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PREPARATION AND STUDY OF ORAL GALENIC FORMS BY DISPERSING INTO EUDRAGIT/MATRIX A POLYACRYLOYL-ACETYLSALICYLIC ANHYDRIDE

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ABSTRACT

Oral galenic forms able to control the drug release in stomach are prepared and studied in this paper. A branched polymer is dispersed in a biocompatible polymer as Eudragit. A Polyanhydride is chosen for this branched polymer and it is obtained by reacting the anhydride with the drug and then polymerizing this branched monomer. The process of release of drug is studied by using in vitro tests with synthetic gastric liquid. The process is proved to be controlled by transient diffusion of the liquid into and the drug out of the galenic form, with constant diffusivities. A simple mathematical model is thus able to describe both these matter transfers. Moreover, the branched polymer itself exhibits a retardancy in the release of drug which is also controlled by diffusion. This retardancy can be of interest, especially in case of accident when the galenic form is broken in the patient's mouth and chewed.

INTRODUCTION

The development of therapeutic systems which release a controlled amount of drug over a defined period of time represents a significant pathway for optimizing drug effect (I,2). Therapeutic systems offer especially important advantages over traditional dosage forms in diseases requiring the most constant possible blood levels over prolonged durations of therapy. The systems can not only enhance the therapeutic ratio and regimens of many existing agents, but can also permit treatments with pharmacologically active substances which would not be useful in conventional dosage forms because of their toxity. In this case, the important signification is not the total dose given but the rate and duration of drug administration. The distribution of the drug in the organism can only be in equilibrium when the rate of administration is constant and equal to the rate of continuous elimination over a prolonged period. So the study of factors that affect the extent and speed of liberation of a drug from its various physicochemicals forms is surely of high interest (2).

The principle of retardation consists in slowing down the process and delaying it for a definite period of time. Some attemps have been made in order to obtain devices able to release the drug over a prolonged period. Three mechanisms have been considered for this purpose, i.e., diffusion, osmosis and polymer erosion, and sometimes the release is controlled by various mechanisms (3). Special attention has been given to the preparation of monolithic drug-polymer devices, the drug being dispersed into the polymer matrix and this polymer being either biodegradable or non-degradable (4-9).

Another way for drug retardation has been followed by attaching the drug to a biocompatible polymer, this new polymer being able to release the drug after hydrolysis. Polyethylene

glycol (PEG) has often been chosen as the carrier polymer because it is known to be non-toxic and soluble in water. Various drugs have been attached to PEG such procaine (I0), atropine (II) and various salicylates (I2). For this last case, the polymer-drug conjugate showed longer duration of activity due to slow release. Other molecules as penicillin, aspirin, amphetamine, quinidine, atropine (I3) and enzymes (I4) have also been attached to PEG. Pinazzi (I5) has modified polyisoprene to give a polymer chain with some pendant chloroformate functions able to react with drugs like quinine or cholesterol. This branched polymer is able to retard action of the quinidine. Quinidine has also been reacted with polyvinyl-chloroformate and the hydrolysis of the carbonate function in this modified polymer has been tested in basic medium (I6). In all these above cases, the polymer is allowed to react with the drug, and the degree of substitution cannot reach to I00 %. A new way has also been followed to prepare branched polymers, by reacting a monomer with the drug, and then by polymerizing the new molecule. Chloramphenicol has been immobilized on a hydrogel matrix through different bonds slowly hydrolyzable at neutral pH. Methacrylic esters of this drug and its acetal derivatives have been prepared and copolymerized with methacrylate (I7). Glycidyl methacrylate has also been proposed as carrier monomer for salicylic acid and chlorambucil, and the drug carrying monomer thus obtained has been polymerized (I8). The new monomers derived from drugs and leading to hydrolysable therapeutic polymers may take advantage of the opportunities offered by copolymerization for establishing various physichochemical properties to the polymer. Moreover, a good knowledge on the polymeric matrix can be obtained, and a degree of substitution close to I00 % may be expected as well as a higher yield for the release of the drug.

A purpose of this paper is to build galenic forms by dispersing the branched polymer into a biocompatible non-degradable polymer (Eudragit), this latter polymer playing the role of ma-

trix, and to study the release of the drug from this device into synthetic gastric liquid. A survey of the pertinent literature points out some facts of interest about the kinetic of release obtained with these galenic forms. The process of release of drug has been studied by considering the diffusion of the drug and the amount of drug transferred has been described by a square-root law of time (7,I9-27) with a constant diffusivity. Simultaneous transfers of matters have been reported in previous papers. A transfer of the liquid into, and plasticizer out of plasticized PVC has been observed when the polymer is contacted with various liquids (28,29). In case of galenic forms obtained by dispersing a drug into various polymers (8,9,30), the process of drug release was proved to follow this way : the liquid enters the polymer matrix, dissolves the drug, and then the drug in solution can diffuse through the polymer into the external liquid.

A polyanhydride has been chosen in the present study, because it reacts easily with water provoking the release of the drug at human temperature. It is obtained by following the second way, i.e., by preparing a branched monomer and then polymerizing this monomer. The monomer is made by reacting the potassium salt of acetyl salicylic acid with acryloyl chloride.

This branched polymer is dispersed into Eudragit as polymer matrix, and pressed into spherical galenic forms. Various compositions and various sizes can easily be prepared. The release of the drug in synthetic gastric liquid is determined in "in vitro" tests by using either the branched polymer itself and the galenic form above-described.

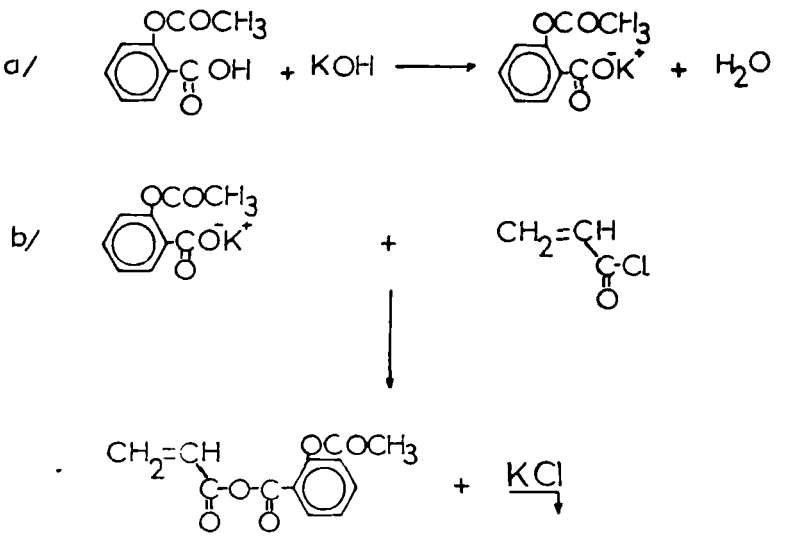
EXPERIMENTAL

The branched monomer is synthetized, and polymerized. The branched polymer is then dispersed into a polymer matrix, and

the galenic forms obtained in this way are tested in synthetic gastric liquid for determining the rate of release of the drug.

Preparation of the monomer

The monomer is obtained by reacting potassium salt of acetyl salicylic acid (0.064 M - I4 g) in anhydrous tetrahydrofuran (I0 cm^3) with acryloyl chloride (0.064 M - 5.8 g) at constant temperature (5°C). Acryloyl chloride is added dropwise in I5 min. while the mixture is stirred. A gentle heating is followed for 20 min. up to ebullition (65°C) and then this temperature and stirring are maintained for 4 hours. After filtration, and evaporation of THF, the monomer is dried under vaccum. The yield obtained for the monomer (6.52 g) is 56 %. After solution and recristallization in chloroform hexan mixtures, the pure monomer is characterized as follows :



Acryloyl-acetyl salicylic anhydride

Elementary Analysis :

%C : 6I,49 (theoret. 6I.53) - %H : 4,I4 (theoret. 4.28)
%O : 34,35 (theoret. 34,2) -

IR spectrum :

I770 and I755 cm^{-I}	: anhydride function
I690 cm^{-I}	: acetyl group
I640 cm^{-I}	: double bond
I600 cm^{-I}	: double bond ring

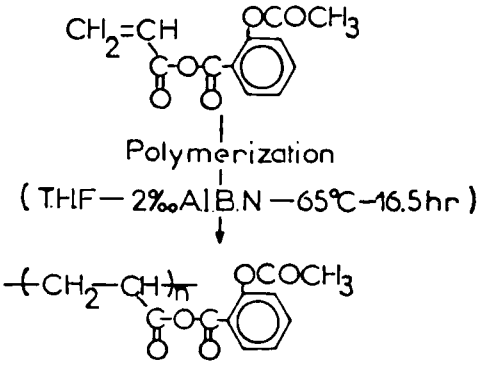
NMR spectrum :

($CDCl_3$ as solvent) :

2.33 ppm (s)	: CH_3-C- (O) acetyl group
6.06 and 6.55 ppm(d)	: $CH_2=CH-$
7.15 to 8.10 ppm (m)	: aromatic

Preparation of the polymer

The monomer (2.54 g - 0.0104 M) is dissolved in anhydrous THF (2 cm^3) with 2°/oo in weight of azobis-isobutyronitrile (AIBN - 4.90 mg) as initiator, and placed in a glass tube. The tube cooled in liquid nitrogen, is connected with a vaccum line (0.1 mm. Hg) for 10 min. to remove the air dissolved, and then sealed. After 16.5 hours of heating at 65°C, the product is dissolved in THF. The polymer is precipitated from the solution by addition of petroleum ether. The yield of 69.4 % is attained for the polymerization (1.70 g of polymer).



The characteristics of the polyacryloyl-acetylsalicylic anhydride are as follows :

IR spectrum :

I770 - I755 cm^{-I}	: anhydride function
I300 cm^{-I}	: stretching anhydride
I695 cm^{-I}	: acetyl group
I600 cm^{-I}	: double bond ring
mp	: I3I - I32°C (DSC)
Tg	: I02°C

The polymer is slightly soluble in THF at room temperature and in hot chloroform.

Preparation of galenic forms

The polyacryloyl-acetylsalicylic anhydride above-described and Eudragit RL (copolymer of dimethylaminoethylacrylate and ethylmethacrylate, Mn = I50,000, from Röhm Pharma) in powder form, are intimately dispersed and transformed into an homogeneous thick paste after pulverisation of a small amount of ethanol which is a solvent of Eudragit. Spherical beads are pressed from this paste and ethanol is evaporated after drying for 4 days at room temperature.

Conditions in the test "in vitro"

Experiments are carried out with synthetic gastric liquid (I00 ml.) well stirred in a closed flask kept at 37°C. The pH of I.2 is obtained as follows : I000 ml. of aqueous solution, 80 ml. HCl IN and 2 g. NaCl. The galenic forms (about 400 mg) inserted in a permeable fiberglass are soaked into the liquid.

Samples of liquid are taken at intervals for analysis of the drug and the galenic forms weighed. The rate of the drug released in the liquid is determined by UV measurements (Beckman DG sphectrophotometer).

The same experiments are made on the polyacryloyl-acetylsalicylic anhydride without Eudragit under the same conditions for measuring the rate of release of drug from the branched polymer itself.

THEORETICAL

As the general problem is very complicated, the following assumptions are made :

i - The galenic form, spherical in shape, is homogeneous, the branched polymer being well dispersed into the polymer matrix Eudragit.

ii - Two matter transfers take place as shown previously (8,9, 30) : the liquid enters the polymer matrix, and reacts with the branched polymer ; the drug then diffuses through both polymer into the exterior liquid.

iii - Both matter transfers are controlled by transient diffusion, as shown in the paper.

iv - A matter transfer is observed for the liquid which enters the branched polymer, this transfer being controlled by transient diffusion.

Transient diffusion through a sphere is described by the Fick's equation :

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

This equation must be used not only for the spherical galenic forms, but also for the grains of branched polymer, either for the liquid and for the drug.

Moreover, the rate of the drug produced by the reaction between the liquid and branched polymer can follow the classical kinetic equation :

$$(2) \quad \frac{D\,[\text{drug}]}{dt} = k.\,[\text{drug}]\,.\,[\text{water}]^{n}$$

where the value of the order n is varied from I to O is attained when the concentration of the liquid (water) is very high with regard to the concentration of the drug. The acid HCl is in large exces (pH I.2) and its concentration can be considered as constant.

Under these conditions, no analytical solution can be obtained for these equations.

However, in case of short times, and only if the rate of matter transfer is controlled by diffusion, the equation 3 can be a solution of Eqn.I either for the liquid and the drug.

$$(3) \quad \frac{M_t}{M_\infty} = 6\left[\frac{D.t}{R^2.\pi}\right]^{0.5}$$

where M_t is the amount of matter transferred at time t, M_∞ the amount transferred at equilibrium.
D is the diffusivity and R is the radius of the sphere.

The particular simple case shown as follows can be considered in the present paper. The process is controlled by diffusion when the rate of reaction is rather high with regard to the rate of diffusion process. An analytical solution can easily be found when the diffusivity of the drug is constant and when the concentration at equilibrium is attained on the surface of the galenic form as soon as it is soaked into the liquid.

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

$$(4)\quad \frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot \exp(-Dn^2\pi^2 t/R^2)$$

n being an integer

RESULTS

As shown in previous papers (8,9,30) the whole process of release of drug from galenic forms (where the drug is dispersed in polymeric matrix) can be divided intro three steps :

i - Diffusion of the liquid entering the galenic form.

ii - Dissolution of the drug in the liquid. In the present case, the reaction takes place and the resulting drug is dissolved.

iii - The drug so dissolved is transferred by diffusion through the galenic form.

For these reasons, the matter transfer is studied either for the liquid and for the drug.

I - Kinetic of release of drug from the branched polymer

The branched polymer, in powder form, is soaked into synthetic gastric liquid and the amount of drug released is determined at intervals in the liquid. The kinetic of the release of drug is studied by trying the one order reaction (Fig.1) and the secondth order reaction (Fig.2). As shown in both these figures, no straight line is obtained, and the kinetic of release of drug cannot be described by a simple classical equation.

It is difficult to obtain the amount of liquid which enters the polymer, because of the small size of polymer grains. Moreover, this polymer is turning into a gel.

2 - Transfer of the liquid into galenic forms

The kinctic of the absorption of liquid is determined by using the various galenic forms (described in Table I) and soa-

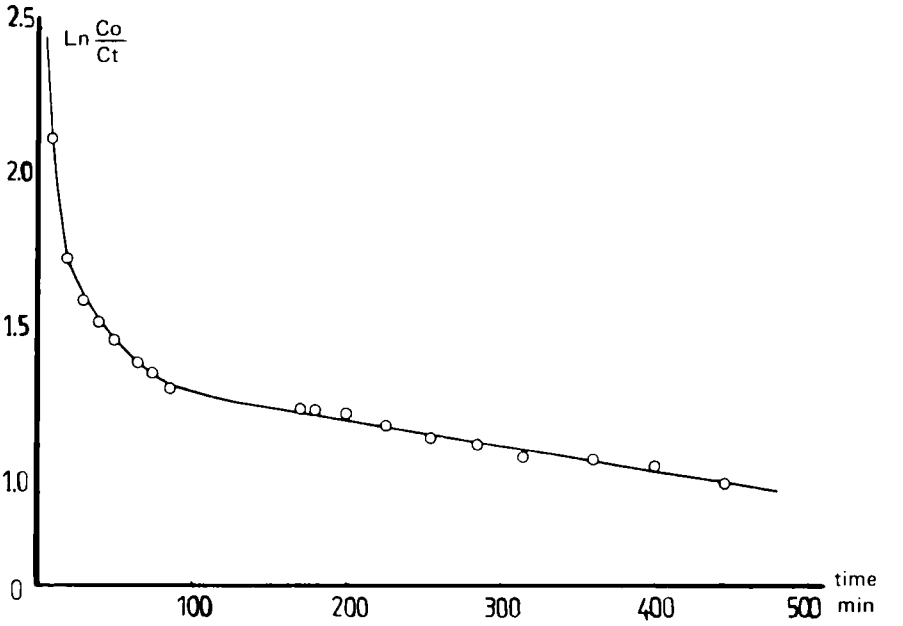


FIGURE 1

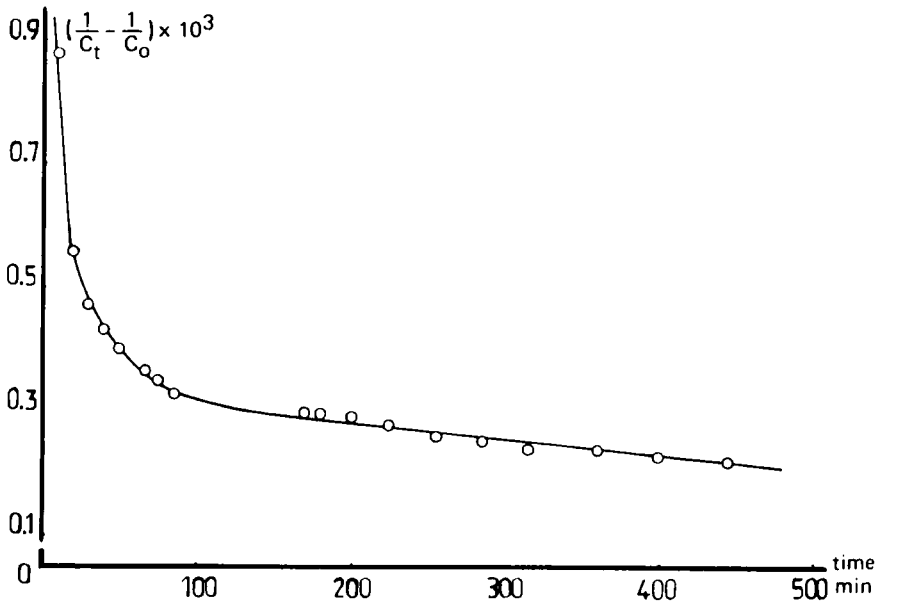


FIGURE 2

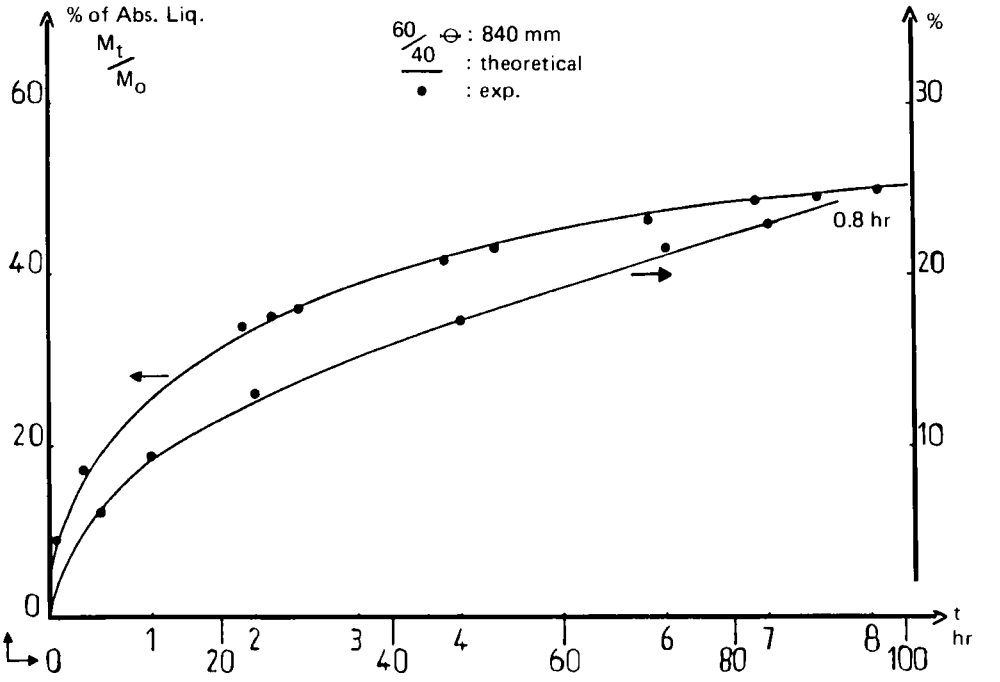


FIGURE 3.1

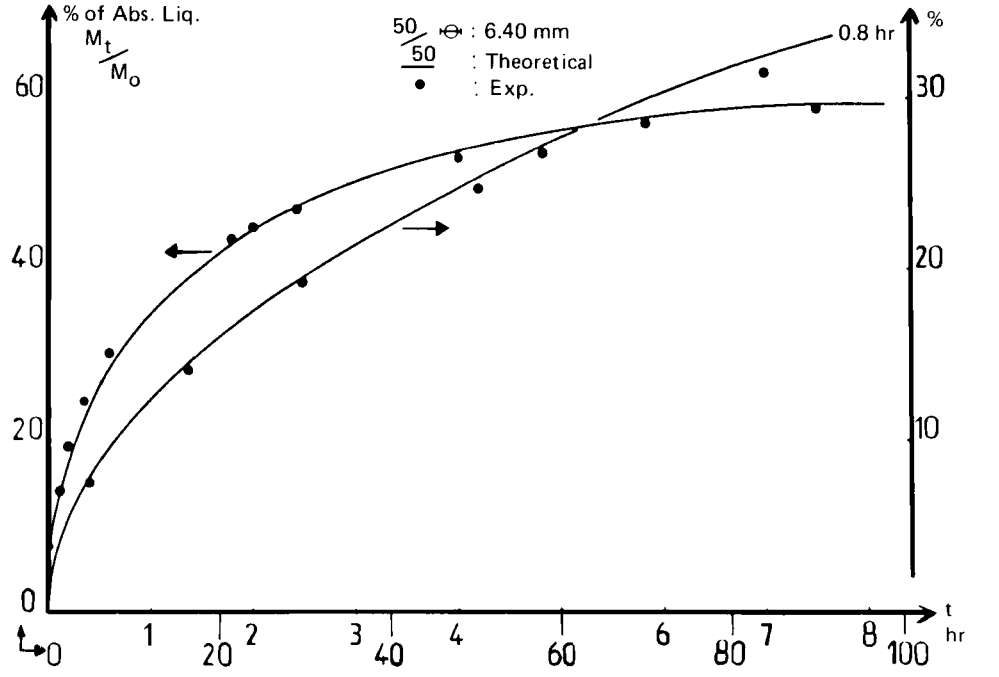


FIGURE 3.2

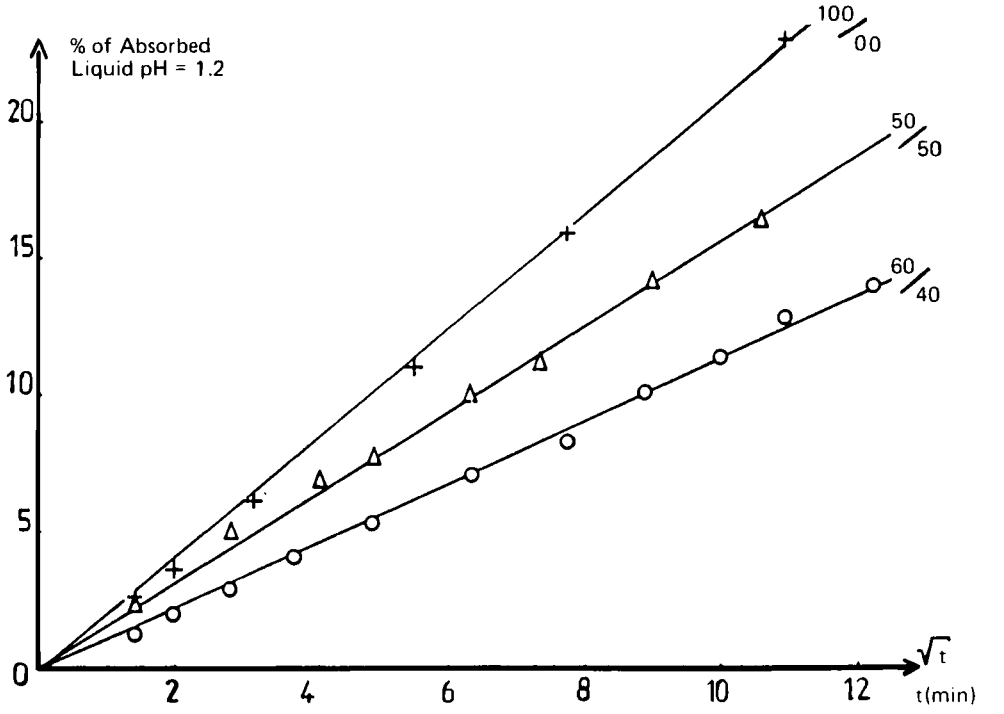


FIGURE 4

king them into synthetic gastric liquid with pH I.2 under the conditions above-described. The curves obtained are drawn in Fig.3. The amount of liquid transferred into the galenic form is also plotted as a function of the square root of time in Fig.4. (for bead made of Eudragit and the other two galenic forms described in Table I and 2).

The following conclusions are worth pointing out from these results :

i - The process of liquid transfer can be considered as controlled by diffusion, because of the linear relationship obtained between the amount of liquid and the square root of time.

Table 1: Characteristics of oral forms

	Diameter	Eudragit	Branched Polymer
1	0.634 cm	60%	40%
2	0.64 cm	50%	50%

Table 2: Diffusivities & Amount at equilibrium

Oral form	$D(cm^2 mn^{-1})$ liquid	drug	Mass (%) liquid	drug
1	67.10^{-7}	$13,83.10^{-7}$	54%	72%
2	62.10^{-7}	83.10^{-7}	60%	87%

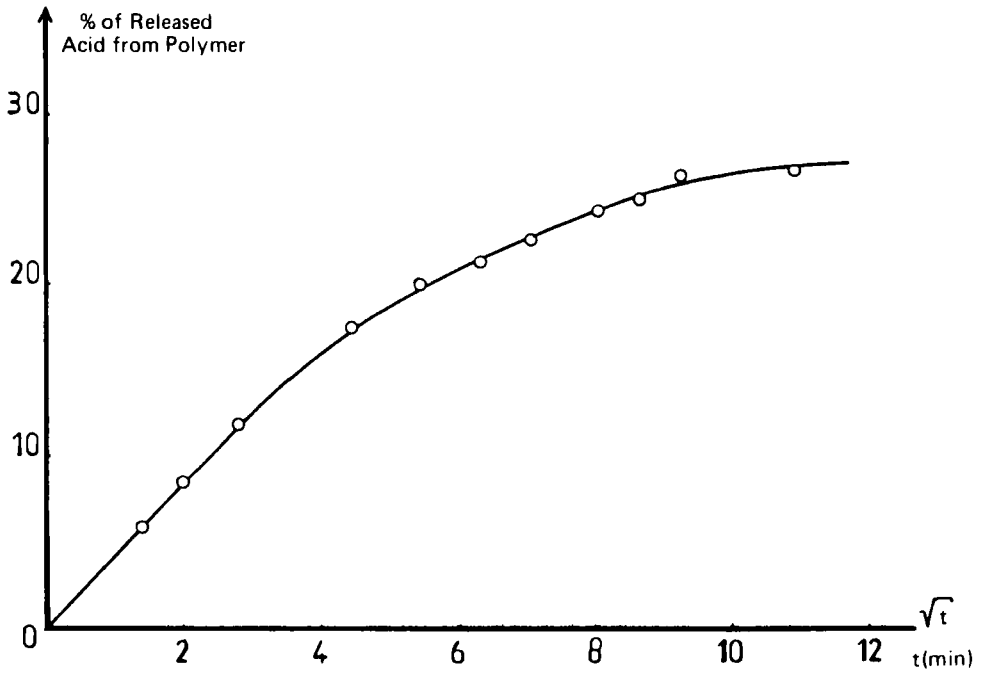


FIGURE 5

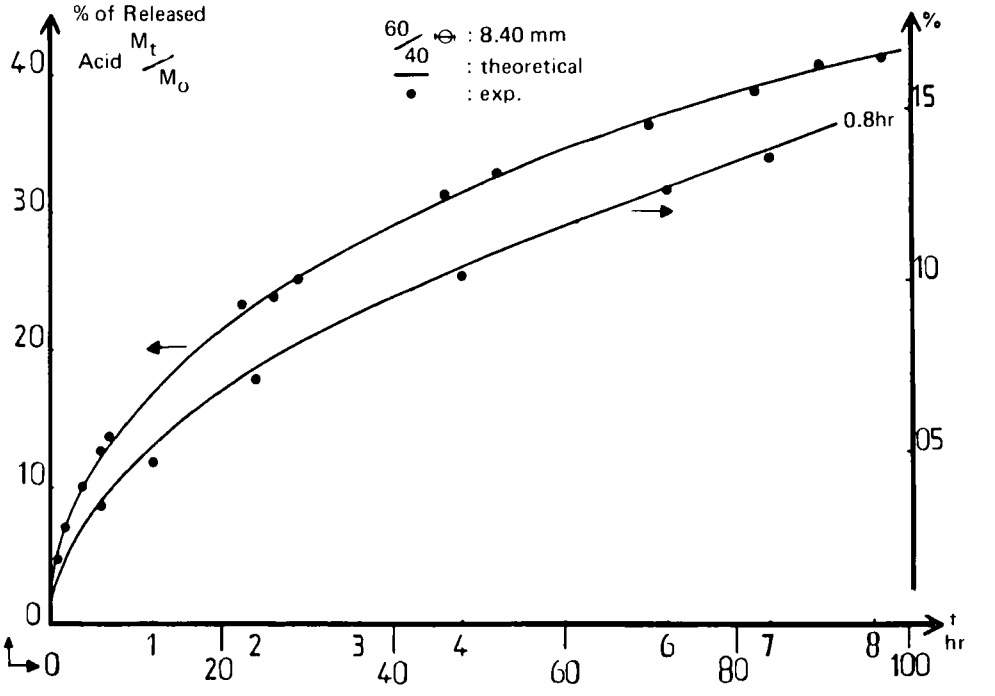


FIGURE 6.1

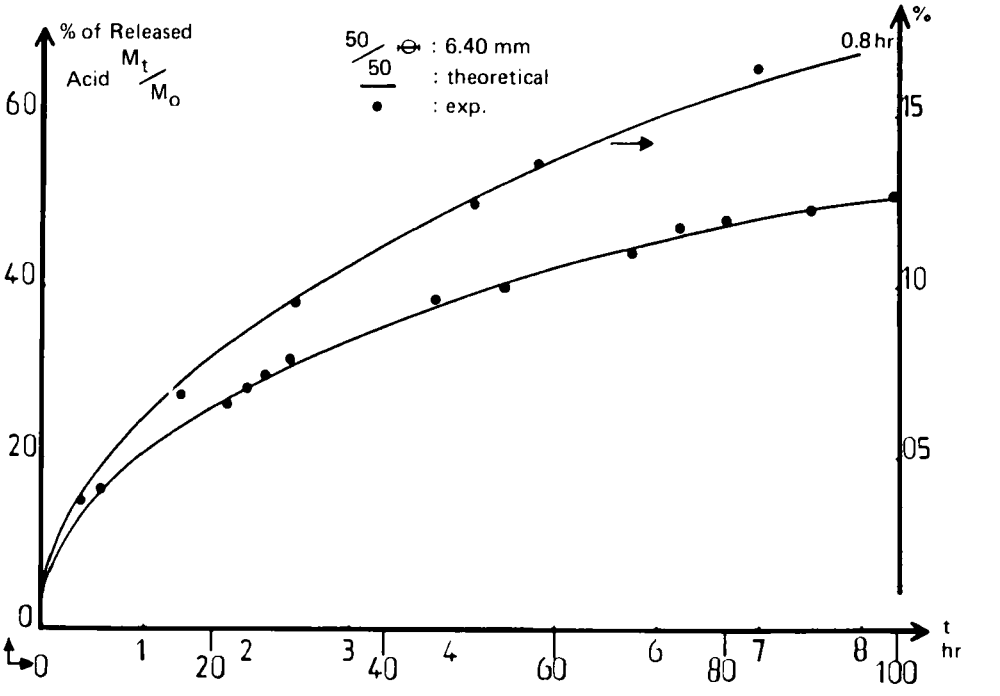


FIGURE 6.2

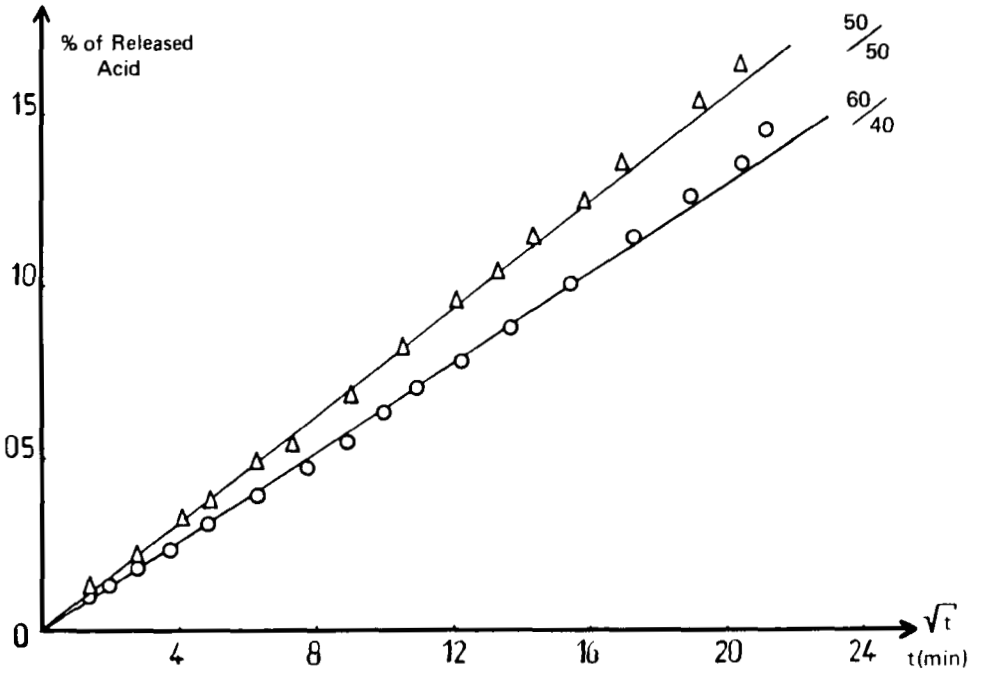


FIGURE 7

ii - The diffusivity varies slightly with the composition of the galenic form, and can be considered as constant during the whole process.

iii - The amount of liquid at equilibrium is around 50 % for all the samples.

iv - The validity of this simple mathematical model can be appreciated by comparing in Fig.3 the experimental kinetic with the theoretical results obtained by using Eqn.4, with the two galenic forms.

3 - Drug delivery in synthetic gastric liquid

It is easy to measure the amount of drug in the liquid, and the kinetic of release of drug is determined either for the branched polymer itself and for the galenic form. The results obtai-

ned for the branched polymer are shown in Fig.5 by plotting the amount of drug released as a function of the square-root of time. The kinetic of release of drug can be described by a diffusional process because of the straight lines obtained in Fig.5.

The galenic form prepared by dispersing the branched polymer into Eudragit are also studied by determining the amount of drug released when they are soaked into synthetic gastric liquid. The kinetic of release of drug obtained is shown in Fig.6 where the amount of released drug is plotted as a function of time and in Fig.7 where this amount is plotted as a function of the square root of time.

The following conclusions can be drawn from these curves :

i - The process of release of drug from these galenic forms is controlled by transient diffusion, with a constant diffusivity. The kinetic can be described by well-known series, as proved by the good agreement exhibited between theoretical value (full line) and experiments (points).

ii - The amount of drug released at equilibrium reaches to about 80 % of the initial drug introduced in the galenic form.

iii - The galenic forms described in this paper have an advantage over the classical galenic forms obtained by dispersing the drug into Eudragit (30) : the release of the drug is controlled by the diffusion of the liquid not only through the polymeric matrix but also through the branched polymer itself. Thus, two limitations for the release of drug can play a role, and this is of high interest especially if the galenic form is broken in the patient's mouth and chewed.

CONCLUSIONS

This paper has paved the way to new oral galenic forms able to control the release of drug in stomach. They are obtained by dispersing a branched polymer into another biocompatible polymer.

The branched polymer is prepared by reacting the drug with a convenient monomer, and the so branched monomer is polymerized. An anhydride is chosen for the monomer, because of the ease with which it reacts with water and then releases the drug.

The process of release of drug in synthetic gastric liquid has been studied by determining the kinetics of absorption of water by the galenic form and of release of the drug. Both these matter transfers are controlled by transient diffusion with constant diffusivity, and they can be described by a simple mathematical model.

As the branched polymer itself exhibits a retardancy for the release of drug when contacted with the liquid, it is clear that the galenic forms described in the paper have an advantage of interest over the classical galenic forms : if these galenic forms are broken in the mouth and chewed, the release of drug is then controlled by the diffusion through the branched polymer.

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