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Dosage form with salicylic acid attached to a polyanhydride polymer dispersed in an Eudragit matrix

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Summary

A new method is presented for preparing dosage forms capable of delivering drug at a controlled rate. They are prepared by dispersing in a polymeric matrix such as Eudragit, a polymer to which the drug is attached. The branched polymer is obtained by polymerizing a monomer previously attached to the drug by a covalent bond. The anhydride function was chosen for branching the salicylic acid, since it reacts readily with water. The pharmaceutical dosage forms obtained, release the drug when contacted with aqueous solutions of various pH values, ranging from 1 to 8. The transfer of drug is controlled by transient diffusion with a constant diffusivity, as well as the transfer of the liquid throughout the dosage form. A simple model was successfully tested for the release of the drug.

Introduction

The development of therapeutic systems that release a controlled amount of drug over a defined period of time represents a significant pathway for optimizing drug effects through dosage forms. These systems offer important advantages over traditional dosage forms in disease that require constant blood levels over a prolonged duration of therapy. Such dosage forms can often decrease the total daily dosage of agent, and therefore decrease the number and frequency of side-effects, and facilitate the treatment.

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The absorption and elimination of most drugs follow first-order kinetics. Almost all conventional dosage forms are characterized by first- and second-order delivery kinetics, whereas the rate of liberation of a drug from a therapeutic system depends largely on the formulation. The recognition that the first kinetic event, i.e. the release of drug from the dosage form, may be influenced and perhaps technologically monitored, was surely decisive in the conception of therapeutic systems (Heilman, 1984).

The retardation in the release process can be attained by using devices able to release the drug over a prolonged period. For this purpose 3 various mechanisms have been examined, i.e. osmosis, polymer erosion and diffusion (Feijen, 1984). A case of interest has often been considered with monolithic devices which are prepared by disper-

sing the drug into a polymer; this polymer may be either a biodegradable or non-degradable matrix (Heller, 1984; Fessy et al., 1982; Focher et al., 1984; Touitou and Donbrow, 1982; Droin et al., 1985; Malley et al., 1987). More recently, another method has been explored, by attaching the drug to the polymer by a labile chemical bond.

This paper is devoted to the preparation and study of another type of galenic form, in which the drug is firstly attached to a biocompatible polymer and then dispersed into a second biocompatible polymer such as Eudragit. So it is of interest to survey the literature concerned with these following two aspects: branching the drug to the polymer, and release of the drug from drug–polymer device.

Two ways have been used for attaching the drug to a biocompatible polymer. The first method consists of attaching the drug to the polymer (Wiener et al., 1976; Davis et al., 1976; Zalipsky et al., 1983; Cramichon et al., 1982; Pinazzi et al., 1977); the second method is based on the following two steps: synthesizing a monomer with the branched drug, and then polymerizing this new monomer (Meslard et al., 1986; Brosse and Soutif, 1986). Some advantages are inherent to this latter technique, e.g. a good knowledge for the polymeric matrix, degree of substitution reaching 100%, and perhaps a higher yield of the drug release.

The drug delivery from novel dosage forms obtained by dispersing the drug in a polymeric matrix has been studied in various cases. Very often, the transport of drug has been described by a square-root of time relationships (Touitou and Donbrow, 1982; Higuchi, 1961; Brossard et al., 1983; Gurny et al., 1982; Tojo and Chien, 1984; Nicklasson et al., 1985; Peppas, 1985; Peppas and Segot-Chicq, 1985; Teillaud and Pourcelot-Roubeau, 1984), corresponding to a transient diffusion of the drug. Other studies have reported simultaneous transfers of the liquid into, and plasticizer out of plasticized PVC when brought into contact with liquids of many types (Messadi and Vergnaud, 1981). In case of the galenic form prepared by dispersing the drug into a polymer matrix, the process has been shown to follow the following mechanism: the liquid enters the polymer and dissolves the drug which can then diffuse out of the dosage form (Droin et al., 1985; Malley et al., 1987; Armand et al., 1987).

The purpose of this work was to prepare and study a branched polymer with a polyanhydride function which was obtained by reacting the drug with an acid chloride and then by polymerizing this new monomer. The drug chosen was sodium salicylate and the monomer was the methacryloyl chloride. The polymer obtained by a radical polymerization was present as a fine powder (2–10 μm).

Another aim in the present paper was to obtain dosage forms prepared by dispersing the branched polymer into an acrylic resin polymer matrix (Eudragit RL). These formulations were then tested in simulated gastric liquid, as well as the branched polymer itself, by using in vitro tests to determine the kinetics of transfers of the liquid entering the dosage form (or polymer) as well as the release of the drug.

Theoretical

Assumptions

The whole process is rather complicated, due to several successive and simultaneous steps: diffusion of the liquid into the galenic matrix made of Eudragit RL and into the branched polymer; reaction between the liquid and the branched polymer; diffusion of the dissolved drug obtained from the reaction, into the branched polymer and the polymer matrix. So, the following assumptions are made in order to simplify the problem.

(i) The spherical dosage forms are homogeneous, the branched polymer being well dispersed into Eudragit matrix.

(ii) Two matter transfers take place as shown previously (Droin et al., 1985; Malley et al., 1987; Armand et al., 1987); the liquid entering the galenic form, and the drug leaving the dosage form. They are studied successively, but not simultaneously.

(iii) Both these matter transfers are controlled by transient diffusion throughout the galenic form, as well as the transfer of drug within the branched polymer (Chafi et al., 1988).

(iv) The rate of the reaction between the liquid

and branched polymer is not considered, because it does not control the process.
(v) The diffusivities are nearly constant during the whole process. The concentration at equilibrium is attained on the external face of the dosage form as soon as it is soaked in the simulated gastric liquid.

Mathematical treatment

The transient diffusion for the liquid and the drug can be described by the Fick's equation:

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

where D is the diffusivity, and r is the radial abscisse in the sphere.

The well-known analytical solution (Crank, 1975) can be obtained for the Eqn. 1 with the above assumptions.

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot \exp\left[- \frac{Dn^2 \cdot \pi^2}{r^2} \cdot t \right] \quad (2)$$

where M_t and M_∞ are the amount of matter transferred at time t and at equilibrium when the process is achieved, respectively and n is an integer.

For very small times, another well-known analytical solution is obtained, expressing the linear relationship between the amount of matter transferred and the square-root to time.

$$\frac{M_t}{M_\infty} = \frac{6}{R}\left[\frac{D \cdot t}{\pi} \right]^{0.5} \quad (3)$$

Experimental

Preparation of anhydride monomer

The sodium salicylate (0.05 mole; 8 g) is dissolved in anhydrous tetrahydrofuran (12 ml), placed in a dry 150 ml three-necked flask, equipped with a magnetic stirrer and a reflux condenser with a Drierite-filled drying tube, and kept at a temperature around 4–6 °C with an ice-bath.

The solution of methacryloyl chloride (0.05 mole; 5.23 g) in anhydrous tetrahydrofuran (6 ml) is added dropwise in the flask under stirring. The temperature of 4–6 °C is maintained during the whole addition (15–20 min).

After this addition, the reaction medium is gently heated for 20 min, after which the mixture is stirred for 4 h.

The precipitate of NaCl is filtered and washed with a small amount of dry tetrahydrofuran. The solvent is removed from the filtrate in an rotary evaporator, and a white powder of anhydride is obtained and purified by recrystallization in a mixture of chloroform and hexane. After drying, the amount of anhydride is 5.30 g, with a yield of 52%.

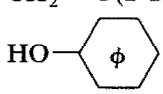
Characteristics of the monomer:

m.p. = 69 °C.

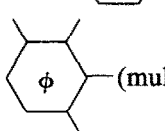
NMR spectrum ($CDCl_3$/TMS), (chemical shift in ppm).

$CH_3-C=C$: (singlet, 32)

$CH_2=C$ (2 doublets: 5.73 and 6.38)



(singlet: 6.23 by addition of a drop of CF_3COOH)



(multiplet: 6.85–8.10)

IR spectrum: 1695 cm^{-1} and 1740 cm^{-1}: anhydride function
1640 cm^{-1}: vinyl double bond
1600 cm^{-1}: aromatic double bond

Microanalysis: (Theoretical/Experimental in % weight) C = 64.07/63.49; H = 4.85/4.90; O = 31.07/31.31.

Preparation of the polymer

The monomer (0.0194 mole, 4 g) dissolved in anhydrous tetrahydrofuran (1 cm^3) with 2‰ in weight of azobisisobutyronitrile (8 mg) is placed in a glass tube. The air dissolved is removed by a nitrogen stream for 10 min and the tube is sealed under vacuum. After 16.5 h of heating at 65 °C, the polymer is dissolved in tetrahydrofuran (4 days) under stirring (obtention of a gel). The polymer is then precipitated by addition of petroleum ether. After drying, a yield of 90.7% is attained for the polymer (3.63 g).

The characteristics of the polymer are:

IR spectrum: 1690 cm^{-1} and 1745 cm^{-1}: anhydride function
1600 cm^{-1}: aromatic double bond.

Microanalysis: (Theoretical/Experimental, in % weight)
C = 64.07/63.81; H = 4.85/5.12; O = 31.07/30.93

T_g(DSC): 114°C; glass transition temperature

Preparation of galenic forms

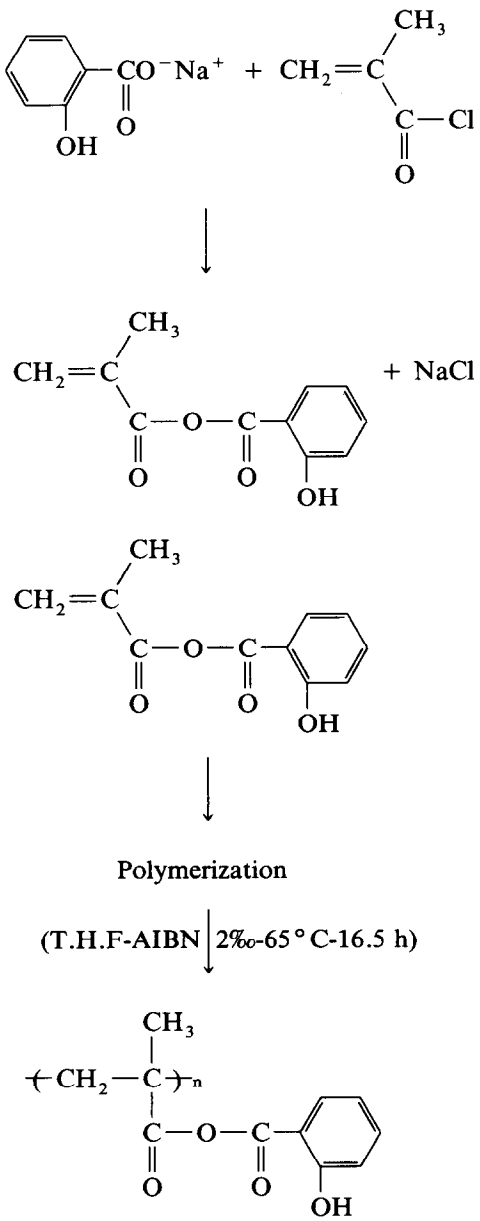
The branched polymer and Eudragit RL (a copolymer of dimethylaminoethylacrylate and ethylmethacrylate, mol. wt. 150,000; Röhm Pharma), both in powder form, are intimately dispersed, and transformed into a thick homogeneous paste after pulverization of a small amount of ethanol. Spherical beads are then obtained from this paste, and dried until complete evaporation of ethanol (4 days at room temperature).

In vitro test

These experiments are carried out in a closed flask kept at 37°C, with a controlled rate of stirring. The beads (about 400 mg), inserted in a permeable fiberglass basket, are soaked either in simulated gastric liquid at pH 1.2 (1000 ml of aqueous solution, 80 ml HCl 1 N and 2 g NaCl), and in a liquid at pH 8 (50 ml borax at 0.025 M; 20.5 ml HCl 0.1 N).

Samples of liquid are taken at intervals for analysis and the beads weighed. The amount of drug released from the beads is determined by using a double-beam UV spectrophotometer (Beckman).

The same experiments are also made with the branched polymer, by soaking it in synthetic gastric liquid under the same conditions (pH 1.2, temperature).



Formulae of materials

Results

Two main purposes are considered in this paper: the one is to prepare and investigate a branched polymer able to deliver the drug; the other is to study the behavior of galenic forms obtained by dispersing the branched polymer into a non-degradable polymer. These galenic forms are of interest because of their wide possibilities.

(i) Various parameters are of help to control the rate of drug delivery: the diameter of the bead, and percent drug (Armand et al., 1987).

(ii) Their mechanical properties, as stability, are excellent.

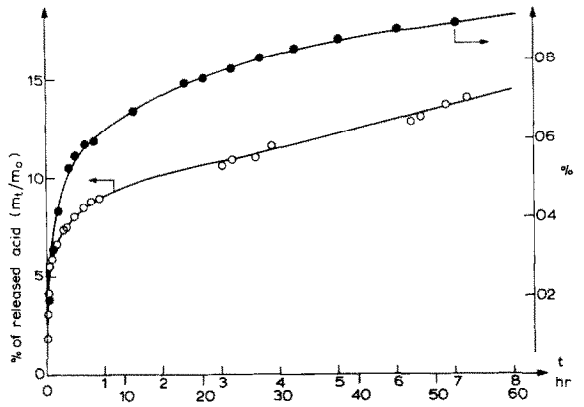


Fig. 1. Kinetic of release of drug from the branched polymer in synthetic gastric liquid (pH = 1.2; 37 ° C).

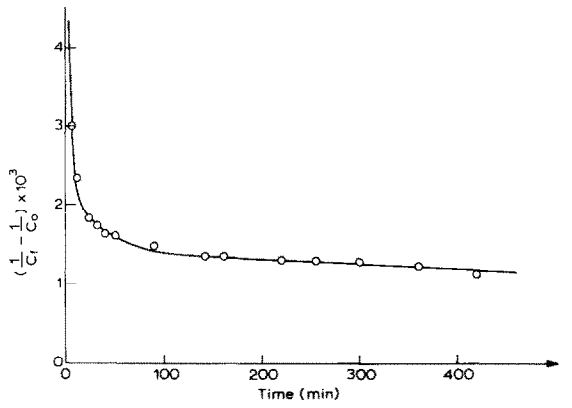


Fig. 3. Second-order kinetic for the release of drug from the branched polymer in synthetic gastric liquid (pH = 1.2; 37 ° C).

Release of drug from the branched polymer

When the branched polymer in powder form is soaked into simulated gastric liquid, a liberation of the drug (salicylic acid) is observed, with typical kinetics as shown in Fig. 1. These kinetics of drug delivery cannot be expressed by first- or second-order reactions since no linear line was obtained as seen in Fig. 2 (1st-order) and Fig. 3 (2nd-order). However, the diffusional aspect of this delivery is illustrated in Fig. 4 where the amount of the drug liberated is plotted as a function of the square-root of time. A linear relationship is observed for short times as in the case of a process controlled by diffusion (Crank, 1975). It is difficult to estimate the value of the diffusivity from this curve because of the lack of accuracy in measurement of the average size of the powder. Moreover, this branched polymer became gelatinous during the process.

From these experiments some conclusions may be made. (i) The process of matter transfer is not simple for the branched polymer when contacted with synthetic gastric liquid. Two matter transfers take place: the liquid enters the polymer provoking on the one hand an important gelling, and on the other hand a dissolution of the drug; the drug can then leave the polymer. (ii) The whole process of drug delivery is controlled by diffusion throughout the branched polymer itself, in spite of

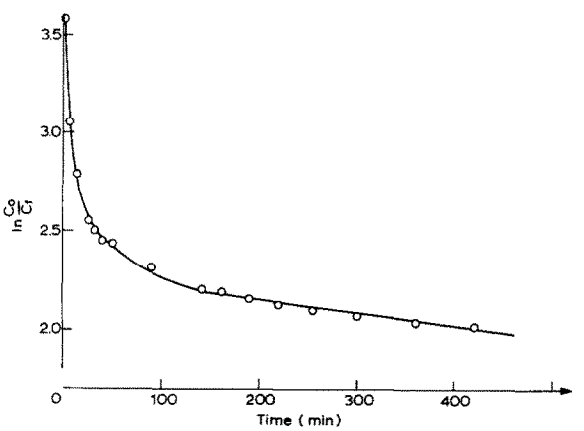


Fig. 2. First-order kinetic for the release of drug from the branched polymer in synthetic gastric liquid (pH = 1.2, 37 ° C).

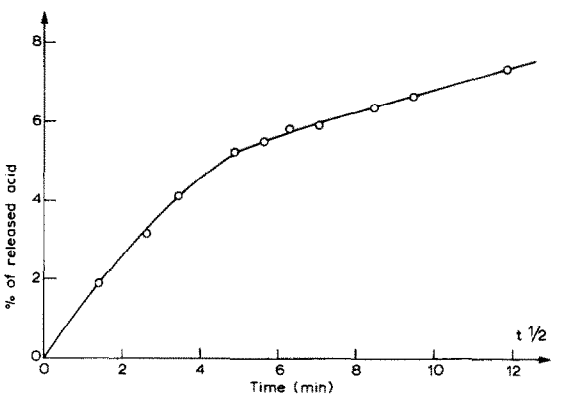


Fig. 4. Diffusional effect. Drug released from the branched polymer in synthetic gastric liquid as a function of the square-root of time (pH = 1.2, 37 ° C).

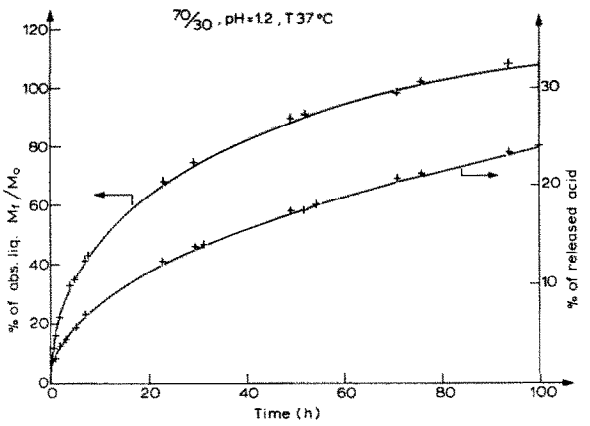


Fig. 5. Kinetic of matter transfer (drug, liquid) with dosage form (Eudragit: branched polymer 70:30) pH = 1.2, 37 °C; +, experimental; ———, theoretical.

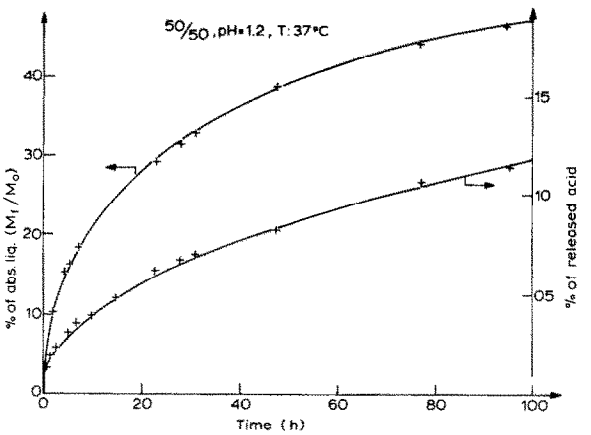


Fig. 7. Kinetic of matter transfer (drug, liquid) with dosage form (Eudragit: branched polymer 50:50) pH = 1.2, 37 °C; +, experimental; ———, theoretical.

the fact that reactions between the active part of the branched polymer and the liquid have to take place.

Release of the drug from the galenic form

The branched polymer is dispersed in Eudragit RL which functions as a polymeric matrix. As shown in previous papers concerned with the use of matrices able to be shaped in a convenient galenic form of either drug (Droin et al., 1985; Malley et al., 1987; Armand et al., 1987) or a branched polymer (Chafi, 1988), it may be of interest not only to determine the kinetics of drug delivery but also the kinetics of the liquid transport.

The kinetics of release of drug from the galenic forms in simulated gastric liquid are obtained by using various dosage forms of the same size but with different extents of branched polymer, as shown in Fig. 5 (30% branched polymer), Fig. 6 (40% branched polymer) and Fig. 7 (50% branched polymer).

In contrast to the branched polymer, the kinetics for the transfer of liquid can be readily de-

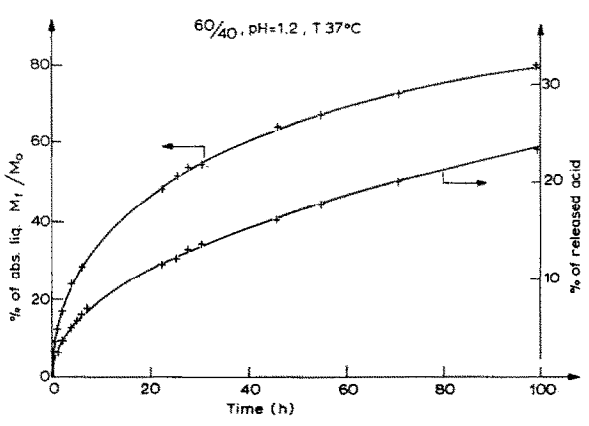


Fig. 6. Kinetic of matter transfer (drug, liquid) with dosage form (Eudragit: branched polymer 60:40) pH = 1.2, 37 °C; +, experimental; ———, theoretical.

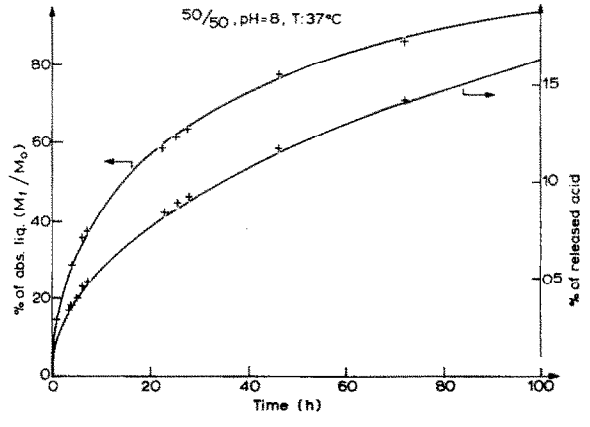


Fig. 8. Kinetic of matter transfer (drug, liquid) with dosage form (Eudragit: branched polymer 50:50) pH = 8, 37 °C; +, experimental; ———, theoretical.

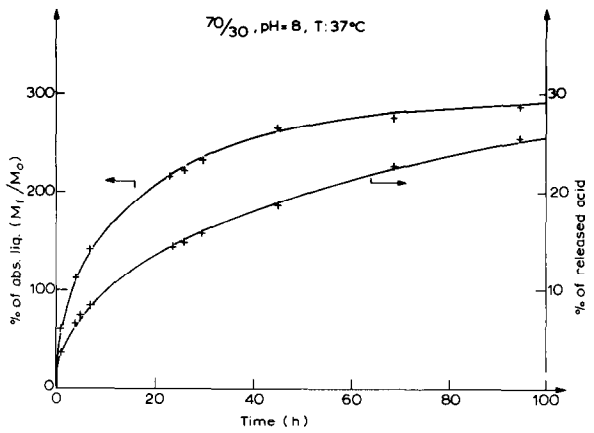


Fig. 9. Kinetic of matter transfer (drug, liquid) with dosage form (Eudragit: branched polymer 70:30) pH = 8, 37 °C; +, experimental; ———, theoretical.

termined from the weight of the dosage form measured at intervals and from the amount of drug released. The results for the liquid are indicated in Figs. 5–7 with the same dosage forms.

Another parameter of interest is the pH of the liquid with which the dosage form is in contact (Eddine et al., 1986). An attempt has been made with a liquid of pH 8, and the results are shown in Fig. 8 (50% branched polymer) and in Fig. 9 (30% branched polymer).

It is often of interest to build a model, even a rough and simple model, able to describe the process, because mathematical simulations are then possible. In the case of the dosage forms containing the branched polymer, the diffusional model with constant diffusivity expressed by Eqn. 2 is successfully tested either for the transport of the drug and for that of the liquid, as shown in Figs. 5–9.

From these results, the following conclusions can be drawn.

(i) The liquid transport is described by a diffusional process, with a constant diffusivity.

(ii) The drug delivery is controlled by diffusion, with a constant diffusivity, as shown in Table 1.

(iii) The rate of transfer as well as the amount of matter transferred at equilibrium is higher for the liquid than for the drug.

(iv) The dosage form keeps its good physical properties during the process of drug delivery, in contrast with the branched polymer itself which exhibits the inconvenience of turning into gel when soaked into the liquid.

(v) The rate of release of the drug is lower for the dosage forms than for the branched polymer, the retardation effect of the matrix being superimposed on the retardation due to the branched polymer itself.

As shown in Table 1, the total amount of drug branched and located in the galenic form is not completely delivered (between 40% and 69%). Another experiment is done by soaking the galenic form firstly in simulated gastric liquid (pH 1.2) until the equilibrium of transfer is attained, and then extracting the galenic form and soaking it again in aqueous solution of pH 8. The results are

TABLE 1

Characteristics of the dosage forms

Eudragit/Branched polymer	pH	D_{liquid} [a] $(cm^2/s) \times 10^8$	D_{drug} [a] $(cm^2/s) \times 10^8$	M_{liquid} [b] (%)	M_{drug} [c] (%)
70:30	1.2	8.3	0.67	122	68
60:40	1.2	8.3	0.67	90	69
50:50	1.2	8.3	0.47	53	41
50:50	8	11	1.0	102	42
70:30 [d]	8	17	33	295	38

[a] The diffusivities are expressed in cm^2/s for diffusion.

[b] The percent liquid.

[c] The amount of drug delivered at equilibrium is expressed in percent weight of the initial drug.

[d] This result corresponds with the second soaking, the first being achieved in aqueous solution of pH 1.2 up to equilibrium. The 38% of drug delivered is applied to the remaining drug at the end of the first extration (32%).

obtained with a dosage (Eudragit : branched polymer 70 : 30), and shown in Fig. 1 for the delivery in solution of pH 1.2, and in Fig. 9 for the second delivery in solution of pH 8. As illustrated in Fig. 9, a fast and deep liquid transfer is obtained as well as a rather fast transfer of drug in the second delivery. The total amount of the drug delivered at the end of the following two transfers is around 80% of the initial drug.

Discussion

A new way is explored for preparing dosage forms exhibiting a controlled release of the drug in gastric liquid. The drug is previously attached to a reactive monomer, and this new molecule is then polymerized. The branched polymer obtained can be dispersed in a polymer matrix, and the galenic form built in this way reveals interesting good mechanical properties.

The detailed process of the release of the drug is complicated, with the matter transfers of the liquid and of the drug taking place either within the matrix and the branched polymer, and with the reaction between the liquid and branched polymer which is responsible for the drug liberation.

However, a simple model is built and successfully tested for these dosage forms. By considering that the whole process is controlled by transient diffusion throughout the materials with a constant apparent diffusivity, the well-known analytical expression for homogenous spheres is able to describe the kinetics of drug delivery.

A polyanhydride is studied in this paper because it can be considered as easily hydrolysable in gastric liquid and in other aqueous solution.

This type of dosage form may be of some interest, especially for the patient's safety. First of all, it has acquired a good physical stability due to the presence of Eudragit as a polymeric matrix. Secondly, if the dosage form is crushed by mistake instead of being swallowed whole, another means of controlled release exists involving the branched polymer itself.

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