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Spherical oral polymer–drug device with two polymers for constant drug delivery

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Summary

In order to attain a constant rate of delivery of sodium salicylate as a drug, spherical oral devices were prepared and studied. They were obtained by following this two-stop process: (i) the drug was dispersed in Eudragit as polymer, with the help of a little alcohol, and the mixture was pressed into calibrated spheres; and (ii) the spheres, previously dried, were surrounded with a thin layer of constant thickness of gelucire. These devices exhibited a constant rate of delivery of the drug when soaked in a synthetic gastric liquid. A model built for the study of membranes in spherical form was successfully tested. As a result, the rate of delivery was shown to be inversely proportional to the thickness of the layer of Gelucire.

Introduction

All conventional dosage forms, except for continuous intravenous perfusion, do not release drugs according to the kinetics of a first-order reaction. For an oral form, the drug is usually very rapidly liberated from its dosage form and quickly builds up to a high concentration, which then falls exponentially under the next dose. As a result, there is an undulating concentration pattern of the drug in the blood and tissues, in which high concentrations alternate with low concentrations. The optimal therapeutic level is only briefly present in this case.

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Distribution of a drug in an organism can only be in equilibrium when its rate of continuous administration is the same as the rate of continuous elimination over a prolonged period. Until now, achievement of this equilibrium has not been possible in therapeutics, since conventional oral forms do not release the drug continuously (Heilman, 1984; Peppas et al., 1980; Peppas, 1985).

Recently, efforts have been directed to the development of methods for the safer administration of drugs than the conventional methods. Special attention was given to regulating the amount of drug released by means of monolithic devices where the drug was previously dispersed in a polymer matrix (Fessi et al., 1982; Touitou and Donbrow, 1982; Heller, 1984; Focher et al., 1984). In order to describe the dissolution process of the drug from the polymer matrix, several theories were put forward (Gurny et al., 1982; Touitou and

Donbrow, 1982; Brossard et al., 1983; Teillaud and Pourcelot-Roubeau, 1984; Nicklasson et al. 1985). In all cases, experimental data were obtained only for short periods of time, and the process could be expressed as the square-root law of time dependence with the amount of drug transferred. Other studies have reported results on the simultaneous transfer of the liquid into, and the drug out of the polymer matrix when the galenic form made contact with the liquid (Messadi and Vergnaud, 1981; Messadi et al., 1983; Taverdet and Vergnaud, 1984; Droin et al., 1985; Eddine et al., 1986). In the case of a solid drug, the liquid penetrated the matrix and dissolved the drug which could diffuse out into the exterior liquid. Both these transfers were found to be controlled by diffusion under transient conditions.

The purpose of the present paper was to show that galenic forms able to deliver the drug at constant rate could be attained by using simple devices. The basis of the method was to use simultaneously: (i) a spherical form obtained by dispersing the drug in a biocompatible and non-degradable polymer such as Eudragit; and (ii) a spherical membrane made of polyglycide fatty esters with controlled hydrophilic properties. The former device, spherical in shape, was surrounded with a membrane of waxy form. As it is well known (Crank, 1975) that a membrane separating two media with constant concentrations is able to deliver the diffusing matter at a constant rate when stationary conditions are attained. In the case at hand, the layer made of Gelucire could play the role of the above membrane if the drug located in the internal polymer sphere had a high enough rate.

Another purpose of the present work was to describe a simple model able to describe the process of drug delivery and to correlate the rate of release with some parameters of interest, such as the thickness of the layer of Gelucire. The model considered was that of a membrane with constant layer surrounding a sphere with a constant concentration. As our aim was to obtain oral galenic forms, experiments were carried out in synthetic gastric liquid.

Theoretical

Assumptions

The following assumptions were made to describe the process in order to simplify the problem.

(i) The galenic form was made of two concentric spheres of radius R_1 and R_2. The smaller sphere of radius R_1 was obtained by dispersing the drug in Eudragit as polymer, while the spherical part between the radius R_1 and R_2 was full of Gelucire.

(ii) Two matter transfers took place: the former was concerned with the liquid entering the polymer and dissolving the drug, and the latter was concerned with the drug dissolved into the liquid located in the polymer (Droin, 1985; Eddine, 1986).

(iii) Both these transfers were controlled by transient diffusion.

(iv) The diffusivity was higher for the liquid than for the drug, as it was observed from experiments, either through the polymer Eudragit or through the Gelucire.

Mathematical treatment

In spite of the complexity of the problem, a mathematical treatment could be made with the help of the above assumptions in order to describe the process.

The Fick's equation describing the transient diffusion through a sphere was:

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

which became when D is constant:

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

The initial and boundary conditions corresponding with the above assumptions were as follows (Fig. 1) (Crank, 1975, p. 99)

Internal sphere

$$t = 0 \quad r \leqslant R_1 \quad C_s = C_{si} \tag{3}$$
$$R_1 < r < R_2 \quad C_s = 0$$

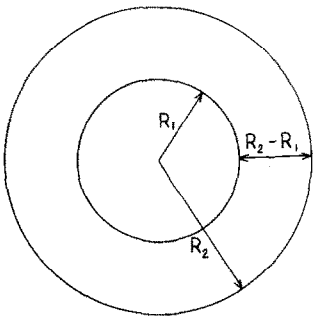

Fig. 1. Scheme of the spherical galenic form. R_1 = radius of the sphere made of Eudragit and sodium salicylate. $R_2 - R_1$ = thickness of the layer of Gelucire playing the role of membrane.

Constant

$$t > 0 \quad \begin{cases} r = R_1 & C_s = C_{si} \quad (4) \\ r \geqslant R_2 & C_s = 0 \quad (4') \\ 0 < r < R_2 & C_s = C_{sr} \quad (4'') \end{cases}$$

Under these conditions an analytical solution could be found for Eqn. 2, and the concentration of the drug through the sphere of radius R_2 was:

$$C(r, t) = \frac{R_1 \cdot C_{si}}{r} + \frac{R_1 \cdot C_{si}(R_1 - r)}{r(R_2 - R_1)} - \frac{2}{r\pi} \cdot \sum_{n=1}^{\infty} \frac{R_1 \cdot C_{si}}{n} \cdot \sin\left(\frac{n\pi(r - R_1)}{R_2 - R_1}\right) \times \exp\left[-\frac{n^2 \cdot \pi^2 \cdot D \cdot t}{(R_2 - R_1)^2}\right] \quad (5)$$

The amount of drug transferred from the galenic form into the external liquid up to time t was obtained by integrating:

$$M_t = 4\pi R_2^2 \int_0^t -D \cdot \frac{\partial C}{\partial r} \cdot dt \quad \text{for } r = R_2 \quad (6)$$

which gave:

$$M_t = \frac{R_1 \cdot C_{si} \cdot D}{R_2(R_2 - R_1)} \cdot t - \frac{2(R_2 - R_1)^2}{\pi^2 \cdot D} \cdot \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} \cdot \exp\left(-\frac{n^2 \cdot \pi^2 \cdot D \cdot t}{(R_2 - R_1)^2}\right) - \frac{(-1)^n}{n^2} \cdot 4\pi R_2^2 \quad (7)$$

The series in Eqn. 7 is convergent and tends to 0 for high value of time. In the case of a long time Eqn. 7 became:

$$M_t = \frac{C_{si} \cdot R_1 \cdot D}{R_2(R_2 - R_1)} \cdot \left[t - \frac{(R_2 - R_1)^2}{6 \cdot D}\right] \cdot 4\pi R_2^2 \quad (7')$$

the rate of the matter transfer being constant with the time.

As shown in Fig. 2, two characteristics were of interest, the slope of the linear $M_t - t$ curve and the intercept on the ordinate of this straight line:

Intercepts on the ordinate: $t = \frac{(R_2 - R_1)^2}{6 \cdot D}$ (8)

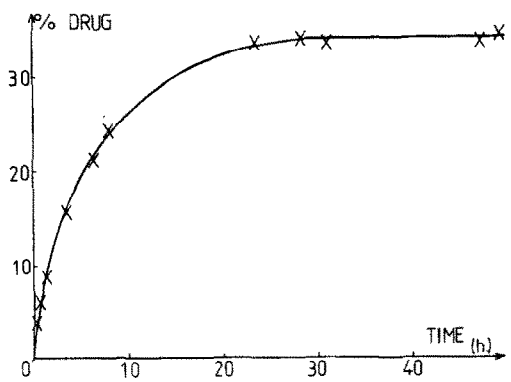

Fig. 2. Kinetics of the drug released in synthetic gastric liquid by using a spherical device made of Eudragit and sodium salicylate. Eudragit–drug: 50/50% in weight. Diameter = 0.85 cm; 415 mg; pH = 1.2.

Slope of linear $M_t - t$ curve:

$$S = \frac{C_{si} \cdot R_1 \cdot D}{R_2(R_2 - R_1)} \cdot 4\pi R_2^2 \qquad (9)$$

List of symbols

C = concentration C_{si} initial concentration
D = diffusivity of the drug
R_1 = radius of the sphere made of Eudragit and drug
R_2 = radius of the spherical device
$R_2 - R_1$ = thickness of the layer of Gelucire
n = integer for calculating the value in the series
M_t = amount of drug delivered at time t
S = slope of the straight line shown in Figs. 3–6 and Eqn. 9.

Experimental

Materials

The following materials were used:

Sodium salicylate as the drug

Eudragit RS, a copolymer of dimethylaminoethylacrylate and ethylmethacrylate of mol. wt. = 150,000 (Röhm Pharma) as polymer matrix for the sphere of radius R_1

Gelucire 46/07, a waxy solid made of partial glycerides and polyglycides fatty esters with controlled hydrophilic properties (Gattefossé, France) was chosen for the spherical coating surrounding the sphere of radius R_1

Eudragit and drug in powder form were mixed in a mortar, and transformed into an homogeneous thick paste after pulverisation with a small amount of ethanol which is a solvent of Eudragit. Spherical beads were obtained from this paste, and dried until complete evaporation of ethanol (for days at room temperature).

These spheres made of Eudragit and drug were surrounded with a spherical coating made of Gelucire, by dropping the sphere into liquid Gelucire at 60 °C for 2–5 s. The coating became hard after cooling to room temperature. The thickness of the coating of Gelucire was controlled either by selecting the right time of soaking for thin coatings, and by soaking in Gelucire for a recent time the galenic form with Gelucire for obtaining thicker coatings.

Determination of parameters of matter transfers

Experiments were carried out in a closed flask with a controlled rate of stirring. The spheres (405–415 mg), inserted in a fiberglass basket, were soaked in synthetic gastric liquid (100 ml) kept at 37 °C with the composition: pH = 1.2; 1000 ml of aqueous solution; 80 ml HCl 1 N; 2 g NaCl.

Samples of liquid were taken at intervals for analysis and the spheres weighed. The amount of sodium salicylate released from the galenic form was measured by using a double-beam UV spectrophotometer (Beckman D-G) calibrated at 303 nm.

Characteristics of the samples

Several galenic forms were prepared with the constant percentage of drug (50% in weight) for the sphere of radius R_1, and with various values for the thickness of Gelucire ranging from 0.014 to 0.020 cm.

Results

Some results were obtained for the kinetics of release of the drug into synthetic gastric liquid from the two following kinds of drug–polymer devices. (i) The device was made by dispersing the drug into the polymer, with a ratio of 50% in weight. (ii) The new device was prepared by surrounding the above device with a layer of Gelucire with a definite thickness.

An attempt at a theoretical study was then made in order to find a relation between the rate of delivery for the drug and the thickness of the layer of Gelucire surrounding the former device.

Experimental results

Case of the former device

The kinetics of release of the drug in synthetic gastric liquid is shown in Fig. 2, in case of the former device, when the drug was dispersed into Eudragit as polymer. Some results could be not-

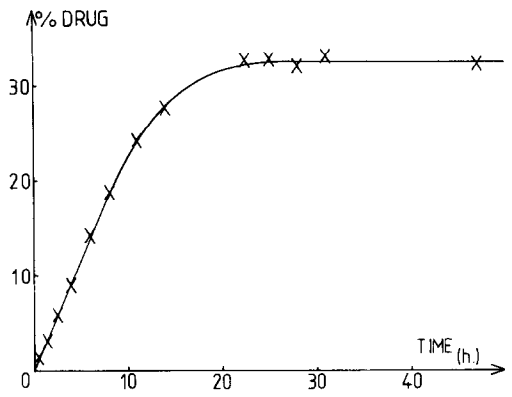

Fig. 3. Kinetics of the drug released in synthetic gastric liquid obtained with our polymer–drug device. Eudragit–drug: 50/50% in weight. Diameter = 0.85 cm; thickness of Gelucire = 0.14 mm; pH = 1.2; 406 mg.

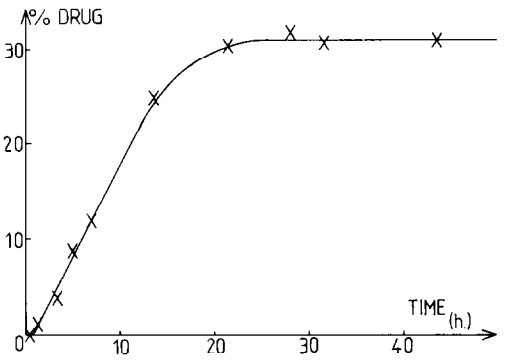

Fig. 5. Kinetics of the drug released in synthetic gastric liquid obtained with our polymer–drug device. Eudragit–drug: 50/50% in weight. Diameter = 0.85 cm; thickness of Gelucire = 0.17 mm; pH = 1.2; 414 mg.

iced from this curve. (i) The amount of drug in the liquid at the end of the process, at equilibrium, is around 34%, when the device contained 50% of drug originally. (ii) The rate of delivery was very high at the beginning of the process, and then decreased regularly with time.

Case of the latter device

The kinetics of release of the drug in the synthetic gastric liquid obtained by using the latter device containing a layer of Gelucire, is shown in Figs. 3–6 for various thicknesses of this layer ranging from 0.14 to 0.20 mm, while the internal part of the device was the same with 50% of drug in weight. Four results of interest are worth pointing out.

(i) The amount of drug delivered at equilibrium into the synthetic gastric liquid was around 30–33%. A slight increase in this amount of drug transferred into the liquid could be appreciated when the thickness of the layer of Gelucire was increased.

(ii) In all cases, a straight line was obtained for the kinetics of drug released into the liquid. The rate of delivery was constant within a very large range of the transfer, and we can say that this rate is constant along the whole process.

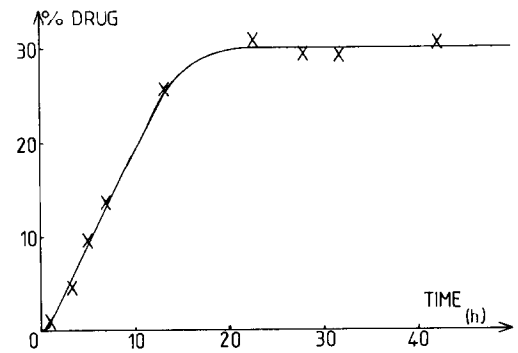

Fig. 4. Kinetics of the drug released in synthetic gastric liquid obtained with our polymer–drug device. Eudragit–drug: 50/50% in weight. Diameter = 0.85 cm; thickness of Gelucire = 0.16 mm; pH = 1.2; 410 mg.

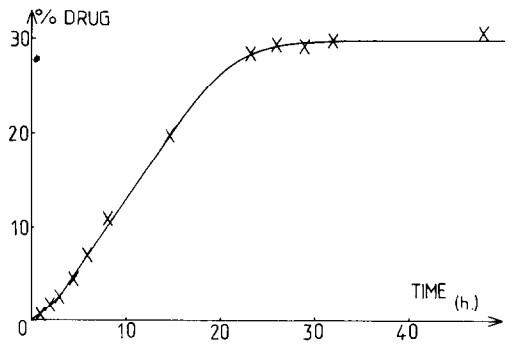

Fig. 6. Kinetics of the drug released in synthetic gastric liquid obtained with our polymer–drug device. Eudragit–drug: 50/50% in weight. Diameter = 0.85 cm; thickness of Gelucire = 0.20 mm; pH = 1.2; 409 mg.

(iii) The rate of delivery of drug in the liquid was found to be inversely proportional to the thickness of the layer of Gelucire.

(iv) The time for which the process was conducted under transient conditions was very short.

All these results found for the latter device were of great interest in the case of oral galenic forms. They showed that the purpose of having a release of drug with a constant rate could be attained with galenic forms which were not difficult to prepare.

Theoretical attempts for describing the process

As shown in our experiments, the process was followed to form the oral form which was then soaked in the synthetic gastric liquid: the liquid entered the Gelucire and polymer Eudragit, provoking a swelling of polymers, then dissolved the drug and was responsible for the transfer of the drug into the liquid.

An attempt for a theoretical study was made by considering that the process was controlled by diffusion as shown in previous studies.

By assuming that the rate of transfer of the drug was higher through the polymer Eudragit than through the polymer Gelucire, we found that the drug was constantly available in the Eudragit part, providing a concentration which could be considered as constant on the internal face of Gelucire. On the other hand, the concentration of the drug was very low during the whole process in the liquid phase.

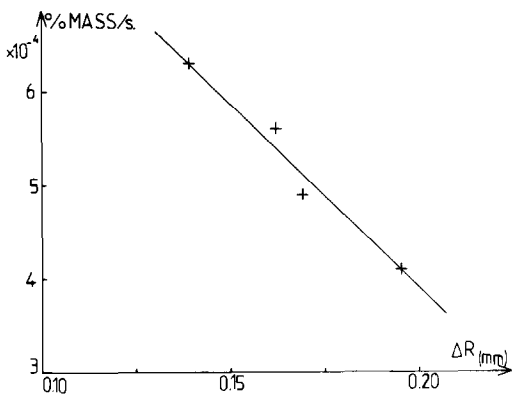

Fig. 7. Rate of delivery of the drug in synthetic gastric liquid as a function of the thickness of the layer of Gelucire (loss in weight of drug per second). Layer in mm; pH = 1.2.

TABLE 1

Rate of drug delivery and thickness of Gelucire layer

Thickness (mm)	Rate of delivery (mg/h)	Duration for constant rate (h)
0.14	9.4	11
0.16	8.4	12
0.17	8.0	13
0.20	6.0	16

Under these conditions, a simple model based on a spherical membrane separating two media with a constant concentration of drug could be tried and tested.

The most important result in the present work was certainly the rate of delivery of the drug. So, the model was tested by considering the Eqn. 9 obtained in this case, and by plotting the rate of delivery of the drug as a function of the thickness of Gelucire playing the role of membrane. The straight line obtained in Fig. 7 could be appreciated, showing the validity of the model. The values of the rate of the drug delivery were shown in Table 1 (expressed in mg/h). The duration for which this constant rate was obtained was also noticed, as well as the thickness of the layer of Gelucire playing the role of membrane.

Moreover, this relation between the rate of release of the drug and the thickness of the membrane was of interest, particularly from a theoretical point of view. It enabled any users to build galenic forms prepared in this way by giving the right value of the external Gelucire layer necessary for obtaining the desired rate of drug released.

TABLE 2

Diffusivity for the drug diffusion

Thickness of layer (mm)	Diffusivity $\times 10^9$ (cm^2/s)
0.14	6.5
0.16	6.3
0.17	6.0
0.20	5.8

The values of diffusivities could be obtained from experiments with help of Eqn. 9 and the rates of delivery of the drug shown in Figs. 3–6.

These values noted in Table 2 were considerably lower than those obtained in the case of an oral form made of drug dispersed in Eudragit as polymer (shown in Fig. 2), the diffusivity of this latter device being of the order of magnitude of 2×10^{-7} with the same units (cm^2/s). This fact could be considered as interesting from a theoretical point of view, because our model was built on the basis that the rate of drug transfer was higher within the first device made of Eudragit and drug than through the membrane of Gelucire.

Conclusions

Oral galenic forms prepared by surrounding a spheric drug–polymer device with a layer of Gelucire having a constant thickness were experimented with in synthetic gastric liquid. These galenic forms were found to deliver the drug, sodium salicylate, into the liquid with a constant rate for a long time (from the beginning to the end of the process).

A simple model based on a membrane of constant thickness separating two media located in concentric spheres was successfully tested. Not only was the model able to follow the kinetics of release of drug in the liquid, but it could also correlate with good agreement the rate of drug delivery with the thickness of the layer of Gelucire playing the role of membrane. As a result, the rate of release of drug was found to be inversely proportional to the thickness of Gelucire.

Since the way of preparing the device was not complicated, and the layer of the membrane could be controlled, these kinds of devices could be experimented with in various cases of oral forms.

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