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New oral dosage form with two polymers: Gelucire and Sumikagel

D. Bidah and J.M. Vergnaud

Laboratory of Materials and Chemical Engineering, Faculty of Sciences, University of Saint-Etienne, 23, Docteur Paul Michelon, Saint-Etienne 42023 (France)

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Summary

A new oral dosage form is described and studied. It consists of dispersing the drug into Gelucire, with an addition of a small amount of a polymer called Sumikagel^{R}. Gelucire plays a role of an erodible polymer matrix with a low rate of erosion. Sumikagel swells to various extents depending on the pH of the liquid in which it is immersed. As a result these new dosage forms disintegrated completely in aqueous solution of pH 8 in less than 1 h, while the rate of drug delivery remained constant during the whole process. The delivery of the drug is successfully described by transient diffusion when the liquid is acid with pH 1.2. A simulation of the gastrointestinal tract is studied by using in-vitro tests, from the experimental and theoretical point of view.

Introduction

The release of drug from classical dosage forms administered via the gastrointestinal tract is controlled by dissolution. The drug being dissolved very rapidly, the drug concentration in the gastric liquid and blood builds up to a high value and then falls exponentially until the following dose, provoking an undulating concentration history with various drawbacks for the patient (Peppas et al., 1980; Heilman, 1984; Peppas, 1985).

Correspondence: J.M. Vergnaud, Laboratory of Materials and Chemical Engineering, Faculty of Sciences, University of Saint-Etienne, 23, Docteur Paul Michelon, Saint-Etienne 42023, France.

Therapeutic systems able to control amount of drug over a defined period of time have laid the way for optimizing drug effects through oral dosage forms. Among them, monolithic devices where the drug is dispersed in polymer playing the role of a matrix have been considered, this polymer being non-degradable (Fessi et al., 1982; Touitou and Donbrow, 1982; Focher et al., 1984; Droin et al., 1985; Malley et al., 1987) or degradable (Heller, 1984; Laghoueg et al., 1989; Bidah and Vergnaud, 1990).

Various theories have been elaborated in order to describe the process of release of the drug, by considering either diffusion (Gurny et al., 1982; Touitou and Donbrow, 1982; Brossard et al., 1983; Teillaud and Pourcelot-Roubeau, 1984; Nicklas-

son et al., 1985; Armand et al., 1987; Saber et al., 1988) in the case of non-erodible polymers, or erosion with erodible polymers (Magron et al., 1987; Laghoueg et al., 1989; Bidah and Vergnaud, 1990). In fact, the problem is rather complex, especially with dosage forms made of an erodible polymer, as not only erosion of the polymer takes place, but also diffusion of the liquid through the polymer and even diffusion of the drug through the liquid located within the polymer (Taverdet and Vergnaud, 1986; Liu et al,. 1988; Vergnaud, 1990).

There are two other problems also of interest:

(i) When the solubility of the drug is low in the acid gastric liquid as well as the rate of dissolution, and when it is necessary to help the drug dissolve in this liquid by provoking the extraction of the drug out of the dosage form.

(ii) When the solubility is very low in the acid gastric liquid, and rather high in the intestine where the pH is around 8.

The first purpose in this paper is to describe a new dosage form where the drug is dispersed in an erodible polymer such as Gelucire, with an addition of a small amount of another polymer in powder form called Sumikagel. The main property of Sumikagel is a high capacity of absorption of water which depends on the pH of the liquid: rather high in acid liquid, it becomes still higher in a liquid of pH 8. The change in dimension of Sumikagel is then capable of provoking a faster erosion of Gelucire and controlling the delivery of the drug.

Another aim of this study is to find a solution for the release of a drug, the solubility of which is very low in the acid gastric liquid, and higher in the intestine liquid of pH around 8. The kinetics of release of drug from these dosage forms are thus determined either in an acid liquid of pH 1.2 or in liquid of pH 8, and the process of release is described by considering diffusion which can explain the square root of time dependence of the drug delivery. Moreover, experiments are performed by immersing the dosage form in an acid synthetic gastric liquid, and then in another liquid of pH 8, successively, in order to simulate the gastrointestinal path of the dosage form.

Experimental

Materials

The following components have been used. Sodium salicylate in powder form (COPER) for the drug. Gelucire 46.7 (Gattefossé, 1983) for the erodible polymer matrix. Gelucire is a mixture of polyglycide fatty esters with well defined hydrophilic properties. The ratio between the number of quaternary ammonium and ester terminals is about 1 : 20. Gelucire 46.7 melts at 46 °C (drop point: Mettler) and its hydrophilic-lipid balance value (HLB) is 7, in the middle of the 1–14 range. Sumikagel (Sumitomo Chemical Co. Ltd, Japan) in white powder has been used for the swelling polymer. This is an acrylic acid-vinyl alcohol copolymer. The SP-520 grade with a diameter average of 20 μm for the grain has been selected. Its absorbing capacity in w/w% ranges between 500 and 700 in pure water and 40 and 60 in salted water (0.9% NaCl). This resin is safe in terms of health hazard (Sumikagel).

Preparation of dosage forms

The grains of sodium salicylate and Sumikagel intimately mixed are dispersed in melted Gelucire heated to around 50 °C. The liquid mixture is stirred thoroughly in order to have the components distributed properly. Various spherical beads are prepared from this paste, with a ratio in wt%: sodium salicylate 45%-Simikagel 10%-Gelucire 45%.

In vitro tests

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

Two kinds of liquid have been prepared: the one simulating the acid gastric liquid, with 1000 ml of aqueous solution with 80 ml HCl (1 N) and 2 g NaCl, at pH 1.2; the other simulating the intestine liquid with 50 ml of 0.025 M borax solution and 20.5 ml HCl (0.1 N), at pH 8. The 0.025 M borax solution is obtained with 9534 g borax ($Na_2B_4O_4 \cdot 10\ H_2O$) in 1000 ml of aqueous solution.

A small sample (1 ml) of liquid is extracted for analysis of the drug, by using a UV spectrophotometer (Hitachi U-1100) calibrated at 207 nm, after dilution in 50 ml of liquid at pH 1.2.

For the experiments needing a change of solution, the bead in the fiber-glass basket is extracted out of the first solution, and immersed in the second solution. In our experiments, the pH of the first solution is 1.2, while the pH of the second solution is 8. Great care is taken to eliminate all the liquid wetting the bead and the basket before reimmersing it in the second solution.

Theoretical

Assumptions

The following assumptions are made in order to clarify the problem.

(i) The dosage forms are spherical in shape. The drug and Sumikagel are very well distributed in the polymer matrix, so that the dosage form is homogeneous.

(ii) The liquid is transferred within the dosage form by a process controlled by diffusion, as shown in many cases, whatever the polymer (Droin et al., 1985; Armand et al., 1987; Malley et al., 1987; Saber et al., 1988) and dissolves drug. The drug can thus diffuse out of the dosage form through this liquid located in the polymer.

(iii) The process of drug delivery is thus controlled by transient diffusion, as proved by the square root dependence of the amount of drug liberated with time.

(iv) The radius of the bead does not change significantly, at least at the beginning of the process, and the diffusivity is constant.

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

(vi) The concentration of the drug on the surface of the dosage form falls to a very low value, as soon as this dosage form has been immersed in the liquid.

Mathematical treatment

The change in concentration of drug in the spherical dosage form is described by Fick's law expressing the transient diffusion:

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

where C is the concentration of drug at position r and time t and D is the constant diffusivity.

The initial and boundary conditions are very simple.

$$t = 0 \quad 0 \le r \le R \quad C = C_{in} \quad \text{dosage form} \tag{2}$$

$$t > 0 \quad r = R \quad C = 0 \quad \text{bead surface} \tag{3}$$

where R is the radius of the dosage form and C_{in} is the uniform initial concentration of drug in the dosage form.

In the case of constant diffusivity, and with these simple initial and boundary conditions, an analytical solution exists for Eqn 1. The amount of drug leaving the dosage form up to time t, M_t, is expressed as a fraction of the corresponding amount after infinite time, M_∞, by Eqn 4 (Crank, 1975):

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(- \frac{n^2 \pi^2}{R^2} Dt \right) \tag{4}$$

n being an integer.

For a very short period of time, when $M_t/M_\infty < 0.4$, the amount of drug leaving the dosage form is proportional to the square root of time:

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

Results and Discussion

Two kinds of results are of interest: (i) the study of the behaviour of the new dosage forms with Gelucire and Sumikagel as polymer matrices when they are immersed into a liquid of pH 1.2 or a liquid of pH 8, by considering especially the kinetics of delivery of the drug; (ii) the kinetics of delivery of the drug when the dosage form is immersed successively in a liquid of pH 1.2 and in a liquid of pH 8.

TABLE 1

Characteristics of the oral dosage forms

Weight (mg)	Radius (cm)	pH of liquid	D ($\times 10^7$) (cm^2/s)	M_∞ (after 1 h)	Fig.
120.1	0.28	1.2	6.6	50%	1
93.2	0.26	8	5.7	50%	2
120.5	0.35	1.2	4.9	37%	3
125.2	0.354	8		96%	4.I
130.8	0.36	8		95%	4.II
126.8	0.356	1.2–8			5.I
122.5	0.352	1.2–8			5.II
129.3	0.358	1.2–8			5.III

Kinetics of delivery of the drug out of the new dosage forms

More simple dosage forms consisting of Gelucire 46.7 (50 wt %) and Na salicylate (50 wt %) are studied firstly by immersing the dosage forms either in synthetic gastric liquid (pH 1.2) or in synthetic intestine liquid (pH 8). The dosage forms have the characteristics described in Table 1. The experimental (plots) as well as the theoretical kinetics of delivery of the drug are drawn in Fig. 1 when the liquid is the synthetic gastric liquid, and in Fig. 2 when the pH of the liquid is 8. In each figure, the amount of drug in the liquid is also plotted as a function of the square root of time. The following conclusions can be drawn:

(i) A straight line is obtained by plotting the amount of drug delivered as a function of the square root of time, at the beginning of the process when $M_t/M_\infty < 0.4$.

(ii) The theoretical curves obtained by using the series in Eqn 4 are very well superimposed with the experimental kinetics.

(iii) The diffusivities for the transport of drug are about the same when the pH of the liquid is 1.2 or 8.

The behaviour of the new dosage forms containing (10%) Sumikagel besides the drug (45%) and Gelucire (45%), is described in Fig. 3 in the case of synthetic gastric liquid and in Fig. 4 when

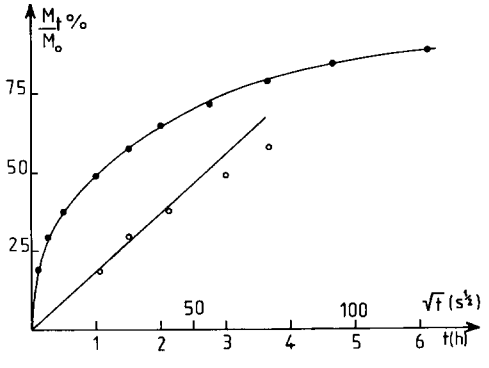

Fig. 1. Kinetics of release of drug in 200 ml of synthetic gastric liquid (pH 1.2) from the oral dosage form: 50% Gelucire-50% sodium salicylate. (●) Experimental; (———) calculated. (○) Amount of drug released vs square root of time.

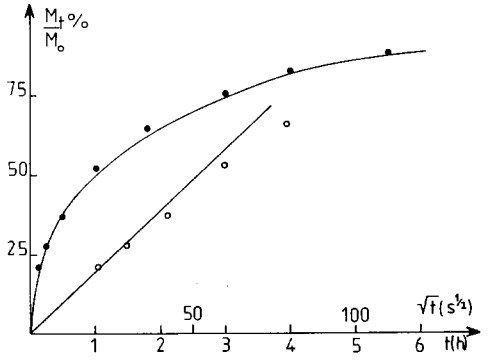

Fig. 2. Kinetics of release of drug in 200 ml of liquid (pH 8) from the oral dosage form: 50% Gelucire-50% sodium salicylate. (●) Experimental; (———) theoretical. (○) Amount of drug released vs square root of time.

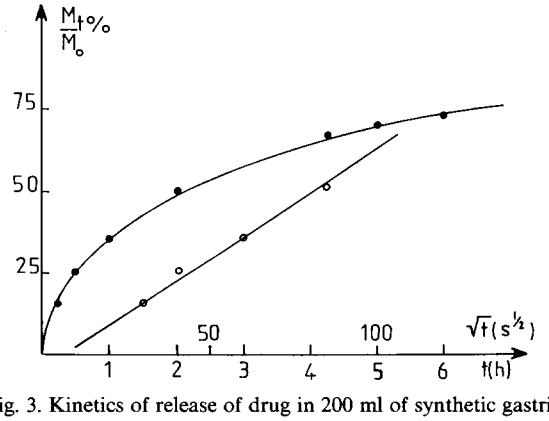

Fig. 3. Kinetics of release of drug in 200 ml of synthetic gastric liquid (pH 1.2) from the new oral dosage form: 45% Gelucire-10% Sumikagel-45% sodium salicylate. (●) Experimental; (———) theoretical. (○) Amount of drug released vs square root of time.

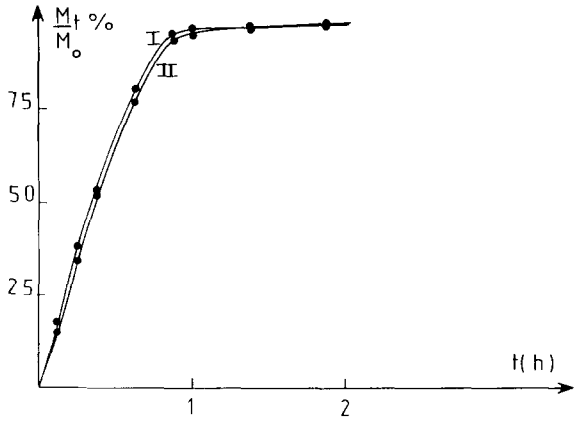

Fig. 4. Kinetics of release of drug in 200 ml of liquid of (pH 8) from the new oral dosage forms: 45% Gelucire-10% Sumikagel-45% sodium salicylate. (I) Bead weight, 125.2 mg; (II) bead weight, 130.8 mg.

the pH of the liquid is 8. The following facts are worth noting:

(i) Transient diffusion can describe the process of drug delivery from the new dosage form in synthetic gastric liquid.

(ii) The diffusivity is of the same order of magnitude as that obtained with the dosage form without Sumikagel, in the case of synthetic gastric liquid.

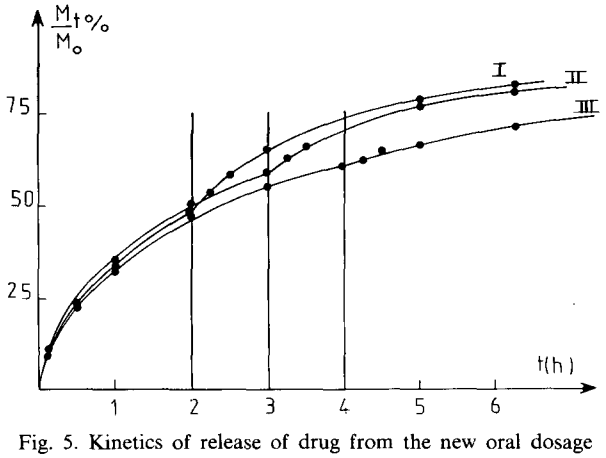

Fig. 5. Kinetics of release of drug from the new oral dosage forms: 45% Gelucire-10% Sumikagel-45% sodium salicylate. The dosage forms are initially immersed in 200 ml of liquid of (pH 1.2) and then in 200 ml of liquid (pH 8) (I) Time of immersion in liquid of pH 1.2, 2 h; (II) time of immersion in liquid of pH 1.2, 3 h; (III) time of immersion in liquid of pH 1.2, 4 h.

(iii) The kinetics for the delivery of the drug in the liquid of pH 8 are quite different. They cannot be described by transient diffusion. The rate of drug delivery is about constant during the whole process.

(iv) In the case of Fig. 4 with the liquid of pH 8 the rate of delivery is not only constant but also higher than that with the liquid of pH 1.2, as all the drug is delivered within a period of time shorter than 1 h, when the radius of the dosage form is around 0.35 cm.

(v) The oral dosage form disintegrates slowly and regularly in the synthetic intestine liquid. The polymer Sumikagel absorbs water to such a high extent that it makes burst out the dosage form layer after layer.

Kinetics of drug delivery out of the new dosage forms on immersion in synthetic gastric liquid (pH 1.2) and then in synthetic intestine liquid (pH 8)

Three dosage forms with the same composition (as shown in Table 1) and with about the same dimensions ranging from 122.5 mg to 129.3 mg, are immersed successively in synthetic gastric liquid and then in synthetic intestine liquid. The time of immersion in synthetic gastric liquid is different for each dosage form, as shown in Fig. 5: 2 h for curve I, 3 h for curve II, and 4 h for curve III.

From the kinetics drawn in Fig. 5, the following conclusions can be drawn:

(i) The process of drug delivery is followed, when the dosage forms are immersed in the second solution of pH 8.

(ii) Of course, the kinetics of drug delivery are described by transient diffusion in the first stage of the process, when the pH of the liquid is 1.2.

(iii) A higher rate for the drug delivery is clearly shown, when the dosage form is immersed in the second solution of pH 8. This increase in the rate of delivery is especially high when the time of contact of the dosage form with the first liquid of pH 1.2 is short, according to the following statement: the shorter the time of contact with the acidic liquid, the higher the increase in the rate of delivery just after the change in aqueous solution.

(iv) These times of contact of the dosage form with the acidic liquid ranging from 2 to 4 h can

represent the time of transit of the dosage form in the stomach and in intestine.

(v) The oral dosage forms disintegrate slowly but regularly in the synthetic intestine liquid. This property is of interest when the solubility of the drug is very low, because the drug is thus disposed into a large volume of liquid.

Conclusions

A new type of oral dosage form is described and studied in this paper. It consists not only of dispersing the drug in a polymer matrix such as Gelucire which is slowly erodible, but also of adding a small amount of a polymer which is able to swell to a very large extent. This polymer, Sumikagel, swells differently according to the value of the pH of the liquid in which it is immersed.

This new dosage form exhibits a higher rate of drug delivery in synthetic intestine liquid with pH 8 than in synthetic gastric liquid with pH 1.2. The kinetics of drug delivery can be described by transient diffusion when the dosage form is in synthetic gastric liquid. The rate, rather high at the very beginning of the process, decreases regularly with time. The kinetics of delivery in the synthetic intestine liquid are quite different: the rate of delivery is about constant during the whole process, and moreover this rate is very high.

The gastrointestinal tract is simulated by immersing the new dosage form in a synthetic gastric liquid for a definite time and then in a synthetic intestine liquid. A higher rate of delivery is obtained after the change in the intestine liquid.

Moreover, as this new oral dosage form disintegrates in the intestine liquid, during a period of time of about 1 h, there is a way to deliver the drug out of the dosage form to completion, and this is very useful when the solubility of the drug is very low.

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