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Dosage form with drug attached to polymer (polyanhydride) dispersed in a Eudragit matrix: preparation and release of drug in gastric liquid

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Summary

A new dosage form that may control the release of drug in gastric liquid has been prepared and studied. It consists of a branched polymer bound to the drug which is dispersed in a stable polymer. This polymer is a polyanhydride prepared by polymerizing the branched monomer. The reactive monomer is obtained by reacting a derivative of benzoic acid as the active agent with the methacryloylchloride. The release of the drug was studied when either the branched polymer and the galenic form were brought into contact with synthetic gastric liquid. In both cases, the process is complicated, because two material transfers are observed: the liquid entering the two polymers, allowing the reaction to take place: and the drug diffusing out of the polymers. These material transfers seem to be controlled by transient diffusion, either completely, for the liquid, or partially, for the drug. These dosage forms are very stable, and have two factors that control the release of the drug: the diffusion through the polymer matrix, the diffusion through the branched polymer and reaction.

Introduction

Systemic treatment is often administered via the gastrointestinal tract, since many dosage forms are easy to swallow. For classical dosage forms, the release of drug generally follows the kinetics of a first-order reaction. The drug is liberated very rapidly from the form, and as a result the drug concentration in the gastric liquid and blood builds up to a maximum concentration and then falls exponentially until the next dose. An undulating concentration figure of the drug is obtained, high concentrations alternating with low concentrations.

In order to facilitate the treatment by reducing the number of tablets taken, the active substance has to be formulated in such a way that its release is retarded and controlled. Moreover, the development of systems able to release a controlled amount of drug over a defined time period represents also an important pathway for optimizing drug effects. These therapeutic systems offer important advantages over traditional dosage forms in diseases requiring the most constant possible blood levels over prolonged duration of therapy: uniform blood levels are achieved, smaller total amounts of drug are needed, side effects are re-

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duced, and the therapy is optimized (Heilman, 1984).

Many devices able to control the release of drug have been prepared in various ways, following 3 mechanisms, i.e., osmosis, polymer erosion and diffusion, the release being often controlled by more than one mechanism (Feijen, 1984). Another way of interest exists by attaching the drug to the polymer with the help of a labile chemical bond.

As our paper is concerned with the last device, attaching the drug to a biocompatible polymer, it is of interest to examine the results which have been obtained previously in the literature.

Various drugs have been attached to low-molecular-weight polyethylene glycol: procaine (Weiner and Zilkha, 1973), atropine (Weiner et al., 1976), esters of salicylic acid (Weiner et al., 1974), penicillin, aspirin, quinidine and atropine (Zalipsky et al., 1983). Molecules of high molecular weight such as enzymes have also been attached to polyethylene glycol (Davis et al., 1976). Polyvinylalcohol has been esterified by *o*-salyciloyl chloride and the release of aspirin in acidic and basic medium has been studied (Kropachev et al., 1969). Quinidine has been reacted with polyvinylchloroformate with a transfer phase catalysis, and the hydrolysis of the carbonate function in this modified polymer has been tested in a basic medium (Gramichon et al., 1982). A special polyisoprene with pendant chloroformate groups has been reacted with quinidine and cholesterol (Pinazzi et al., 1977). In all the above cases, the polymer is allowed to react with the drug, and the degree of substitution cannot reach 100%. The organic function chosen for the polymer-drug bonding is very often ester, carbonate and sometimes acetal (Meslard et al., 1986), because their hydrolysis in acidic or basic media are well-known in organic chemistry.

Another way has been followed more recently, by synthesizing a monomer with the pendant drug, and then by polymerizing this new molecule. Chloramphenicol has been attached to a methacrylic derivative by an acetal function and then copolymerized with 2-hydroxyethylmethacrylate (Meslard et al., 1986). Methacrylic derivatives have also been proposed as drug carrying monomers (Brosse and Soutif, 1986). Some advantages are attached to this technique, as a good knowledge of the polymeric matrix, a high degree of substitution, often close to 100%, and perhaps a higher yield for the release of the drug.

Another purpose of this paper is to study the release of the drug from dosage forms, spherical in shape, prepared by dispersing the polymer bound to the drug into a biocompatible non-degradable polymer as Eudragit, this last polymer playing the role of a polymer matrix. The process of drug delivery has been previously studied by considering the diffusion which is described by a square-root law of time with the amount of drug transferred (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). But in all these previous studies the drug transfer is only considered and the diffusivity is assumed to be constant. Other studies have reported results on simultaneous transfer of the liquid into, and plasticizer out of plasticized PVC when the polymer is contacted with various liquids (Messadi and Vergnaud, 1981). In previous papers (Droin et al., 1985; Malley et al., 1987) concerned with the release of sodium salicylate from various polymers used as matrices, the process was proved to follow this way: the liquid enters the polymer matrix and dissolves the drug, which then can diffuse out of the device.

Chosing to prepare and study a polyanhydride in the present paper, the second way has been followed by reacting an acid chloride with the drug, and polymerizing the substituted monomer. The material chosen for the drug is a derivative of benzoic acid and the chloride acid is the methacryloyl chloride. A new substituted polymer is obtained from this monomer by a radical polymerization. This polymer is in solid form, the grains having a size distribution ranging from 5 to 12 μm.

This substituted polymer has been dispersed into Eudragit as the polymer matrix, and the mixture has been pressed into spherical dosage forms. The release of the drug in synthetic gastric liquid used in in vitro tests has been studied by

using either the substituted polymer itself or the spherical galenic forms made of this polymer and Eudragit.

Theory

The following assumptions able to help to describe the process have been obtained from experiments.

i - The galenic forms are homogeneous, the branched polymer being well dispersed in Eudragit.

ii - Two matter transfers take place as previously shown (Droin et al., 1985; Malley et al., 1987; Eddine et al., 1987). The former is concerned with the liquid which enters the polymer and reacts with the branched polymer; the latter is concerned with the drug which is dissolved in the liquid located in the polymer.

iii - Both these transfers are controlled by transient diffusion.

iv - The rate of transfer is higher for the liquid than for the drug. The rate of transfer of the drug is controlled by the concentration of the liquid in the polymer (Armand et al., 1988).

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

As a result of these facts proved by our experiments, the process is more complex than in case of the drug dispersed into a polymer (Droin et al., 1985; Armand et al., 1988). In the present case two matter transfers take place concerned with the liquid and the drug not only through the tablet but also through the branched polymer itself. Moreover, as shown previously, these matter transfers are connected with each other: the rate of the reaction occurring in the branched polymer is intimately related to the amount of the liquid transferred; the rate of diffusion of the drug is a function of the liquid concentration in the polymer (Armand et al., 1988).

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

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

either for the liquid and the drug, with concentration-dependent diffusivity.

The rate of the drug produced by the reaction between the branched polymer and the liquid can follow the classical equation

$$\frac{\mathrm{d}[drug]}{\mathrm{d}t} = k[drug] \cdot [water]^n \quad (2)$$

with a value of the order n for the water varying perhaps between 1 and 0, as a function of the concentration of the liquid. The value of 0 is attained when the concentration of water is very high compared to the concentration of the drug.

Under these conditions, no analytical solution can be found for these above equations. Only a numerical method with finite differences taking into account all these facts can be of interest to resolve this complicated problem.

Materials and Methods

Preparation of anhydride monomer

A dry 100 ml 3-necked flask, equipped with a magnetic stirrer and a reflux condenser to which is attached a Drierite-Filled drying tube, is used for the purpose.

The mixtures of potassium salt of 4-methoxybenzoic acid (0.0323 mol, 6.14 g) in 10 ml of anhydrous tetrahydrofuran, and of methacryloyl chloride (0.0307 mol, 3 ml) in 5 ml of dry tetrahydrofuran, are added dropwise in the flask kept between 3 and 6 °C.

After the addition has been completed (15 min), a gentle heating follows during 20 min, and then the mixture is stirred during 4 h.

The precipitate of KCl is filtered and washed with dry tetrahydrofuran. The solvent is removed from the filtrate in a rotary evaporator, and a white powder of anhydride is obtained with a yield of 51% (3.6 g).

This product is purified by recrystallization with a mixture of carbon tetrachloride and hexane. The characteristics of the material are as follows:
m.p. = 100–101 °C.
IR spectrum: 1765 and 1805 cm^{-1} (anhydride function)
1650 cm^{-1} (double bond)
NMR spectrum ($CDCl_3$ as solvent, chemical shift in ppm)
CH_3-C = C 2 (s); CH_3O: 3.85; CH_2 = C 5.8 and 6.2 (2d); aromatic 6.9–8 (m.).

Preparation of the polyanhydride

The monomer (0.0136 mol, 3 g) is dissolved in anhydrous benzene (8 ml) with 2‰ w/w of azobisisobutyronitrile (6 mg), and placed in a glass tube. The tube is cooled in liquid nitrogen, and connected with a vacuum line (0.1 mmHg) for 10 min to remove the dissolved air, and then sealed. After 20 h of heating at 65 °C, the product is dissolved in hot dimethylformamide and then precipitated in methanol. A yield of 33% is attained for the polymerization (1 g of polymer).

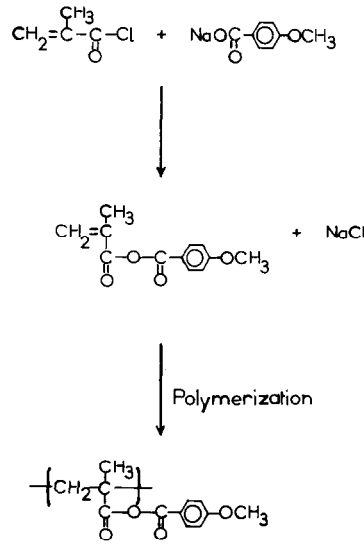
The characteristics of the polymer are: IR spectrum 1765 and 1805 cm^{-1} (anhydride function). The polymer is insoluble in various usual organic solvents, except in hot dimethylformamide.

Preparation of tablets

The branched polymer above-described and Eudragit RL (a copolymer of dimethylaminoethylacrylate and ethylmethacrylate, M = 150,000, from Röhm Pharma), in powder form, are intimately dispersed, and transformed into an homogeneous thick paste after pulverisation in a small amount of ethanol which is a solvent of Eudragit. Spherical beads are pressed from this paste, and dried until complete evaporation of ethanol (some days at room temperature). Two parameters are of interest: the diameter of the spherical beads as shown previously (Armand et al., 1988), and the percent drug located in the tablet (Droin et al., 1985; Malley et al., 1987).

Conditions of the test "in vitro"

Experiments are carried out in a closed flask with a controlled rate of stirring. The spheres



(about 400 mg) inserted in a permeable fiberglass basket, are soaked in synthetic gastric liquid (100 ml) kept at 37 °C with pH = 1.2 (1000 ml of aqueous solution; 80 ml HCl 1 N; 2 g NaCl).

Samples of liquid are taken at intervals for analysis and the galenic forms are weighed. The rate of the drug released from the galenic form is measured by using a double-beam UV spectrophotometer (Beckman D-G).

The same experiments are also completed by soaking the branched polymer itself (in powder form) in synthetic gastric liquid under the same conditions of temperature and pH as those used for the tablets.

Results

As this paper is especially concerned with the preparation of a dosage form able to release the drug in gastric liquid, the release of the drug is particularly studied in the cases when the branched polymer itself is in contact with the liquid, and when the galenic form is soaked into the liquid.

Release of drug from branched polymer

As the branched polymer is dispersed into Eudragit, it is necessary to have a good knowledge

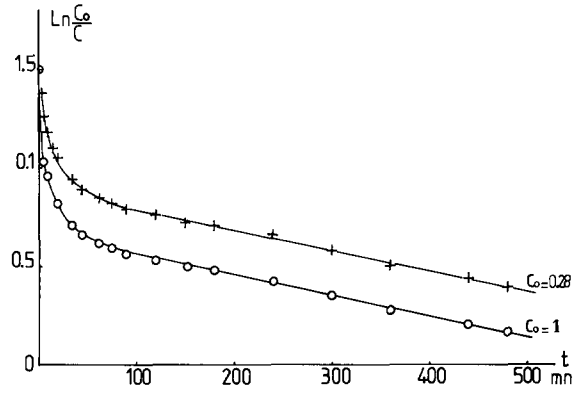


Fig. 1. Kinetic of release of drug from the branched polymer. First-order reaction.

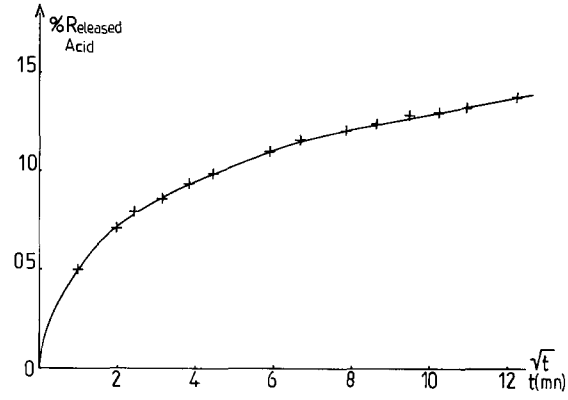


Fig. 3. Kinetic of release of drug from the branched polymer. Transient diffusion with constant diffusivity.

on the reaction taking place between this branched polymer and the liquid.

Some attempts are made to study this reaction between the branched polymer itself and the liquid, and the two values of 1 and 0 for the order n of the water are tested, while the order for the drug is 1 in both cases. As shown in Fig. 1 for the first order reaction and Fig. 2 for the second order, the release of the drug cannot be described by a classical kinetic equation, especially for the short times.

As proved by experiments, the liquid enters the branched polymer, and a gel is formed. It is impossible to follow the transfer of the liquid in this case, but an attempt has been made to test the validity of a diffusional process controlling the release of the drug. In Fig. 3, the amount of drug transferred is plotted as a function of the square-root of time.

From these experimental results, some conclusions are worth pointing out:

i - The process of release is complicated for the branched polymer itself, because two matter transfers take place: the liquid entering the polymer, the drug diffusing out of the polymer.

ii - No classical kinetic equation can describe the drug release.

iii - A diffusion process, which is the limiting factor, is perhaps the best way to attain the kinetic of release of the drug.

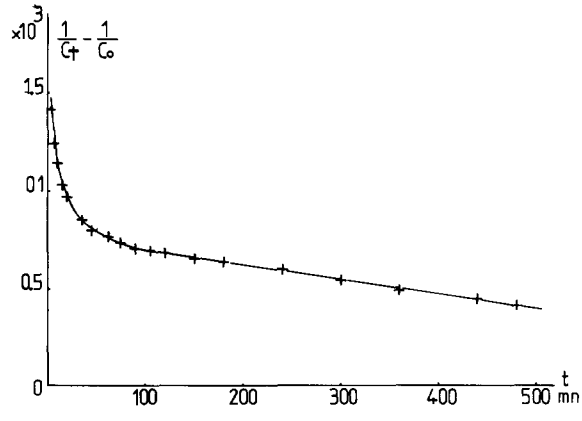


Fig. 2. Kinetic of release of drug from the branched polymer. Second-order reaction.

Release of the drug from the galenic form

These galenic devices are made by dispersing the branched polymer in Eudragit which plays the role of a polymer matrix. In order to afford a further insight into the nature of the process, two kinds of experiment are of interest: the kinetic of the liquid transfer, and the kinetic of the release of drug, when the galenic form is in contact with the synthetic gastric liquid.

In contrast with the branched polymer, it is easy to follow the kinetic of the transfer of liquid into the galenic form by weighing this form at intervals and measuring the amount of the drug released. As indicated in Figs. 4 and 5, the liquid transfer is controlled by diffusion, as previously shown for Eudragit itself (Droin et al., 1985).

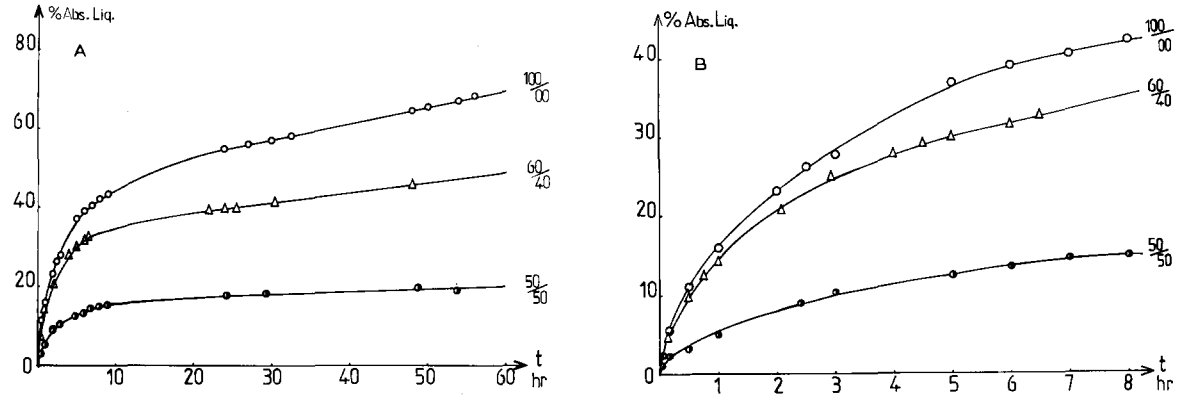


Fig. 4. Liquid transferred in galenic forms as a function of time (A: long time. B: short time) for various compositions: Eudragit 100, Eudragit 60 + branched polymer 40. Eudragit 50 + branched polymer 50.

The kinetic of the release of drug is drawn in Fig. 6 in both cases: the branched polymer itself and galenic forms. The amount of the drug released is also plotted as a function of the square root of time in Fig. 7, in order to appreciate the diffusion effect.

From all these results, the following conclusions can be drawn:

i - The kinetics of the liquid transfer is higher than that of the drug transfer.

ii - The liquid transfer can be described by a diffusion process.

iii - The rate of release of the drug is lower in case of the galenic form than for the branched polymer, because of the additional diffusion through the polymer matrix.

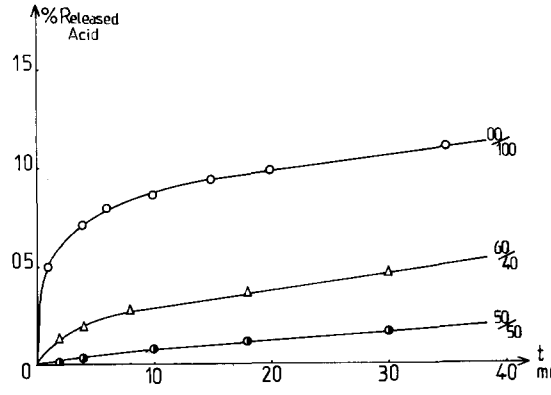


Fig. 6. Drug transferred out of galenic forms as a function of time for various compositions.

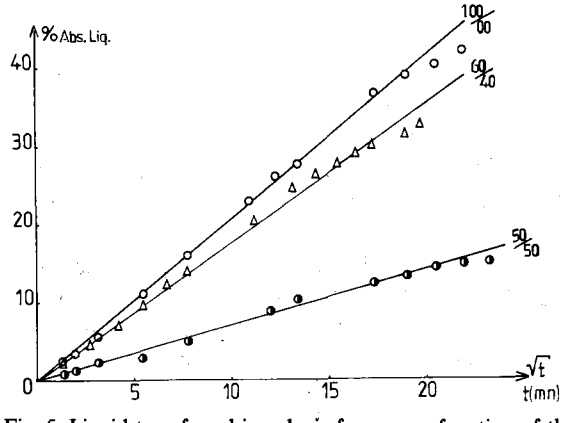


Fig. 5. Liquid transferred in galenic forms as a function of the square root of time for the same compositions as in Fig. 4.

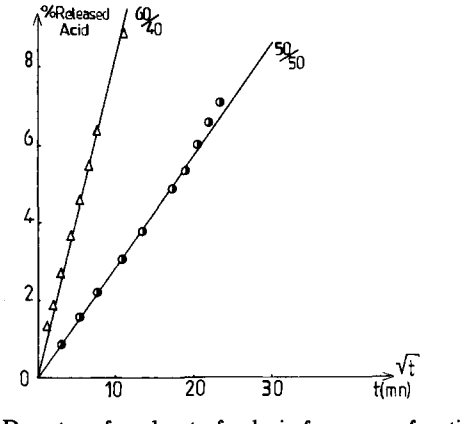


Fig. 7. Drug transferred out of galenic forms as a function of the square root of time, for various compositions.

iv - The galenic form remains stable during the whole process, in contrast with the branched polymer which turns into gel when brought into contact with the liquid.

Conclusions

Amongst the various devices able to control the release of the drug, this paper paves the way to a new technique. In this case, a pharmacologically active polymer is prepared and then dispersed in a stable polymer matrix.

The process of the release of the drug is very complicated, because various matter transfers take place either through the galenic form and within the branched polymer itself. No analytical solution can be found for this problem, and numerical methods with finite differences have to be built in order to describe the whole process.

When the branched polymer is in contact with synthetic gastric liquid, this polymer turns into a gel, because of the liquid transfer into the polymer. On the other hand, a release of the drug is observed, which does not follow a classical kinetic equation, as the kinetics are partially controlled by diffusion.

In case of the galenic form, two matter transfers are also observed: the one concerned with the liquid which enters the polymer matrix and the branched polymer; after reaction, the drug is released out of the branched polymer and polymer matrix. Under these conditions, the process is partially controlled by the diffusion of the liquid through the polymer.

This kind of galenic form has some interest. It is stable because of the presence of the polymer matrix. Moreover, two limitations are able to control the release of the drug: one is concerned with the presence of Eudragit as polymer matrix; in case of accident, the galenic form being crushed for instance, another way of controlling the drug release remains, with the branched polymer and its own kinetic of release.

A polyanhydride has been chosen in this paper; it is a good potential drug-carrier because it is easily hydrolysable in gastric liquid. It is possible to obtain other polyanhydrides by reacting acrylic acid chloride with any drug having a carboxylic acid function, and polymerizing this branched monomer.

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