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Oral dosage forms with a core and shell with the same polymer containing different drug concentrations

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Summary

In order to achieve the controlled release of a drug, dosage forms made of a core and shell were developed and studied. The core and shell were obtained by dispersing the drug in the same polymer, with different concentrations of drug in the core and in the shell. A numerical model taking into account all the known facts was built and tested. The process is as follows: the liquid diffuses into the polymer, dissolves the drug and enables the drug to diffuse out of the form through the liquid located in the polymer. Four parameters appear to be of great interest: the radius of the core, the thickness of the shell, and the initial concentrations of drug in the core and in the shell. The results are given by using either the kinetics of release of drug or the rate at which the drug is released during the process.

Introduction

The techniques allowing the control of drug release from oral dosage forms are classified into three categories based on the mechanism followed by the release of the drug from the device (Feijen, 1984; Heilmann, 1984; Heller, 1984). These mechanisms are osmosis (Kendall et al., 1982), diffusion (Droin et al., 1985; Vergnaud, 1991) and polymer erosion (Laghoueg et al., 1989); they cannot always be considered separately, since the release of drug may be controlled by more than one mechanism, as shown in the case of an erodible shell where erosion (Bidah and Vergnaud, 1990) and diffusion (Bidah et al., 1992) simultaneously play a role.

Monolithic devices where the agent is dispersed in an inert matrix have been studied and developed in particular. Both degradable (Heller, 1984) and non-degradable (Touitou and Donbrow, 1982; Focher et al., 1984) polymers have been utilized for the matrix, the reason being that these polymers are not absorbed in the body but pass through. The process is controlled by diffusion which explains the square-root of time dependence of drug delivery (Brossard et al., 1983; Teillaud and Pourcelot-Roubeau, 1984), at least at the beginning of the process when the amount

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of drug released is half the value at equilibrium for a sheet (Vergnaud, 1991). In fact, the process is far more complex, as the liquid enters the polymer, dissolves the drug, and enables the drug to diffuse out of the dosage form through the liquid located in it, and the transfers of both the liquid and drug are controlled by diffusion (Droin et al., 1985; Armand et al., 1987; Malley et al., 1987). The process of release from these dosage forms is controlled by diffusion, and thus the rate of release is far from constant: the rate of release initially is very high with a vertical tangent in the kinetic curve, and thereafter decreases with time regularly in a complex manner (Vergnaud, 1991).

In order to achieve a constant rate of delivery of the drug from monolithic devices, two procedures have successfully been developed, with devices consisting of a core and shell, that with a shell made of an erodible drug-free polymer (Magron et al., 1987; Laghoueg et al., 1989), the other with a shell made of a non-erodible polymer free of drug (Liu et al., 1988; Vergnaud, 1991). With the latter dosage form, retardation in the release of the drug occurs at the beginning of the process, and the kinetic curve obtained for short times is tangential to the time axis, at the origin of the axes, while with the former, the kinetic curve is tangential to the drug amount axis, at the same origin. The principle of drug release based on the swelling of polymers is certainly of interest (Peppas et al., 1980; Peppas, 1984), however, the study of diffusion of a liquid through a polymer by considering the subsequent change in dimensions of the polymer is rather complex (Senoune et al., 1990; Bakhouya et al., 1992).

The first objective in this paper was to develop the principle of dosage forms consisting of a core and shell, with the same polymer and different initial concentrations of drug for the core and the shell. The kinetics of delivery of the drug in gastric liquid as obtained from in vitro tests were thus drawn, as well as the change in the rate of drug delivery with time. Two parameters were thus of interest, namely, the relative value of the radius of the core and the thickness of the shell, and the relative value of the drug concentrations chosen for the core and shell.

The other main purpose of this investigation was to use a numerical model taking into account all the known facts, with the diffusion of the liquid and drug through the core and shell, and with particular attention being paid to the interface between the core and shell and the liquid and shell. This numerical model has been successfully tested in a previous paper (Liu et al., 1988), and no new experiments were thus performed in order to test the model.

Materials and Methods

The method of preparation of the spherical devices with a core and shell, as well as the general conditions for the in vitro tests, is described below.

Dosage forms

The device is composed of two parts: the core and the shell.

The core was prepared by mixing intimately a given amount of the drug and polymer in powder form, and pressing the mixture into a spherical bead.

The core was then surrounded with another mixture of drug and polymer and pressed again. The thickness of the shell was determined from the weight and density of the material used for the shell.

In the case of sodium salicylate as the drug component and Eudragit as the polymer, the mixture for the core was transformed into a thick paste after pulverization with a small amount of ethanol. After pressing the paste into a spherical bead, the core was dried until completion. The core was thus surrounded with another paste made of Eudragit and drug with a small amount of ethanol. The final dosage bead with core and shell was thus dried again. The drug content in the core and the shell was determined by weighing. (Liu et al., 1988).

Conditions of release

Experiments were performed in a closed flask with a finite volume of liquid. This liquid was stirred vigorously so that the coefficient of matter transfer on the surface of the dosage bead was

very high. The concentration of the drug on the surface of the dosage form was constantly at equilibrium with the concentration of drug in the liquid, the ratio being the partition coefficient. Two other parameters were of interest: the ratio of the amounts of drug released and remaining in the dosage form at equilibrium, and the radius of the dosage form.

Theory

Assumptions

The following assumptions were made:

(i) The core and shell are spherical in shape. They are made of the same polymer, but the concentration of the drug is different in the core and in the shell.

(ii) Transport of the drug is controlled by radial diffusion, with a very high coefficient of matter transfer on the external surface of the bead and on the surface between the core and shell.

(iii) The concentration of drug is thus the same on each side of the interface between the core and shell.

(iv) The concentration of the drug on the external surface of the dosage form is proportional to that in the liquid. The ratio of these concentrations at each time is equal to the partition factor.

(v) The dimensions of the dosage form are constant, the swelling being negligible.

(vi) The diffusivity of the drug is constant, and is the same in the core and in the shell.

Mathematical treatment

The equation for radial diffusion with constant diffusivity is:

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

The initial and boundary conditions are given by:

$$t = 0 \quad 0 \le r < R_1 \quad C = C_{\text{in},1} \tag{2}$$

$$R_1 < r < R \quad C = C_{\text{in},2}$$

$$r = R_1 \quad C_{R_1} = \tfrac{1}{2}(C_{\text{in},1} + C_{\text{in},2}) \tag{3}$$

$$t > 0 \quad r = R \quad C_R = k \cdot C_{\text{ext},t}$$

where R_1 and R are the radius of the core and the shell, respectively, k denotes the partition factor between the dosage form and the liquid, $C_{\text{in},1}$ and $C_{\text{in},2}$ are the initial concentrations in the core and the shell, respectively, and $C_{\text{ext},t}$ represents the uniform concentration of drug in the liquid of finite volume, at time t.

Numerical treatment

The problem is solved using a numerical model. The radius R_1 of the core is thus divided into N_1 increments of space of thickness Δr_1, and the thickness of the shell $R - R_1$ is divided into N_2 increments of space of thickness Δr_2. Each position r is associated with the integer j, as follows:

$$\begin{aligned} &r = j\Delta r_1 && 0 \le j \le N_1 && \text{core} \\ &r = R_1 + (j - N_1)\Delta r_2 && N_1 \le j \le N && \text{shell} \\ &N = N_1 + N_2 \end{aligned} \tag{4}$$

The matter balance is evaluated during the interval of time $[t, t + \Delta t]$ within the spherical membranes of thickness Δr_1 or Δr_2 located in various places in the core and the shell (Liu et al., 1988). The new concentration after the elapse of time Δt can thus be expressed in terms of the previous concentrations by the following equations.

Within the core, with $1 \le j \le N_1 - 1$

$$CN_j = C_j + \frac{1}{M_1\left(j^2 + \frac{1}{12}\right)}\left[\left(j + \tfrac{1}{2}\right)^2 (C_{j+1} - C_j) - \left(j - \tfrac{1}{2}\right)^2 (C_j - C_{j-1})\right] \tag{5}$$

with the dimensionless number M_1

$$M_1 = \frac{(\Delta r_1)^2}{D \cdot \Delta t} \tag{6}$$

At the middle of the core, with $j = 0$

$$CN_0 = C_0 + \frac{6}{M_1}(C_1 - C_0) \tag{7}$$

Within the shell, with $N_1 + 1 \leq j \leq N - 1$

Upon putting:

$$B_j = \frac{R_1}{\Delta r^2} - N_1 + j \tag{8}$$

and the dimensionless number M_2

$$M_2 = \frac{(\Delta r_2)^2}{D \cdot \Delta t} \tag{9}$$

the new concentration is:

$$CN_j = C_j + \frac{1}{M_2\left(B_j^2 + \frac{1}{12}\right)}\left[\left(B_j + \tfrac{1}{2}\right)^2 (C_{j+1} - C_j)\right.$$

$$\left. - \left(B_j - \tfrac{1}{2}\right)^2 (C_j - C_{j-1})\right] \tag{10}$$

At the core-shell interface, with $j = N_1$

The flux of diffusing substance is the same on each side of the core-shell interface, leading to the relationship:

$$\frac{3C_{N_1} - 4C_{N_1-1} + C_{N_1-2}}{\Delta r_1}$$

$$= \frac{3C_{N_1} - 4C_{N_1+1} + C_{N_1+2}}{-\Delta r_2} \tag{11}$$

Upon putting:

$$B = \frac{3}{\Delta r_1} + \frac{3}{\Delta r_2} \tag{12}$$

the new concentration at the interface becomes:

$$C_{N_1} = \frac{1}{B \cdot \Delta r_1}(4C_{N_1-1} - C_{N_1-2})$$

$$+ \frac{1}{B \cdot \Delta r_2}(4C_{N_1+1} - C_{N_1+2}) \tag{13}$$

Amount of drug remaining

In the core:

$$Q_1 = 4\pi(\Delta r_1)^3 \left[\frac{C_0}{24} + \sum_{j=1}^{N_1-2}\left(j^2 + \tfrac{1}{12}\right)C_j\right.$$

$$\left. + \tfrac{9}{8}(N_1 - 1)^2 C_{N_1-1} + \tfrac{3}{8}N_1^2 C_{N_1}\right] \tag{14}$$

in the shell:

$$Q_2 = QA + \frac{3\pi}{2}\Delta r_2 R^2 C_N \tag{15}$$

with:

$$Q_A = 4\pi(\Delta r_2)^3 \sum_{j=N_1+2}^{N-2}\left[\left(\frac{R_1}{\Delta r_2} - N_1 + j\right)^2 + \tfrac{1}{12}\right]C_j$$

$$+ \frac{3\pi}{2}\Delta r_2\left[R_1^2 C_{N_1} + 3(R_1 + \Delta r_2)^2 C_{N_1+1}\right.$$

$$\left. + 3(R - \Delta r_2)^2 C_{N-1}\right] \tag{16}$$

where Q_A is independent of C_N.

Because of the discontinuity of the concentration at the core-shell interface at the beginning of the process, the concentration C_{N_1} is replaced by:

$2C_{N_1-1} - C_{N_1-2}$ in eqn. 14

and by:

$2C_{N_1+1} - C_{N_1+2}$ in eqn. 16

On the surface of the shell, with $j = N$

The volume of the surrounding liquid being constant, the concentration of the drug in the liquid increases during the process. Following assumption (iv), the concentration on the surface

is constantly proportional to the drug concentration in the liquid.

$$C_N = k \cdot C_{ext,t} = k \cdot \frac{Q_t}{V} \tag{17}$$

where Q_t and $C_{ext,t}$ are the amount and the concentration of drug in the liquid at time t, respectively, k denotes the partition factor, and V is the volume of the liquid.

Q_1 being the initial amount of drug in the bead, the following is obtained:

$$Q_t = Q_1 - Q_1 - Q_A - \frac{3\pi}{2} \Delta r_2 R^2 C_N \tag{18}$$

Thus, we obtain:

$$C_N = \frac{k \cdot (Q_1 - Q_1 - Q_A)}{V + \frac{3\pi}{2} k \Delta r_2 R^2} \tag{19}$$

Results

Generally, the results concerned with the release of drug are expressed by the kinetics of drug release. Another way of presenting the results is to construct a plot of the rate at which the drug is released as a function of time. Both types of curves are depicted in this article.

As the dosage forms consist of a core and shell, four parameters are of interest: the radius of the core and its initial concentration of drug; the thickness of the shell and its initial concentration of drug. The effect of the two parameters characterizing the shell, namely, its thickness and initial drug concentration, was studied here.

Effect of the initial concentration of drug in the shell

The core is the same for various dosage forms, with $R_1 = 0.32$ cm and $C_{in,1} = 0.6$ while the shell has a constant thickness (0.08 cm) leading to $R = 0.40$ cm and various concentrations ranging from 0 to 0.6 (weight of drug/weight of mixture).

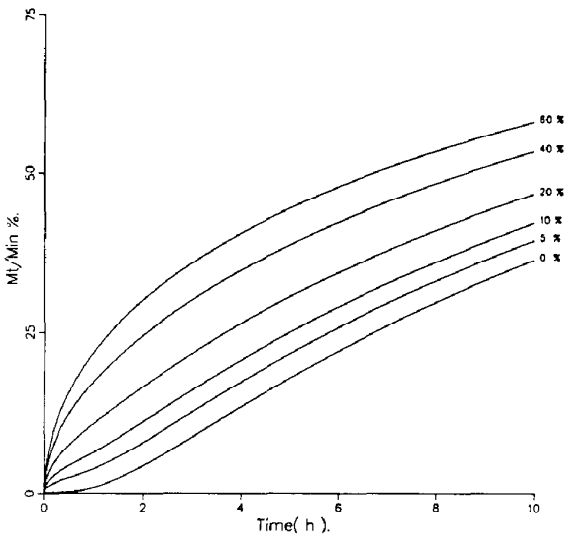

Fig. 1. Kinetics of drug release for dosage forms with a core and shell, and various values of the initial drug concentration in the shell. Core: $R_1 = 0.32$ cm, $C_{in,1} = 0.6$; shell: $R = 0.40$ cm, $C_{in,2}$ is noted.

The effect of the concentration of drug in the shell on the kinetics of release of drug can be observed in Fig. 1. The rate of drug released as a function of time is shown in Fig. 2 for the various concentrations of drug in the shell.

The following conclusions can be drawn:

(i) The shapes of the kinetic profiles of drug released are quite different depending on the concentration of drug in the shell.

(ii) When the shell is free of drug, retardation of the release takes place especially at the beginning of the process, as shown in earlier studies (Liu et al., 1988). The rate of release increases rather slowly up to a maximum which is reached at around 3 h, and subsequently decreases very slowly.

(iii) When the concentration of drug is the same in the core and in the shell, the kinetics of release is typical, with a vertical tangent at the beginning of the process and a rate of release decreasing continuously with time (Armand et al., 1987).

(iv) The kinetics of release associated with the other dosage forms, at a drug concentration in the shell between 0 and 0.6, are intermediate

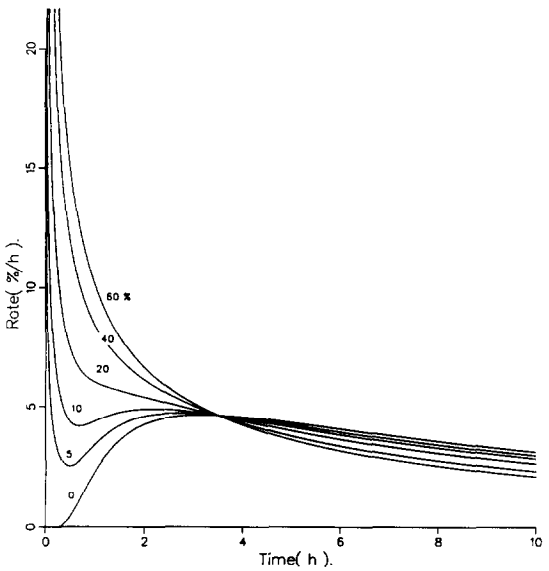

Fig. 2. Rate of drug release as a function of time for dosage forms with a core and shell, and various values of the initial drug concentration in the shell. Core: $R_1 = 0.32$ cm, $C_{in,1} = 0.6$; shell: $R = 0.40$ cm, $C_{in,2}$ is noted.

between the other two curves considered in (ii) and (iii).

(v) A local minimum and a local maximum for the rate of drug released as a function of time are observed when the concentration of drug in the shell is between 0 and 0.15.

(vi) Fig. 2, expressing the change in the rate of release with time, gives more precise information than Fig. 1 with the kinetics of release.

(vii) The diffusivities are the same in the core and the shell, and constant at $2.2 \times 10 - 7$ cm^2/s. Of course the model can be used, after slight changes, with different values of the diffusivities in the core and the shell, and with concentration-dependent diffusivities.

Effect of the thickness of the shell

The effect of the thickness of the shell on the process of drug release was studied by keeping the characteristics of the core constant ($R_1 = 0.32$ cm, $C_{in,1} = 0.6$), as well as the concentration of drug in the shell at either $C_{in,2} = 0.1$ or $C_{in,2} = 0.2$ and by varying the value of the radius R from 0.32 to 0.60 cm.

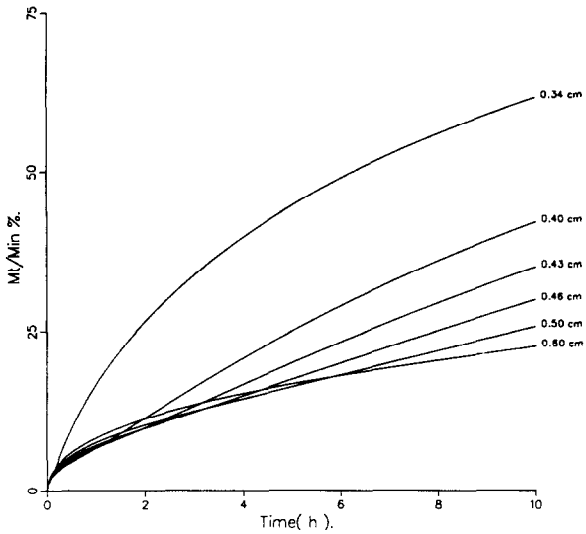

Fig. 3. Kinetics of drug release for dosage forms with a core and shell, and various values of the thickness of the shell. Core: $R_1 = 0.32$ cm, $C_{in,1} = 0.6$; shell: R is noted; $C_{in,2} = 0.1$.

The kinetics of drug release are illustrated in Figs 3 and 5 for drug concentrations in the shell of 0.1 and 0.2, respectively. The variation in the

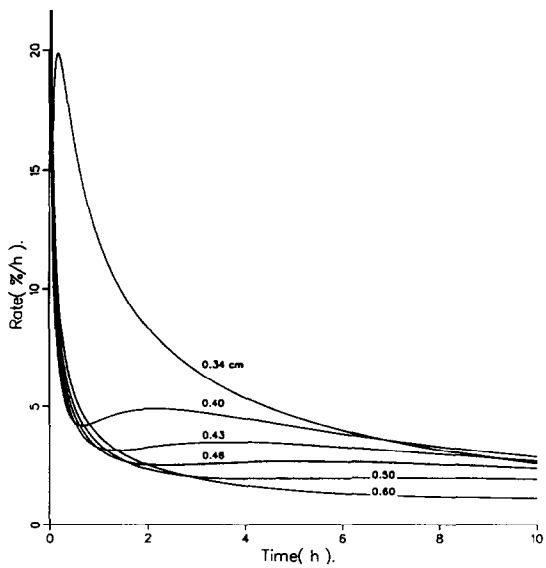

Fig. 4. Rate of drug release as a function of time for dosage forms with a core and shell, and various values of thickness of the shell. Core: $R_1 = 0.32$ cm, $C_{in,1} = 0.6$; shell: R is noted; $C_{in,2} = 0.1$.

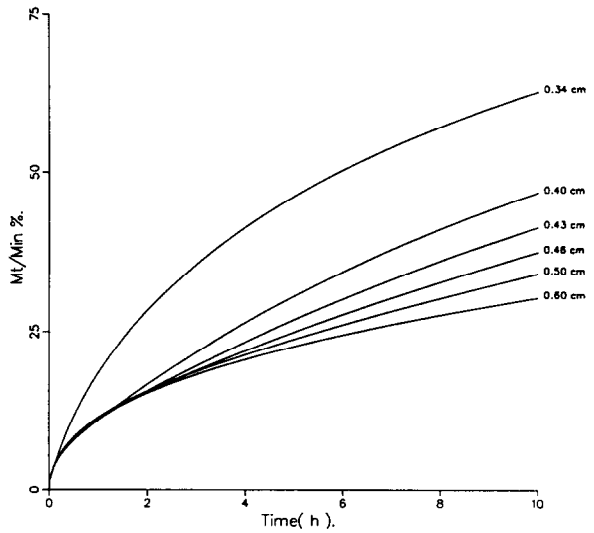

Fig. 5. Kinetics of drug release for dosage forms with a core and shell, and various values of the thickness of the shell. Core: $R_1 = 0.32$ cm, $C_{in,1} = 0.6$; shell: R is noted; $C_{in,2} = 0.2$.

rate of drug release with time is demonstrated in Figs 4 and 6 for drug concentrations in the shell of 0.1 and 0.2.

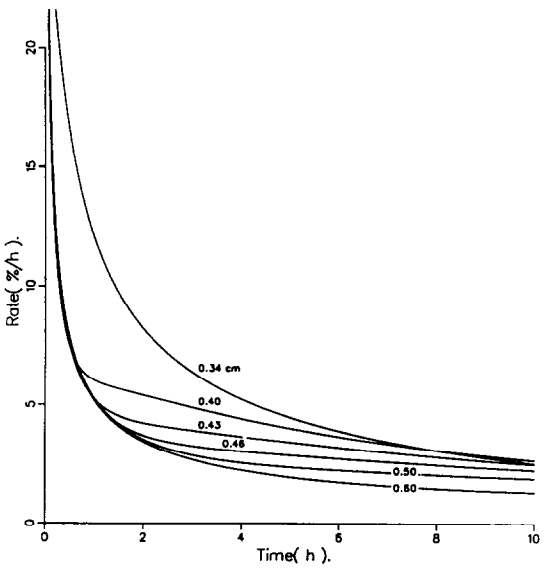

Fig. 6. Rate of drug release as a function of time for dosage forms with a core and shell and various values of thickness of the shell. Core: $R_1 = 0.32$ cm, $C_{in,1} = 0.6$; shell: R is noted; $C_{in,2} = 0.2$.

Some conclusions are worth noting:

(i) The effect of the thickness of the shell on the process is considerable, as shown in particular in Figs 4 and 6.

(ii) For low values of the thickness of the shell, e.g., 0.02 cm, the rate decreases with time in a manner similar to that for a dosage form with a uniform concentration of drug (Armand et al., 1987).

(iii) When the thickness of the shell is less than 0.18 cm, a minimum and a maximum for the rate of release are observed, as demonstrated in Fig. 4 (at a drug concentration of 0.1 in the shell).

(iv) After a rather high value of the rate of release at the beginning of the process, the rate becomes about constant, e.g., between 1 and 10 h for a shell thickness of 0.11 cm and between 2 and more than 10 h for a thickness of 0.14 cm.

(v) No minimum is observed for the rate of release as a function of time, when the initial drug concentration in the shell is 0.2 (Fig. 6). In these cases, the rate of release decreases constantly with time.

Conclusions

After earlier studies paving the way for new dosage forms with core and shell made of non-erodible polymer, further development of these dosage forms has been made in this paper. The initial concentration of drug is lower in the shell than in the core in order to reduce the rate of delivery at the beginning of the process, and to lead to a more constant rate of delivery during the process.

Besides the characteristics of the core with its radius and initial drug concentration, two parameters appear of interest, namely, the initial drug concentration in the shell and its thickness.

Some dosage forms of this type with given values for these parameters are able to deliver the drug at a constant rate throughout the entire duration of the process.

The experiments and calculations described in this paper were conducted with an in vitro test and a constant volume of liquid. With an in vivo test, the problem is different due to the absorp-

tion of drug through the gastric membrane and of the gastrointestinal tract. However, the model can follow the general process with slight changes in the boundary conditions if all the conditions are known.

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