International Journal of Pharmaceutics, 77 (1991) 81–87

IJP 02538

Research Papers

Dosage forms with a polymer matrix and a swelling polymer

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(Received 7 February 1991)
(Modified version received 29 April 1991)
(Accepted 20 May 1991)

Key words: Sodium salicylate; Eudragit RL; Sumikagel; Controlled release; Gastrointestinal tract simulation

Summary

New oral dosage forms able to deliver the drug have been prepared and studied. They consist of Eudragit RL playing the role of a binding and diffusing matrix, and of polymer Sumikagel which swells to various extents according to the nature of the liquid. The rate of drug delivery is thus higher in intestinal liquid than in gastric liquid. A simulation of the gastrointestinal tract is obtained by using in vitro tests, for determining the behaviour of these dosage forms.

Introduction

The fluctuating drug concentrations in blood and tissues caused by conventional dosage forms lead to an insufficient influence on the mechanisms of disease and are related to the excessive use of a drug. Initial overdosing produces a high frequency of side effects, leading under certain circumstances to damage. Workers (Zaffaroni, 1971; Heilman, 1984) have introduced 'therapeutic systems' which can achieve major advances in improving and rationalizing the administration of therapeutic agents. The specification is not the total dose given but the rate and duration of drug administration. Various oral dosage forms able to control the rate of delivery of the drug in the stomach have been prepared and studied. The simplest forms consist of a drug dispersed in a polymer, the polymer playing the role of a matrix (Fessi et al., 1982; Touitou and Donbrow, 1982; Focher et al., 1984; Heller, 1984; Droin et al., 1985; Armand et al., 1987; Bidah and Vergnaud, 1990). The dependence on the square root of time for drug delivery has been explained on the basis of diffusion (Gurny et al., 1982; Brossard et al., 1983; Teillaud and

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List of symbols: n, integer for calculating the value in the series; r, radial abscissa; t, time; C, concentration; R, radius of bead; D, diffusivity; m_0, initial weight of bead; M_{in}, initial amount of drug in bead; M_∞, amount of matter transferred at equilibrium; M_t, amount of matter transferred at time t; $C_{r,t}$, concentration of drug or liquid at time t and position r; C_∞, concentration of liquid at equilibrium; C_{in}, initial concentration of drug.

Pourcelot-Roubeau, 1984; Nicklasson et al., 1985). In fact, the process is not so simple, and a double transfer takes place: the liquid enters the polymer, sometimes introducing swelling, dissolves the drug and enables the drug to diffuse out through the liquid located in the polymer matrix (Droin et al., 1985; Armand et al., 1987; Saber et al., 1988). Both these transfers are controlled by transient diffusion and the diffusivity of the drug increases with the liquid concentration in the dosage form. As a result, the drug delivery in the stomach is effectively controlled, but the rate of delivery is far from constant: with a rather high value at the beginning, the rate decreases steadily with time.

The first objective of this paper is to develop new dosage forms able to deliver the drug at a rate which is not only controlled by diffusion, in order to approach a constant rate. The basic idea for these forms is the introduction of another polymer with the drug in the polymer matrix, this polymer being able to swell to a considerable extent when in contact with a liquid. In fact, the polymer selected in this study, called Sumikagel, is capable of swelling to varying extents according to the nature of the liquid which is absorbed.

Another main purpose in this study is also to simulate the behaviour of these new dosage forms in the gastrointestinal tract with the help of in vitro tests. The dosage form is thus placed firstly in synthetic gastric liquid over a given period of time, and then immersed in synthetic intestinal liquid. The kinetics of drug delivery are followed during this period in the gastrointestinal tract, while the kinetics of liquid absorption by the dosage form are also determined in order to gain a fuller insight into the process.

Experimental

Assumptions

The following assumptions are made:

(i) The transports of liquid into and drug out of the dosage form are controlled by transient diffusion.

(ii) The drug, as well as the polymer Sumikagel are well dispersed into the polymer matrix.

(iii) The dimensions of the dosage form remain constant during the process.

(iv) The diffusivities are constant, as found from experiments.

(v) The concentration of liquid and drug on the surface of the dosage form reaches the equilibrium value as soon as it is immersed in the liquid.

(vi) The volume of liquid is so large with regard to that of the dosage form that the concentration of drug in the liquid is very low.

Mathematical treatment

The transient diffusion of the liquid and drug through the spherical dosage form is described by Fick's equation with constant diffusivity D:

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

With the above assumptions, an analytical solution exists for the problem. The concentration $C_{r,t}$ at position r and time t is given by the trigonometrical series for either the drug or the liquid:

$$\frac{C_{r,t} - C_{\text{in}}}{C_{\text{s}} - C_{\text{in}}} = 1 + \frac{2R}{\pi r} \cdot \sum_{n=1}^{\infty} \frac{(-1)^n}{n} \sin \frac{n\pi r}{R} \cdot \exp\left(- \frac{n^2 \pi^2}{R^2} Dt \right) \tag{2}$$

where C_{in} is the initial concentration of the drug or liquid ($C_{\text{in}} = 0$ for the liquid) and C_{s} denotes the concentration on the surface ($C_{\text{s}} = 0$ for the drug, $C_{\text{s}} = C_{\infty}$ for the liquid).

An easy simplification is obtained when $r = 0$, at the middle of the sphere, since $(R/n\pi r) \cdot \sin(n\pi r/R)$ tends to 1.

The total amount of diffusing substance M_t entering (liquid) or leaving (drug) the spherical dosage form is given by:

$$\frac{M_{\infty} - M_t}{M_{\infty}} = \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(- \frac{n^2 \pi^2}{R^2} Dt \right) \tag{3}$$

where M_∞ is the amount of matter transferred after infinite time.

Materials

The following materials are used for preparation of dosage forms: sodium salicylate as the drug; Sumikagel (Sumitomo Chem. Co., Japan) (Sumikagel, Osaka, Japan) in the form of a white powder is the swelling polymer. This acrylic acid-vinyl alcohol copolymer is safe in terms of health hazard. The grade selected in this study (SP-520) corresponds to a diameter average of 20 μm. The capacity of absorption (w/w%) ranges from 500–700 in pure water to 40–60 in saline (0.9% NaCl). Eudragit RL (Rhöm Pharma) is a copolymer of dimethylaminoethylacrylate and ethylmethacrylate of molecular weight 150000, with a low number of quaternary ammonium terminal groups. The ratio between the numbers of quaternary and ester terminal is around 1:20.

Dosage forms

Two types of dosage forms are prepared and tested as follows.

Dosage form I: sodium salicylate and Eudragit RL (50:50 wt%), in powder forms, are intimately mixed and transformed into a thick paste by adding a small amount of ethanol which is not a solvent for these materials (Droin et al., 1985; Magron et al., 1987; Laghoueg et al., 1989). Spherical beads are prepared from this paste and dried to completion at room temperature for 4 days.

Dosage form II: sodium salicylate, Eudragit RL and Sumikagel (45:45:10 wt%), in powder forms, are intimately mixed, and the paste obtained with a small addition of ethanol is transformed into spherical beads. These beads are dried in the same way as for dosage form I.

In vitro tests

Experiments are carried out in a closed flask with controlled temperature (37 °C) and rate of stirring. The dosage form in a fiber-glass basket is immersed in 200 ml of liquid.

Two types of liquid are used: (i) synthetic gastric liquid at pH 1.2, obtained by adding 80 ml HCl (1 N) and 2 g NaCl in 1000 ml of aqueous solution; (ii) synthetic intestinal liquid at pH 8, with 50 ml of 0.025 M borax solution and 20.5 ml HCl (0.1 N).

Small samples (0.2 ml) of liquid are taken at intervals, for measuring the concentration of drug with the help of a UV spectrophotometer (Hitachi 1100) calibrated at 207 nm, while the dosage form is weighed.

Experiments needing a change in solution are performed by immersing the dosage bead in synthetic gastric liquid, and then in synthetic intestinal liquid, successively.

Results

Two types of results are of interest: (i) The kinetics of drug release as well as those of absorption of liquid obtained with oral dosage form II (composed of Eudragit-Sumikagel-drug, 45:10:45 wt%), which compare favourably with the kinetics obtained with dosage form I (comprising Eudragit-drug, 50:50 wt%). These kinetics are determined either in synthetic gastric liquid at pH 1.2 or in synthetic intestinal liquid at pH 8. (ii) In vitro tests are used to simulate the gastrointestinal tract, by immersing the dosage form firstly in synthetic gastric liquid and then in synthetic intestinal liquid.

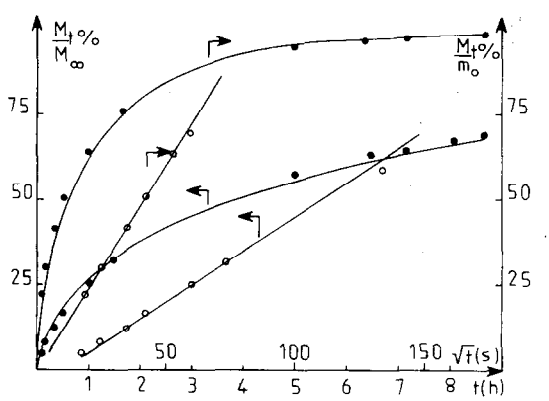

Fig. 1. Kinetics of release of drug (left) and of absorption of liquid (right) in synthetic gastric liquid at 37 °C. Dosage form II (Eudragit RL-Sumikagel-sodium salicylate, 45:10:45 wt%). $m_0 = 142.7$ mg; $R = 0.36$ cm, (●) Experimental; (—) calculated; (○) amount of liquid absorbed or drug released vs square root of time.

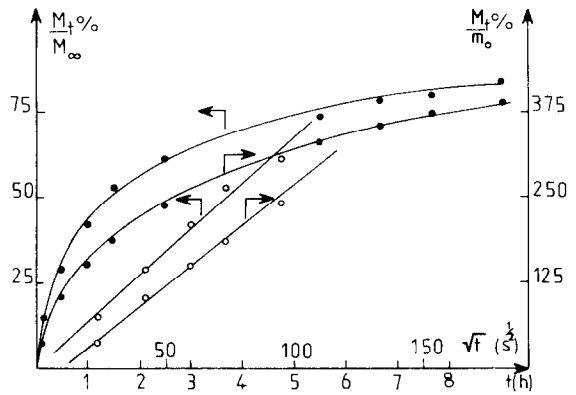

Fig. 2. Kinetics of release of drug (left) and absorption of liquid (right) in synthetic intestinal liquid at 37 °C. Dosage form II (Eudragit RL-Sumikagel-sodium salicylate, 45:10:45 wt%). $m_0 = 171.9$ mg; $R = 0.39$ cm. (●) Experimental; (—) calculated; (○) amount of liquid absorbed or drug released vs square root of time.

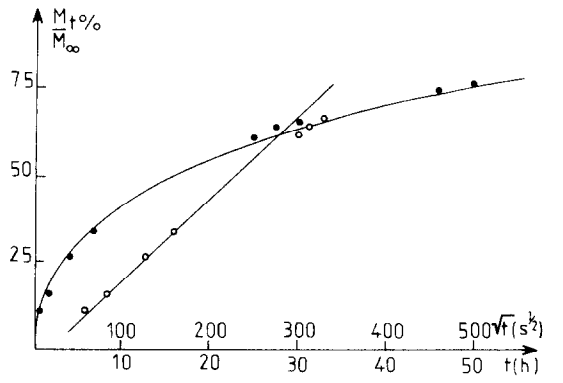

Fig. 3. Kinetics of release of drug in synthetic gastric liquid at 37 °C. Dosage form I (Eudragit RL-sodium salicylate, 50:50 wt%). $m_0 = 175.6$ mg; $R = 0.32$ cm. (●) Experimental; (—) calculated; (○) amount of drug released vs square root of time.

Kinetics of transport with the new dosage forms

The new oral dosage forms (dosage form II) are tested by immersing them either in synthetic gastric liquid at pH 1.2 or synthetic intestinal liquid at pH 8. From the measurements made on the concentration of drug in the liquid and in the weight of the dosage form, the kinetics of release of drug are determined as well as those of absorption of liquid by this form.

The kinetics determined from experiments are depicted in Fig. 1 for the case of dosage form II immersed in synthetic gastric liquid, and in Fig. 2 for immersion in synthetic intestinal liquid. From the slopes of the straight lines obtained by plotting the amount of matter transferred as a function of the square root of time, constant diffusivities are calculated with the help of Eqn 6:

$$\frac{M_t}{M_\infty} = \frac{6}{R}\left(\frac{D \cdot t}{\pi}\right)^{0.5} . \qquad (4)$$

The kinetics calculated by using Eqn 3 for either the liquid entering or the drug leaving the dosage forms are also shown in Fig. 1 for gastric liquid and in Fig. 2 for intestinal liquid.

The same kinetics are also observed and calculated for dosage forms of type I, composed of Eudragit and drug (50:50 wt%), in either synthetic gastric liquid (Fig. 3), or intestinal liquid (Fig. 4).

A number of conclusions can be drawn from these results:

(i) The process of drug delivery from dosage forms of type I (Eudragit-drug, 50:50 wt%) is controlled by transient diffusion, as shown previously (Droin et al., 1985). In fact, the process is more complex: the liquid enters the polymer, dissolves the drug and enables the drug to diffuse through the liquid located in the polymer (Armand et al., 1987; Saber et al., 1988).

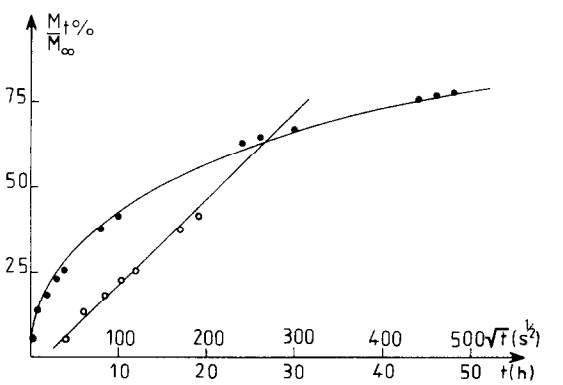

Fig. 4. Kinetics of release of drug in synthetic intestinal liquid at 37 °C. Dosage form I (Eudragit RL-sodium salicylate, 50:50 wt%). $m_0 = 152.7$ mg; $R = 0.31$ cm. (●) Experimental; (—) calculated; (○) amount of drug release vs square root of time.

(ii) The process for the two matter transports with dosage form II is also controlled by transient diffusion, with constant diffusivities. In fact, the diffusivities of the liquid and of the drug are constant, as shown in Figs 1 and 2, but a slight difference appears for the drug. The straight line obtained by plotting the amount of drug delivered as a function of the square root of time does not pass through the origin of the axes. There is a slight time delay for the release of drug at the beginning of the process. This is due to the fact that a significant amount of liquid in the dosage form is needed to dissolve the drug and thus permit its transport (Armand et al., 1987; Saber et al., 1988).

(iii) The diffusivity of drug in the case of dosage form I is about the same when the drug is immersed in synthetic gastric liquid or in synthetic intestinal liquid. All the drug located in the dosage form is released after a period of about 200 h.

(iv) The diffusivity of the drug is higher in the case of dosage form II than for dosage form I, as shown in Table 1. This difference which is already significant in the liquid of pH 1.2 is even more sensitive in the liquid of pH 8.

(v) The diffusivity in the case of dosage form II is higher for the liquid than for the drug when there are immersed in synthetic gastric liquid. The diffusivity is a little lower for the liquid than for the drug in the case of intestinal liquid. The amount of liquid absorbed by dosage form II is 5-fold higher in the case of intestinal liquid (500%) as compared to gastric liquid (100%).

TABLE 1

Diffusivities (cm^2/s; $D \times 10^8$)

	Dosage form	Diffusivities (cm^2/s) ($D \times 10^8$)		$100 \times M_\infty / M_{in}$	
		Gastric liquid	Intestinal liquid	Gastric liquid	Intestinal liquid
Drug	I	5.6	5.7	99	99
Drug	II	28	65	99	99
				$100 \times M_\infty / m_0$	
Liquid	II	163	48	100	500

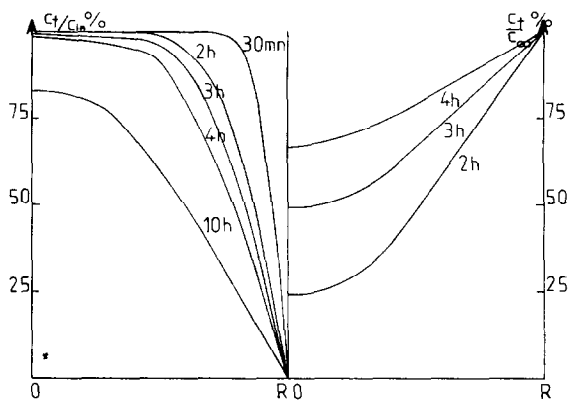

Fig. 5. Profiles of concentration developed within dosage form II in synthetic gastric liquid at 37 °C, at various times: drug (left); liquid (right).

(vi) The large amount of liquid absorbed by dosage form II is due to the presence of Sumikagel which is capable of swelling to a greater extent when in contact with liquid at pH 8 (500 wt%). Moreover, a synergistic effect is clearly obtained with the liquid at pH 8, as the increase in the amount of liquid absorbed by dosage form II is considerably higher than the amount of liquid due to Sumikagel.

Simulation of the gastrointestinal tract

For simulating the gastrointestinal tract, dosage forms II are immersed successively in synthetic gastric liquid and then in intestinal liquid. The time of immersion in synthetic gastric liquid is a parameter of interest, and is selected to be within the range 2–4 h.

In order to gain further insight into the process, especially at the end of the stage of immersion in synthetic gastric liquid, the profiles of concentration developed within the dosage form are plotted for the drug (Fig. 5, left) and the liquid (Fig. 5, right). Of course, these profiles are calculated by using Eqn 2 and the values of diffusivities obtained in the gastric liquid.

The kinetics of drug delivery and of liquid absorption are illustrated for various times of immersion in gastric liquid: 2 h (Fig. 6), 3 h (Fig. 7) and 4 h (Fig. 8).

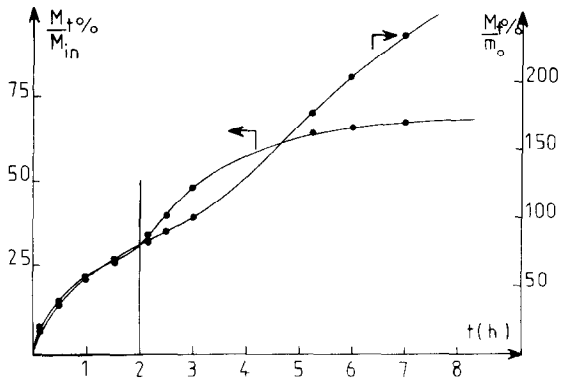

Fig. 6. Kinetics of release of drug (left) and absorption of liquid (right) from dosage form II (Eudragit RL-Sumikagel-sodium salicylate, 45:10:45 wt%) when immersed for 2 h in synthetic gastric liquid, and then in synthetic intestinal liquid. $m_0 = 151.7$ mg; $R = 0.366$ cm.

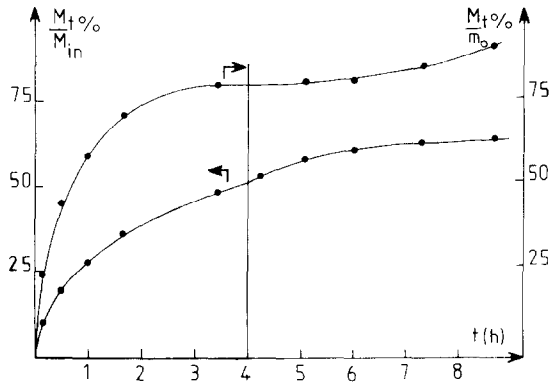

Fig. 8. Kinetics of release of drug (left) and absorption of liquid (right) from dosage form II (Eudragit RL-Sumikagel-sodium salicylate, 45:10:45 wt%) at 37 °C, when immersed for 4 h in synthetic gastric liquid, and then in synthetic intestinal liquid. $m_0 = 136.9$ mg; $R = 0.355$ cm.

Some results are worth noting:

(i) The drug is, of course, delivered partly in gastric liquid and in intestinal liquid.

(ii) The rates of delivery of the drug are higher in intestinal liquid than in gastric liquid, and are responsible for the change in shape of the kinetic curves at the time at which the dosage forms are immersed in intestinal liquid.

(iii) Eqns 2 and 3 can be used for calculating the profiles of concentration and the kinetics of drug delivery only during the initial stage of immersion in gastric liquid, as these equations are determined with an initially uniform concentration within the dosage form. A numerical model is thus necessary for calculating the kinetics of release of drug in the second stage of immersion in intestinal liquid.

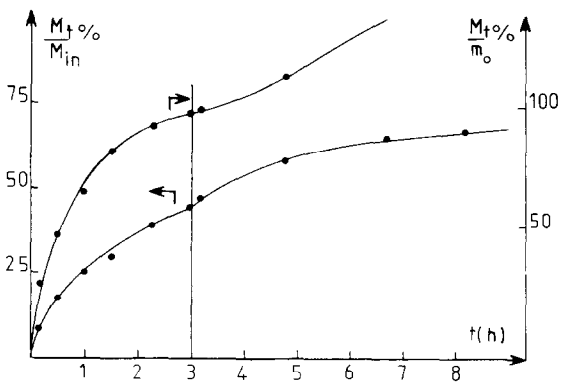

Fig. 7. Kinetics of release of drug (left) and absorption of liquid (right) from dosage form II (Eudragit RL-Sumikagel-sodium salicylate, 45:10:45 wt%) when immersed for 3 h in synthetic gastric liquid, and in synthetic intestinal liquid. $m_0 = 146.1$ mg; $R = 0.362$ cm.

Conclusions

A new type of oral dosage forms is described, composed of two polymers mixed with the drug. The polymer matrix is Eudragit RL, while the polymer Sumikagel plays the role of a swelling agent. Sumikagel is capable of swelling to differing extents according to the nature of the liquid in which it is immersed, e.g., it swells to a significant extent in liquid at pH 1.2 and to an even greater extent in liquid at pH 8. Eudragit RL, well known for its binding properties, is a good matrix for the dosage forms.

The presence of Sumikagel in dosage forms is able to increase the diffusion of the liquid and of the drug within the bead, and especially in synthetic intestinal liquid at pH 8.

The kinetics of matter transfers (liquid, drug) with these dosage forms are studied by simulating the gastrointestinal tract with the help of in vitro tests. These forms are able to release the drug in gastric liquid as well as in intestinal liquid at a

higher rate than the classical forms made of Eudragit and drug.

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