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Spherical dosage form with a core and shell. Experiments and modelling

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Summary

A particular galenic form has been prepared and studied with the help of experiments and a mathematical model. The device, spherical in shape, is composed of two concentric parts: the core, made of an homogeneous mixture of drug and polymer; the shell made of polymer. Eudragit is used as polymer in both these parts. As a result, the release of drug in synthetic gastric liquid shows interesting kinetics of release: the rate of drug delivery increases with a positive acceleration when the process is developed for a long duration of time. Modelling of the process has been successfully obtained in spite of the complexity of the process. The liquid enters both polymers, dissolves the drug and enables the drug in solution to diffuse out of the device. Diffusivities, especially for the drug, are found to be very concentration-dependent. These devices are useful to make some galenic forms able to deliver the drug with a constant rate in the future, by combining them with classical devices made only of the core.

Introduction

An interesting route for drug administration is represented by some new therapeutic systems. These systems are of concern because of the following facts. The drug must be delivered to the target organ continuously over a fixed duration with a constant rate, and the first two results are: steady blood levels are obtained, smaller total amounts of drug are needed. Consequently, the side effects produced by high drug concentration are reduced, and the therapy is optimized (Heilman, 1984).

For this purpose, the first objective is to obtain some systems or drug dosage forms able to deliver the drug with a constant or a controlled rate. These controlled release techniques are generally divided into 3 categories based on the mechanism controlling the delivery of the active agent from the delivery device. These mechanisms are diffusion, osmosis and polymer erosion, but very often the drug release is controlled simultaneously by various mechanisms (Feijen, 1984). On the other hand various theories have been developed in order to describe the details of the process, with the dissolution of the drug from an inert matrix system. Some models considered a combination of

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hydrodynamic and diffusive effects (Nicklasson et al., 1985). Very often, experiments have been performed for a short period of time, so that the process can be successfully described by square-root laws of time dependence with the amount of drug transferred (Crank, 1975; Gurny et al., 1982; Touitou and Donbrow, 1982; Brossard et al., 1983; Teillaud and Pourcelot-Roubeau, 1984; Tojo and Chien, 1984; Peppas, 1985; Peppas and Segot-Chicq, 1985). A complex but interesting theory has been built up, based on the existence of pseudo-steady-state conditions especially in some glassy polymers. As a result, a sharp linear concentration front of the drug is formed between the extracted part and the untouched portion, and this front is found to move with an about constant rate (Higuchi, 1961; Lee, 1980; Higushi et al., 1983; Teillaud and Pourcelot-Roubeau, 1984). Some studies have been made in the same way as in kinetic studies, in order to find a kinetic of release of drug with a zero order (Peppas, 1985; Peppas, 1984; Teillaud and Pourcelot-Roubeau, 1984; Peppas and Segot-Chicq, 1985). In all cases, drastic assumptions have been made; only the drug transfer is considered, the diffusivity of the drug is considered to be non-concentration dependent.

Other results of interest have been attained by considering the liquid as well as the drug, the liquid being responsible for a swelling of the polymer (Peppas, 1984; Peppas et al., 1980). Simultaneous transfer of the liquid into, and plasticizer out of the plasticized PVC have been observed when the plasticized PVC is contacted with various kinds of liquids (Messadi and Vergnaud, 1981; Messadi et al., 1983). In case of devices made of biocompatible polymer in which the solid drug is dispersed, both transfers have been shown: the liquid enters the polymer matrix and dissolves the drug, enabling the drug to diffuse out of the matrix into the exterior liquid (Droin et al., 1985; Malley et al., 1988; Eddine et al., 1986).

In most studies, the matter transfers are found to be controlled by diffusion, following the Fick's laws. As a result, the kinetic of delivery of the drug exhibits a very high rate at the beginning of the process, corresponding with a vertical tangent of the curve, as shown in Fig. 1 (curve a) (Armand et al., 1988). The drawback of all these techniques

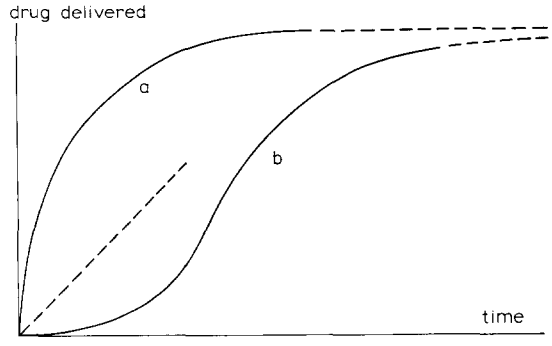

Fig. 1. Curve of the kinetics of drug delivery. a: diffusional curve. b: obtained with the device described in the test.

using devices obtained by dispersing the drug into a polymer is obvious: the rate of delivery is controlled, but it is far from being constant. Some devices have been prepared able to deliver the drug with a constant rate (Magron et al., 1987); they are obtained by surrounding the polymer-drug devices above-described (Droin et al., 1985; Malley et al. 1988) by an erodible material as Gelucire. A drawback may be that Gelucire melts at temperatures over 40 °C. Another way for delivering the drug with a constant rate is by mixing devices able to deliver the drug as shown in Fig. 1 (curve b) with classical well-known devices having the kinetics of delivery shown in the curve a.

The new problem is then to build up devices able to deliver the drug with kinetics described by the curve b illustrated in Fig. 1. New devices are prepared by beads surrounded by pure Eudragit playing the role of a membrane with a constant thickness, the internal beads being made by dispersing the drug into Eudragit (Fig. 2) as usual (Armand et al., 1988). Modelling of the process is another purpose of this paper, in order to describe all the phenomena, and also to optimize the operational conditions, and especially the radius of the bead and the thickness of the external membrane. Models based on numerical methods with finite differences, which have been developed in various cases (Taverdet and Vergnaud, 1984 and 1986; Khatir et al., 1986; Farah et al., 1987), are applied in the case at hand, in spite of its complexity. The kinetics of both matter transfers (liquid, drug) are determined by using the short technique described previously (Taverdet and Vergnaud, 1984),

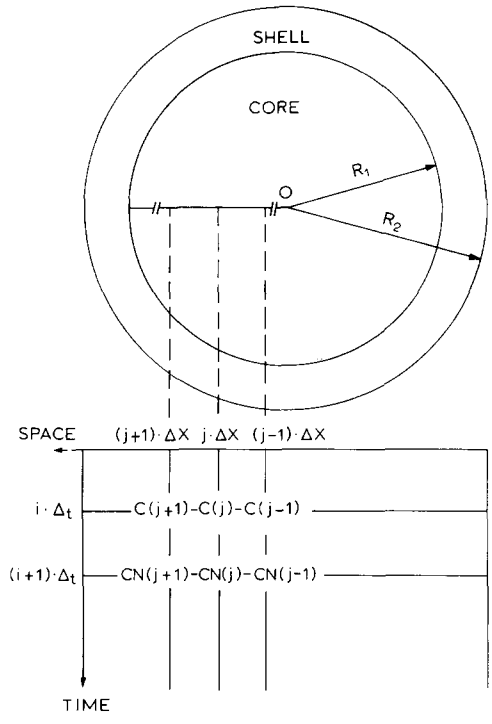

Fig. 2. Scheme of the galenic form for numerical analysis.

whereby the diffusivity for these matters as well as their dependence with a concentration of drug in the device can be attained. Long real experiments are also done in order to test the validity of the model, and to attain some data of interest on e.g. the concentrations of substances (liquid, drug) attained at equilibrium. These devices have a wide field of possibilities, and various parameters of concern such as the concentration of the drug in the polymer, the radius of the internal bead and the thickness of the pure polymeric membrane, have all been studied with regard to the shape of the kinetics curve of drug release.

Theory

Assumptions

Some assumptions are made in order to clarify the problem both on the sample and on the process.

i – The samples are spherical in shape with two parts: the internal sphere being made by dispersing the drug into the polymer, the external membrane being pure polymer.

ii – The thickness of the external pure polymer membrane is constant.

iii – The drug is properly dispersed into the internal polymeric sphere.

iv – Two transfers take place in the sample. The one concerned with the liquid which enters the polymer and dissolves the drug, and then allows the other transfer of the drug into the polymer out of the sample.

v – Both these transfers are controlled by transient diffusion, and are connected with each other.

vi – Diffusivities for both these transfers are concentration-dependent, as they are determined from experiments based on short tests.

vii – The concentration of the liquid on the external surface of the device is attained as soon as this device is soaked in the liquid.

viii – A partition coefficient of drug is considered between the device and the liquid of finite volume in which the device is soaked. This coefficient is helpful for determining the actual concentration of the drug on the external surface of the device.

ix – There is a discontinuity for the concentration of liquid at the interface between the core and shell. The liquid concentrations on both sides of this interface are connected with each other with a partition coefficient.

x – As the polymer swells, a frame of reference is fixed with respect to the original device, in order to simplify calculations (Crank, 1975; Khatir et al., 1986).

Mathematical treatment

The Fick's laws can be written as follows, in case of a spherical sample with a concentration-dependent diffusivity.

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

$$\frac{\partial C}{\partial t} = \frac{1}{r^2} \cdot \frac{\partial}{\partial r}\left[D \cdot r^2 \cdot \frac{\partial C}{\partial r}\right] \tag{2}$$

The initial and boundary conditions are described in Eqns. 3 and 4 (Fig. 2):

$$t=0 \quad 0 \leqslant r < R_1 \quad C = C_{in}, \text{ drug}$$

$$R_1 < r \leqslant R_2 \quad C = 0 \quad \text{drug}$$

$$0 \leqslant r < R_2 \quad C = 0 \quad \text{liquid} \qquad (3)$$

$$t>0 \quad r = R_2 \quad C = C_{eq} \quad \text{liquid} \qquad (4)$$

Analytical solutions for the Eqns. 1 and 2 can be found (Crank, 1975) only in the case of one matter transfer with special boundary conditions and with a constant diffusivity. With the double matter transfer of the liquid and drug connected with each other, some solutions have been found only in a few simple cases (Frisch, 1978). For very short times, the analytical solutions can be reduced to the simple equation:

$$\frac{M_t}{M_\infty} = \frac{6}{R}\left(\frac{D \cdot t}{\pi}\right)^{0.5} \qquad (5)$$

The problem at hand is very difficult, and no analytical solution can be obtained. However, the Eqn. 5 showing a relationship between the amount of matter transferred and the square root of time is very useful for determining the diffusivity from experiments based on short tests (Taverdet and Vergnaud, 1984).

Numerical analysis

The problem must be solved by using numerical methods with finite differences.

By considering the sphere (Fig. 2) with the following radius, $r+\Delta r$, r, $r-\Delta r$, taken in the sample, each radius being defined by an integer j between 1 and N,

$$\text{for} \quad 0 \leqslant j \leqslant N1 \quad r = j \cdot DX$$

$$R_1 = N1 \cdot DX$$

$$\text{for} \quad N1 \leqslant j \leqslant N \quad r = R_1 + (j - N1) \cdot DX_2$$

$$R_2 = R_1 + (N - N1) \cdot DX_2 \qquad (6)$$

the matter balance can be written as follows:

At the middle of the sample ($j = 0$)

$$CNL(0) = CL(0) + \frac{3 \cdot Dt}{(DX)^2}[CL(1) - CL(0)] \times [DL(1) + DL(0)] \qquad (7)$$

$$CNS(0) = CS(0) + \frac{3 \cdot Dt}{(DX)^2}[CS(1) - CS(0)] \times [DS(1) + DS(0)] \qquad (7')$$

– within the sphere of radius R_1 $(1 \leqslant j \leqslant N1 - 1)$

$$CNL(j) = CL(j) + \frac{Dt}{2(DX)^2 \cdot \left(j^2 + \frac{1}{12}\right)} \times [GL(j+1) - GL(j)] \qquad (8)$$

with

$$GL(j) = \left(j - \frac{1}{2}\right)^2 \cdot [CL(j) - CL(j-1)] \times [DL(j) + DL(j-1)] \qquad (9)$$

for $1 \leqslant j \leqslant N1$

$$CNS(j) = CS(j) + \frac{Dt}{2 \cdot (DX)^2 \cdot \left(j^2 + \frac{1}{12}\right)} \times [GS(j+1) - GS(j)] \qquad (8')$$

with

$$GS(j) = \left(j - \frac{1}{2}\right)^2 \cdot [CS(j) - CS(j-1)] \times [DS(j) + DS(j-1)] \qquad (9')$$

– within the part between R_1 and R_2 $(N1 + 1 \leqslant j \leqslant N - 1)$

$$CNL(j) = CL(j) + \frac{Dt \cdot DL_2}{(DX_2)^2 \cdot A_j} \times [GL(j+1) - GL(j)] \qquad (10)$$

with

$$GL(j) = \left[\frac{R_1}{DX_2} - N1 - \frac{1}{2} + j\right]^2 \times [CL_2(j) - CL_2(j-1)] \quad (11)$$

$$CNS(j) = CS(j) + \frac{Dt}{2 \cdot (DX_2)^2 \cdot A_j} \times [GS(j+1) - GL(j)] \quad (10')$$

$$GS(j) = \left[\frac{R_1}{DX_2} - N1 - \frac{1}{2} + j\right]^2 \times [CS(j) - CS(j-1)] \times [DS(j) + DS(j-1)] \quad (11)$$

by writing $A_j = \left(\frac{R_1}{DX_2} - N1 + j\right)^2 + \frac{1}{12}$

Special attention must be given to the interfaces and surfaces, in order to account for a discontinuity of the matter concentration.

– At the interface of radius R_1 $(j = N1)$

$$CNL(N1) = CL(N1) - \frac{DX}{3 \cdot B}\left(1 - \frac{1}{N1}\right)^2 \times [CNL(N1-1) - CL(N1-1)] - \frac{DX_2}{3 \cdot B}\left(1 + \frac{DX_2}{R_1}\right)^2 \times [CNL_2(N1+1) - CL_2(N1+1)] + \frac{8}{3}\frac{Dt \cdot DX_2 \cdot DL_2}{B \cdot R_1^2} GL(N1+1) - \frac{4}{3}\frac{Dt \cdot DX}{B \cdot R_1^2} GL(N1) \quad (12)$$

where the concentration of liquid varies discontinuously through the interface as follows:

$$CL_2(N1) = CL(NK)\frac{CEL_2}{CEL_1} \quad (13)$$

$$CNS(N1) = CS(N1) - \frac{DX}{3(DX + DX_2)}\left(1 - \frac{1}{N1}\right)^2 \times [CNS(N1-1) - CS(N1-1)] - \frac{DX_2}{3(DX + DX_2)}\left(1 + \frac{DX_2}{R_1}\right)^2 \times [CNS(N1+1) - CS(N1+1)] + \frac{4}{3}\frac{Dt \cdot DX_2}{(DX + DX_2)R_1^2} \cdot GS(N1+1) - \frac{4}{3}\frac{Dt \cdot DX}{(DX + DX_2)R_1^2} \cdot GS(N1) \quad (12')$$

by writing

$$B = DX + DX_2 \cdot \frac{CEL_2}{CEL_1}$$

– On the external surface of radius R_2 $(j = N)$

$$CL(N) = CEL_2 \quad (14)$$

$$CNS(N) = \frac{K(CIS \cdot V1 - MSI)}{V + \frac{3}{2} \cdot \pi \cdot K \cdot R_2^2 \cdot DX_2} \quad (15)$$

where the partition coefficient K is

$$K = \frac{MIS - M_\infty}{M_\infty} \quad (16)$$

and $V1$ and V are the volumes of the spheres of radius R_1 and R_2, respectively.

The value indicated in *MSI*, which is the amount of the drug in the sphere, excluding the

amount located in the half slide next to the surface, must be calculated as follows:

$$\frac{MSI}{4\pi} = \left[\frac{CS(0)}{24} + \tfrac{9}{8} CS(N1-1)\cdot(N1-1)^2 + \tfrac{3}{8} CS(N1)\cdot N1^2 + \sum_{j=1}^{N1-2} CS(j)\cdot\left(j^2+\frac{1}{12}\right)\right]\cdot(DX)^3 + \left[\tfrac{3}{8} CS(N1)\cdot R1^2 + \tfrac{9}{8} CS(N1+1) \times (R_1+DX_2)^2 + \tfrac{9}{8} CS(N-1) \times (R_2-DX_2)^2\right](DX_2) + \sum_{j=N1+2}^{N-2} CS(j)\cdot A_j\cdot(DX_2)^3 \qquad (17)$$

Amount of drug and liquid in the sample The amount of drug and liquid located in the galenic form at any time can be obtained by the following relations:

$$\frac{ML}{4\pi} = \left[\frac{CL(0)}{24} + \tfrac{9}{8} CL(N1-1)\cdot(N1-1)^2 + \tfrac{3}{8} CL(N1)\cdot N1^2 + \sum_{j=12}^{N1-2} CL(j)\cdot\left(j^2+\frac{1}{12}\right)\right]\cdot(DX)^3 + \left[\tfrac{3}{8} CL_2(N1)\cdot R_1^2 + \tfrac{9}{8} CL_2(N1+1)\cdot(R_1+DX_2)^2 + \tfrac{9}{8} CL_2(N-1)\cdot(R_2-DX_2)^2\right](DX_2) + \sum_{j=N1+2}^{N=2} CL_2(j)\cdot A_j\cdot(DX_2)^3 + \tfrac{3}{8}\left[2CL_2(N-1) - CL_2(N-2)\right] \times (DX_2)\cdot R_2^2 \qquad (18)$$

$$\frac{MS}{4\pi} = \frac{MSI}{4\pi} + \tfrac{3}{8} CS(N)\cdot R_2^2\cdot DX_2 \qquad (19)$$

At the initial moment, the concentration of drug on the surface of the core, $CS(N_1)$, is indeterminate between zero and CIS. This value must be chosen so, that the Eqns. 17 and 19 give, at the initial moment, the exact value $MS = MIS$. Thus the initial value of the interface will be:

$$CS(N_1) = CIS\cdot\frac{DX}{DX+DX_2} \qquad (20)$$

Materials and Methods

The method of preparation of the spherical devices is described, as well as the materials used for the preparation and the conditions of testing the devices.

Materials

Sodium salicylate (COPER) in powder form is used as the drug component. Eudragit (Rhöm Pharma), a copolymer of dimethylaminoethylacrylate and ethylmethacrylate, of M_r 150,000 is used for the polymer matrix (core and shell).

The device is composed of two parts: the core and the shell, as shown in Fig. 2.

The core is prepared by mixing intimately the two materials in powder form, and transforming the mixture into a thick paste after pulverization with a small amount of ethanol. Spherical beads of various sizes are obtained by pressing the paste in a mold and drying until complete evaporation of ethanol (2 days).

The core above-described is then surrounded with pure Eudragit by using a paste of Eudragit and ethanol. The final device is dried under the same conditions as for the core. The thickness of the Eudragit shell surrounding the core is determined by the variation in weight of the device and can be controlled by the conditions of soaking.

Various devices are prepared with various sizes of the core (and the shell, characterized by the value of the radii R_1 and R_2).

Conditions of testing (in vitro experiments)

Experiments are performed in a closed flask with high-speed stirring. The spherical devices

(400–500 mg) are inserted in a fiber glass basket, and soaked into synthetic gastric liquid (100 ml) at 37 °C.

The composition of the liquid is as follows, for a pH of 1.2: 80 ml HCl 1 N, 2 g NaCl for 1000 ml solution

At intervals, a sample of liquid is taken for analysis and the spheres are weighed. The amount of drug released is determined by using a double-beam spectrophotometer calibrated at 300 nm (Beckman DB-G).

Calculations

Short tests are performed (Taverdet and Vergnaud, 1984) in order to obtain the diffusivity for the liquid and for the drug.

Long real tests are done for testing the validity of the model, and mesuring the amounts of matter transferred at equilibrium.

The profiles of concentration of the drug and liquid developed through the device are calculated with the help of the model. The kinetics of the matters transferred (liquid, drug) are determined by integrating the profiles of concentration.

Results

Three points are of concern in the present study: experiments are done in order to obtain data as diffusivity and matter transferred at equilibrium; the determination of the validity of the model when used for simulating the process; the effect of parameters of interest on the process, or the effect of the thickness of the surrounding layer of Eudragit on the retardation of drug delivery.

Experimental results

Experiments are carried out under the operational conditions described in the experimental part, with various values of the thickness of the shell, this shell being made of pure Eudragit. The core is obtained with the mixture of Eudragit and sodium salicylate 50–50 in weight.

In all these cases, two simultaneous matter transfers are observed as previously shown in various cases (Messadi and Vergnaud 1981 and 1983; Taverdet and Vergnaud, 1984; Droin et al., 1985; Malley et al., 1988; Eddine et al., 1986; Magron et al., 1987; Armand et al., 1988): (i) the liquid enters the polymeric device, within the shell and the core, and dissolves the drug; (ii) the dissolved drug then diffuses through the polymer out of the device.

TABLE 1

Diffusivities (cm^2/s) and Matters transferred at equilibrium (%)

Drug (in core and shell)	$DS = 2.9\times10^{-6} \times\exp\left[-\frac{125}{CL}\right]$	$CES = 38\%$
Liquid (in core)	$DL_1 = 4.5\times10^{-4} \times\exp\left[-\frac{320}{CL+CS}\right]$	$CEL_1 = 55\%$
Liquid (in shell)	$DL_2 = 1.4\times10^{-7}$	$CEL_2 = 29\%$

Both these transfers are shown to be controlled by diffusion, and the diffusivities are determined either with pure Eudragit sample and with samples having the same composition as the core (Armand et al., 1988). From the straight lines obtained by plotting the amount of matter transferred during short tests (Taverdet and Vergnaud, 1984; Armand et al., 1988) as a function of the square root of time, we calculate the diffusivity with the help of Eqn. 5.

From long experiments the values of matter transferred at equilibrium were calculated.

The values characterizing the rates of transfer and the amount transferred at equilibrium are shown in Table 1.

Some interesting conclusions can be pointed out:

i – the diffusivity of the liquid is constant in pure Eudragit, but it depends largely on the initial concentration of the drug located previously in the polymer.

ii – the diffusivity of the drug is strongly affected by the concentration of the liquid; of course, it increases largely with the concentration of liquid.

iii – the amount of liquid transferred at equilibrium is not the same in case of pure Eudragit and for the core; it is higher when the drug is previously present in the polymer.

These conclusions, in fact, have already been observed in previous papers with galenic forms,

made of same components but with different shapes (Droin et al., 1985; Armand et al., 1988).

Validity of the model

The galenic form swells during the whole process, because the rate of liquid transferred is higher than that of the drug. However, calculations have been made easy by taking a fixed frame of reference which is the original sphere, as has been successfully done before (Crank, 1975; Khatir et al., 1986 and 1988; Armand et al., 1988).

Experimental and theoretical kinetics of transfer obtained for the drug (left) and the liquid (right) are shown in Figs. 3–8 for various cases. The radius of the core is about the same in all cases, around 0.43 cm, but the thickness of the Eudragit shell is varying from 0.002 to 0.02 cm.

In all cases, a good agreement between the theoretical and experimental curves can be appreciated, either for the liquid and for the drug, or for the whole process.

As the validity of the model is very high, the following conclusions can be drawn:

i – the model describes the process in a perfect way.

ii – the data obtained from short tests are of interest, and especially the diffusivities and their concentration–dependence laws.

iii – the model can be used under various other conditions, especially with various size of the sample and initial concentration of the drug in the sample.

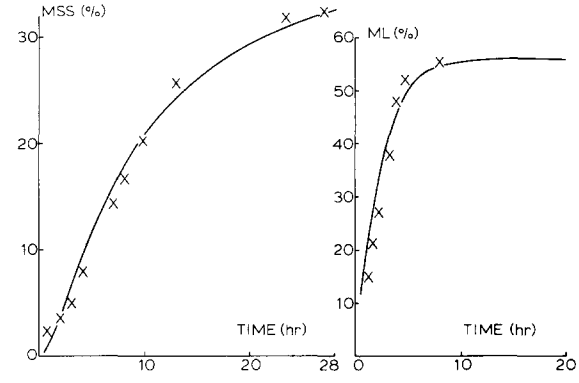

Fig. 4. Kinetics of delivery for the drug (left) and liquid (right). $R_1 = 0.430$ cm; thickness of the shell = 0.0030 cm.

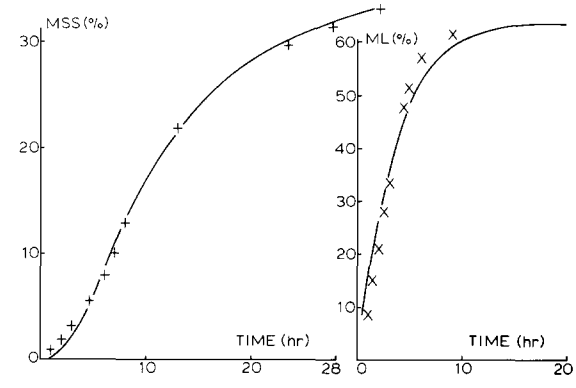

Fig. 5. Kinetics of delivery for the drug (left) and liquid (right). $R_1 = 0.424$ cm; thickness of the shell = 0.0050 cm.

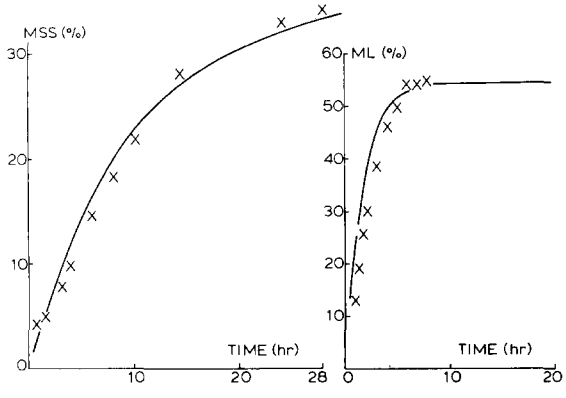

Fig. 3. Kinetics of delivery for the drug (left) and liquid (right). $R_1 = 0.435$ cm; thickness of the shell = 0.002 cm.

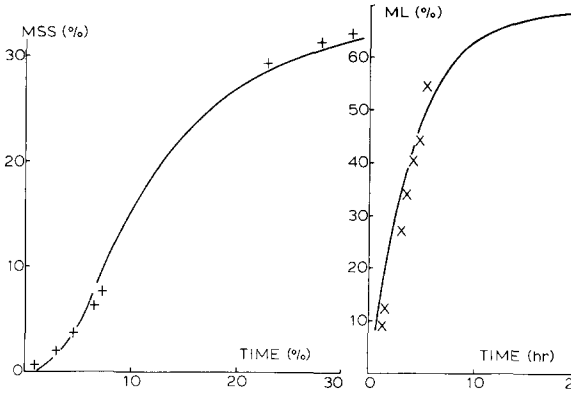

Fig. 6. Kinetics of delivery for the drug (left) and liquid (right). $R_1 = 0.425$ cm; thickness of the shell = 0.0055 cm.

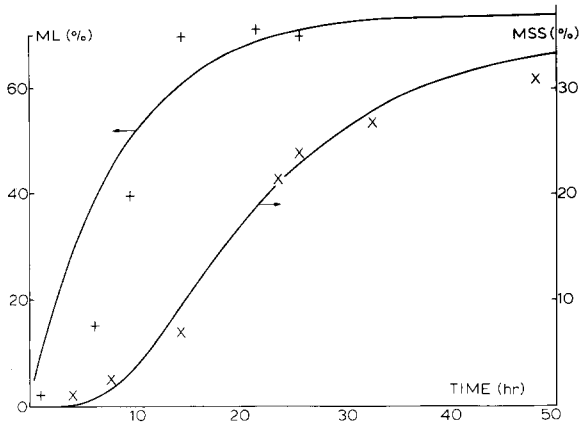

Fig. 7. Kinetics of delivery for the drug (left) and liquid (right). $R_1 = 0.441$ cm; thickness of the shell = 0.0105 cm.

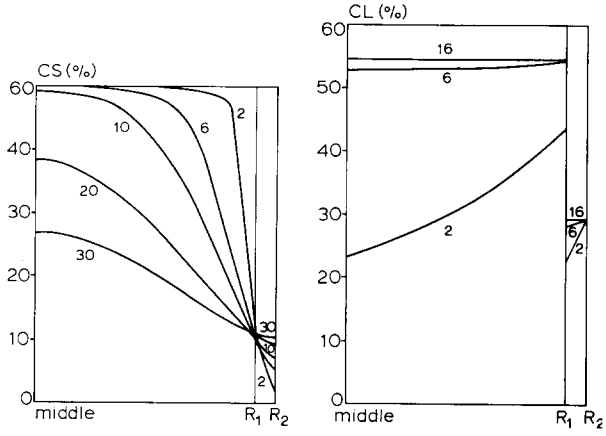

Fig. 9. Profiles of concentration of the drug (left) and liquid (right) through the sample. $R_1 = 0.435$ cm; thickness of the shell = 0.002 cm.

Effect of parameters

Two facts are of interest: the effect of the thickness of the shell on the drug delivery, and the profiles of concentration developed through the thickness of the sample.

A small value for the thickness of the shell may already result in a change in the shape of the kinetics curve of the drug. This point can be appreciated in Fig. 4 for a thickness of only 0.003 cm. This fact is increased as the thickness is increased.

The model is able to give more information than experiments. For instance, it is possible to obtain the profiles of concentration of the liquid and the drug as they are developed with the sample as a function of time. It is difficult to make some measurements for proving the validity of these profiles (Messadi and Vergnaud 1981; Messadi et al., 1983). However, as the kinetics of the matters transferred are obtained by integrating these profiles of concentration, the validity of the model shown above can be expanded in the profiles of concentration. Some profiles of concentration are drawn for the drug (left) and the liquid (right) in two cases, for thicknesses of 0.002 cm (Fig. 9) and 0.02 cm (Fig. 10).

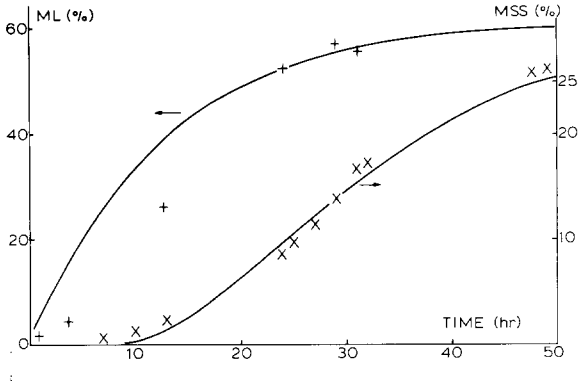

Fig. 8. Kinetics of delivery for the drug (left) and liquid (right). $R_1 = 0.415$ cm; thickness of the shell = 0.020 cm.

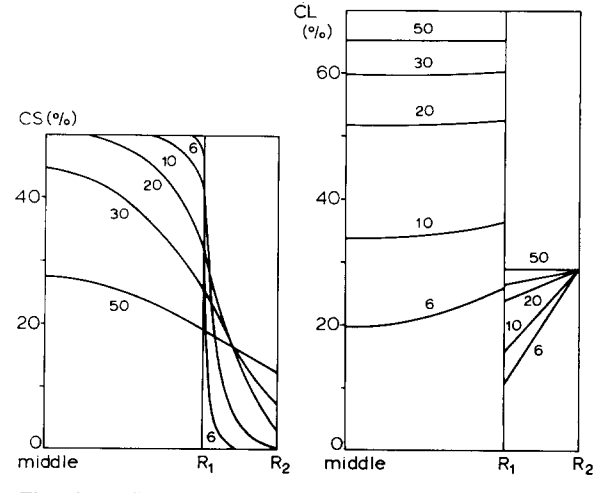

Fig. 10. Profiles of concentration of the drug (left) and liquid (right) through the sample. $R_1 = 0.415$ cm; thickness of the shell = 0.020 cm.

The following conclusions can be drawn from these profiles of concentration:
i – the liquid penetrates the sample, and a strong discontinuity is observed at the interface between the shell and the core. This is due to the various values of the liquid at equilibrium found in pure Eudragit and in the core.
ii – steep gradients of drug are developed through the sample.
iii – the shell plays the role of limitation for the drug as well as for the liquid.

Conclusions

In order to prepare galenic forms able to deliver the drug in the stomach with a constant rate an attempt has been made in the way of finding devices delivering the drug with a particular rate: the rate of release is very low at the beginning of the process, and then increases progressively with a positive acceleration. The reason for these special devices is that when they are combined with classical devices, the drug being dispersed in the polymer, the result can be an about constant rate of delivery for a long time.

These devices have been prepared by surrounding a classical device considered as a core with a pure polymer playing the role of a shell. The core is obtained by dispersing the drug into polymer and compressing the mixture into beads, and the polymer is the same for the core and shell (Eudragit).

Experiments done with various thicknesses of the shell have proved that these kinds of devices are capable of aiming at this purpose. The thickness plays the role of a very important parameter, regulating the retardation of the release and the rate of acceleration of the delivery.

Modelling of the process, in spite of the complexity of the phenomenon, has been shown to be able to describe all the facts: the liquid enters the polymer, dissolves the drug and enables the transport of the drug out of the device. These matter transfers are controlled by transient diffusion, and the diffusivity for the drug increases largely with the concentration of the liquid in the device.

List of symbols

R_1, R_2	the radius of the core and the sphere, respectively
N_1, N	the number of slides in the core and in the shell, respectively
$DX = R_1/N_1$	increment of space in the core
$DX_2 = (R_2 - R_1)/(N - N_1)$	increment of space in the shell
Dt	increment of time
V_1, V	the volume of core and sphere, respectively
DL_1, DL_2	diffusion coefficient of liquid in the core and in the shell, respectively
DS	diffusion coefficient of drug in the sphere
CS, CNS	the concentration of drug at time t and (t + Δt) respectively
CL, CNL	the concentration of liquid in the core at time t and (t + Δt), respectively
CL_2, CNL_2	the concentration of liquid in the shell at time t and $(t + \Delta t)$, respectively
CEL_1, CEL_2	the equilibrium concentration of liquid, in the core and the shell, respectively
CIS	the initial concentration of drug (only in the core)
MIS	the initial amount of drug in sphere
MSI	the amount of drug in the sphere, but excluding that in the half slide of surface at time t
MS	the total amount of drug in the sphere at time t
ML	the total amount of liquid in the sphere at time t
MSS, M_∞	the lost amount of drug from sphere, at time t and at infinite time, respectively
K	partition coefficient of the drug between the polymer and the liquid

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