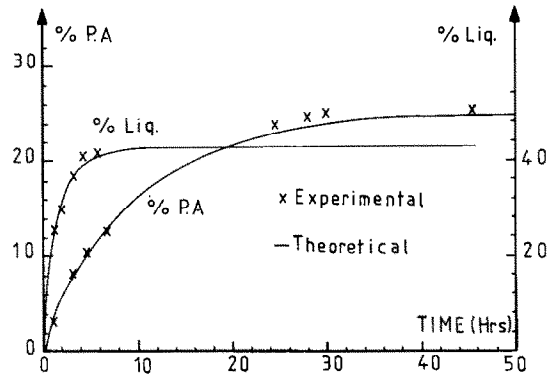

Fig. 3. Kinetics of the matter transferred (liquid, drug). Drug-polymer, 40–60 in weight; radius = 0.435 cm; pH = 1.2; 37 °C.

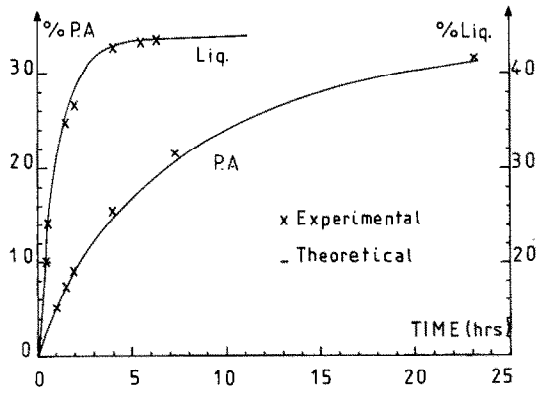

Fig. 2. Kinetics of the matter transferred (liquid, drug). Drug-polymer, 50–50 in weight; radius = 0.435 cm; pH = 1.2; 37 °C.

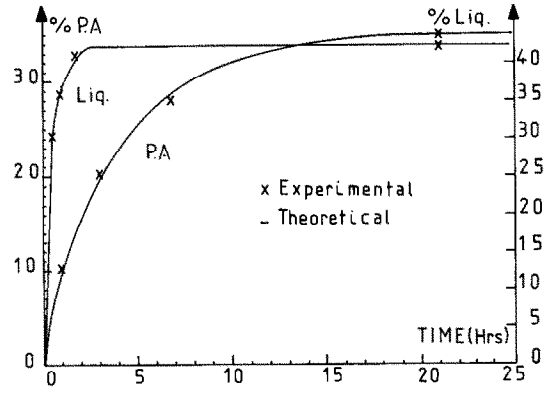

Fig. 4. Kinetics of the matter transferred (liquid, drug). Drug-polymer, 50–50 in weight; radius = 0.31 cm; pH = 1.2; 37 °C.

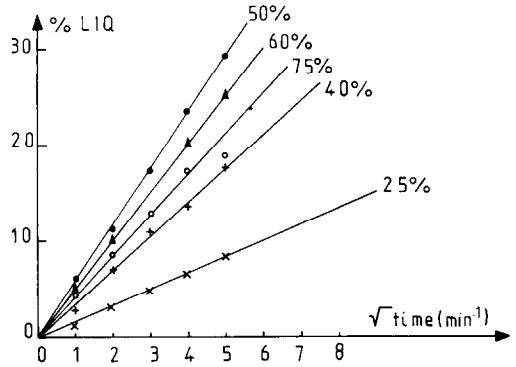

Fig. 5. Gastric liquid (wt. % of initial sphere) transferred as a function of $(\text{time})^{0.5}$, for various initial concentrations of sodium salicylate; pH = 1.2; 37 °C; radius = 0.435 cm.

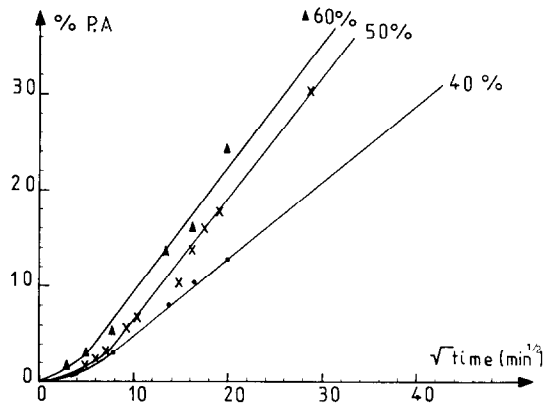

Fig. 6. Sodium salicylate (wt. % of initial sphere) transferred as a function of $(\text{time})^{0.5}$, for various initial concentrations of sodium salicylate; pH = 1.2; 37 °C; radius = 0.435 cm.

to attain a constant value. In agreement with these results, the slopes of the kinetics of drug transferred at the beginning of the process are not infinite in Figs. 2–4.

Conclusions of interest have been drawn from these above results: (i) The process can be described as follows: the liquid enters the galenic form, dissolves the drug, and then the drug transfer takes place. (ii) The transfer of the liquid is controlled by diffusion under transient conditions, as soon as the process is started. (iii) The transfer of the drug is conducted by a more complex process. By assuming that this transfer is controlled by diffusion through the liquid located in the polymer, the diffusivity is zero when no liquid is present in the galenic form, increases with the concentration of the liquid, and then reaches a constant value when the concentration of the liquid has risen to the maximum value.

The value of diffusivities for the liquid and drug, as well as the amount of matter transferred at equilibrium have been shown in Table I.

The data in Table I show that (i) The diffusivity of the liquid is the same for all 3 cases, while the amount of liquid transferred at equilibrium is about the same, around 42–43%. (ii) The diffusivity of the drug is expressed as a function of the concentration of the liquid by the same law for all these 3 cases. (iii) The drug transferred at equilibrium is found to depend largely on the composition of the original form as shown in previous papers (Droin et al., 1985; Malley et al., 1987). (iv) A part of the drug remains in the galenic form at the end of the process, and a partition coefficient can be determined. The partition coefficient has been found to be about the same (6.6–7) for the 3 samples (the partition coefficient is the ratio of the concentration of the drug in the galenic form and in the liquid at equilibrium).

TABLE 1

Diffusivities and amounts of matter transferred at equilibrium

Composition of galenic form	Radius (cm)	Dd (cm^2/s)	Dl (cm^2/s)	Md (%)	Ml (%)
Drug–polymer: 50/50	0.435	$6 \times 10^{-3} \cdot \exp - \frac{400}{CL}$	4.3×10^{-6}	33	43.7
Drug–polymer: 50/50	0.31	$6 \times 10^{-3} \cdot \exp - \frac{400}{CL}$	4.3×10^{-6}	35	42
Drug–polymer: 40/60	0.435	$6 \times 10^{-3} \cdot \exp - \frac{400}{CL}$	4.3×10^{-6}	25	42.5

Validity of the model

Although a swelling of the galenic forms takes place as soon as they have been brought into the liquid, because the rate of liquid transfer is higher than that of the drug, a frame of reference with respect to the original sphere has been considered for calculations, as it has been successfully set up in previous works (Crank, 1975; Khatir et al., 1986; Khatir et al., 1987).

Figs. 2–4 showing the experimental and theoretical kinetics of transfer for the drug and liquid, illustrate the validity of the model for these two transfers in various cases of concentrations and sizes of the galenic form. A good agreement is obtained not only for the drug but also for the liquid throughout the whole process.

The model has thus proved to give valuable information for both the matter transfers whatever is the concentration or the size of the original galenic form. The effect of the size of the spheres used in the paper on the rate of the matter transfer has been found to be of high importance. As shown in Fig. 2 (radius = 0.435 cm) and Fig. 4 (radius = 0.31 cm), obtained with the same composition (50–50), the rates of transfer for the liquid and drug are higher when the same amount of drug is presented in smaller galenic froms. So these two parameters should be considered with high interest for the development of these galenic forms.

Profiles of concentrations developed through the galenic form

The model described above was able to give the concentration of the drug and liquid in various places within the sphere at various times. No experiment in the present work has been carried out in order to measure these profiles of concentration, because that difficulty was shown previously with of thin sheets of material (Messadi et al., 1981). However, as these values of concentration obtained from calculation have been used for determining the kinetics of the matter transfers, they might be considered of value for the description of the process.

The profiles of concentration of liquid and drug have been shown in Figs. 7, 8 and 9, as they are developed through the radius of spheric galenic forms, at various times, for various cases: Fig. 7 for 50% of drug and radius of 0.435 cm., Fig. 8 for 40% of drug and radius of 0.435 cm., Fig. 9 for 50% of drug and radius of 0.31 cm.

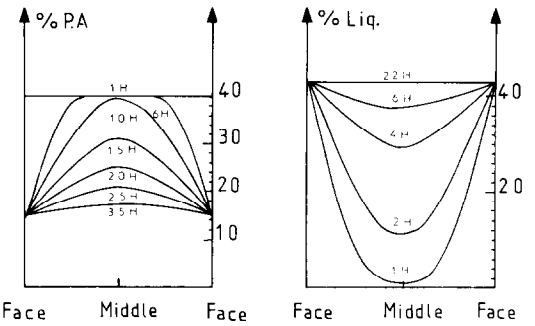

Fig. 8. Profiles of concentration developed through the radius. Left, drug; right, liquid. Drug–polymer, 40–60 in weight; radius, 0.435 cm; pH = 1.2; 37 °C.

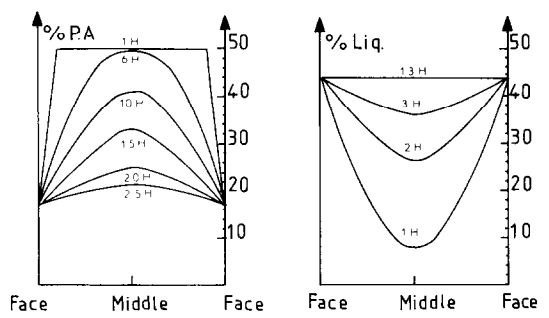

Fig. 7. Profiles of concentration developed through the radius. Left, drug; right, liquid. Drug-polymer, 50–50 in weight; radius = 0.435 cm; pH = 1.2; 37 °C.

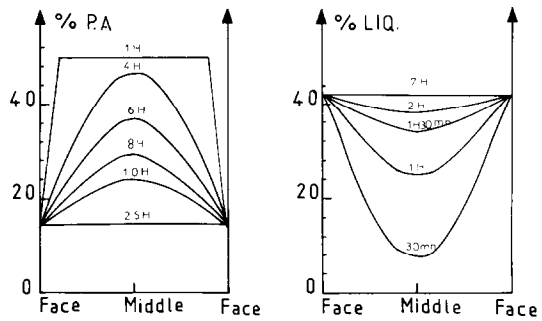

Fig. 9. Profiles of concentration developed through the radius. Left, drug; right, liquid. Drug-polymer, 50–50 in weight; radius = 0.3 cm; pH = 1.2; 37 °C.

Conclusions

The process of drug release has been elucidated in the important case of spheric galenic forms made of the mixture of sodium salicylate and Eudragit RS. Simultaneous transient diffusion of the liquid into, and the previously dispersed drug out of the polymer bead has been observed. More precisely, the liquid enters the polymer, dissolves the drug and then provokes a diffusion of the drug out of the galenic form. The galenic form swells because of the higher rate of transfer for the liquid, but this swelling is not detrimental to the solidity and stability of the form.

Within the narrow range, used for the concentrations of the original forms, the diffusivity of the liquid has been found to be about constant, while the diffusivity of the drug has been proved to depend highly on the concentration of the liquid. The effect of the liquid concentration on the drug diffusivity is very high especially at the beginning of the process, when the liquid penetrates the polymer. When the concentration of the liquid has reached to about 20%, the diffusivity of the drug becomes about constant. At the end of the process, when the equilibrium is reached, a partition coefficient has been found to be about constant whatever has been the initial concentration of the drug in the galenic form and the size of this galenic form.

The model described above, based on the explicit numerical method with finite differences, has given results in good agreement with experiments for the kinetics of matter (drug and liquid) developed within the galenic form. Two parameters of high interest for the development of these galenic forms have been found: the concentration of the drug dispersed in the polymer and the size of the galenic form.

List of symbols

$C(j)$	concentration at position j and time $i\Delta t$
$CN(J)$	concentration at position j and time $(i+1)\Delta t$
$CN(O)$	concentration at the middle of sample at time $(i+I)\Delta t$
$C(O)$	concentration at the middle of sample at time $i\Delta t$
D	diffusivity of the matter
Dl, Dd	diffusivity of the liquid and drug, respectively
J	flux of matter transferred per unit area
M_t, M_∞	amount of matter transferred up to time t and at equilibrium, respectively
Ml_∞, Md_∞	value of M_∞ for the liquid and drug, respectively
Δr, Δt	increments of space (radius) and time
j, i	integers characterizing the position on the radius and the time, respectively
r	value given to the position between 0 and R
R	value of the radius of spheric bead
n	number of concentric spheres for the galenic form (Eqn. 9)
t	time
$G(j)$	function expressed by Eqn. 8

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