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Release of 2-aminothiazole from polymer carriers

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Summary

New dosage forms able to control drug release in the stomach have been prepared and investigated in this paper. Three different types of bonding of medicinal agent (MA) were chosen in order to examine drug release: (i) MA attached to ethylenic monomer, the polymer carrier being obtained by polymerizing this monomer; (ii) MA linked to an organic product, which possesses the same function, the molecule then being enclosed in a polymer matrix; (iii) MA dispersed in its original form into a Eudragit RL matrix. Theoretical and experimental analyses of the kinetics of controlled release of MA from polymer systems or MA carriers were conducted for the case of contact with synthetic gastric fluid (pH 1.2). The process was found to be controlled by transient diffusion of the liquid into, and MA out of the dosage form, with constant diffusivities. The data on drug release provide the opportunity for predicting quantitatively the rate of MA release from the polymer carrier or dosage forms, directly into the organism. A mathematical treatment, according to Fick's law, led to the amount of matter transferred at time t being evaluated. The present study demonstrates that it is possible to derive an expression for the rate of diffusion of MA.

Introduction

In this paper, we have focused our attention on the preparation of devices, by bonding the drug to a polymer and then by dispersing the bonded polymer in another polymer such as Eudragit RL playing the role of a matrix. In fact, two ways exist for preparing a drug bonded to a polymer: one, by bonding the drug to a polymer, this polymer generally having a low molecular weight; the other, by bonding the drug to an ethylenic monomer, and then by polymerizing the bonded monomer.

As the second method was selected for the present paper, a survey of the literature on this method was carried out. Chloramphenicol was previously attached to a methacrylic derivative by an acetal function and then copolymerized with 2-hydroxyethyl methacrylate (Meslard et al., 1986). Methacrylic derivatives have also been proposed as a carrier monomer for salicylic acid, chlorambucil, antivitamin K, and the drug carrying monomer thus obtained has been polymerized (Pinazzi et al., 1977; Brosse and Soutif, 1986). 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

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have been attached to PEG such as procaine (Weiner and Zilkha, 1973), atropine (Weiner et al., 1976) and various salicylates (Weiner et al., 1974).

Other molecules, penicillin, aspirin, amphetamine, quinidine and enzymes (Davis et al., 1976; Zalipsky et al., 1983) have been attached to PEG. Pinazzi et al. (1977) modified polyisoprene to give a polymer chain with some pendant chloroformate functions able to react with drugs like quinine or cholesterol. This polymer carrier is able to retard the action of quinidine. Quinidine reacts via transfer phase catalysis with polyvinylchloroformate and the hydrolysis of the carbonate function of modified polymer was examined in basic medium (Gramichon et al., 1982). In all the above cases, the polymer carrier was allowed to react with the synthetic gastric liquid, and the degree of release was unable to reach 100%.

Acryloyl and methacryloyl chlorides have also been proposed as carrier monomer for 4-methoxybenzoic acid, acetylsalicylic acid, salicylic acid and 2-aminothiazole. These carrier monomers have been polymerized (Chafi et al., 1988, 1989a, b; Monthéard et al., 1988). Ringsdorf has proposed the fixation of the drug to a polymerizable group, attached on an organic molecule which is considered as a spacer to favour the enzymatic or hydrolytic release of the drug moiety (Ringsdorf, 1975; Carpino et al., 1976; Hofmann et al., 1976). These polymer carriers must be soluble in water and in lipids, biodegradable and non-toxic for human body (Bauduin et al., 1979, 1981a, b). Similar studies have carried out by Kopecek et al. (1981, 1984) and Rihova et al. (1983). They utilized as polymer carriers *N*-(2-hydroxypropyl)methacrylamide, and the enzymatic hydrolyses were performed using chymotrypsin as a catalyst (Kopecek et al., 1981). Some advantages are expected by using this technique: better knowledge of the polymeric backbone, a high degree of substitution of the drug and perhaps a higher yield of the release of the drug from the bonded polymer. The second purpose of the paper is to compare the kinetics of release of the drug with those determined by dispersing the medicinal agent (drug) in the matrix Eudragit RL, when these devices are immersed in gastric liquid. Previous studies have reported that the process proceeds as follows: the liquid enters the polymer matrix of the device, solubilizes the drug, and then enables the drug to diffuse out of the device through the liquid located in the device (Chafi et al., 1988, 1989a, b). Both the transfer of the liquid into, and the transfer of the drug out, of the device are controlled by transient diffusion (Messadi and Vergnaud, 1981; Touitou and Donbrow, 1982; Brossard et al., 1983; Teillaud and Pourcelot-Roubeau, 1984; Droin et al., 1985; Peppas, 1985; Peppas and Segot-Chicq, 1985; Malley et al., 1987).

The literature survey provided some important information about the kinetics of release obtained with these galenic forms. The process of release has been studied by considering the diffusion of the drug. The amount transferred has been described by a square-root law of time, with constant diffusivity (Higuchi, 1961; Touitou and Donbrow, 1982; Teillaud and Pourcelot-Roubeau, 1984). Various compositions and sizes have been prepared and the release of the drug in synthetic gastric liquid is determined in in vitro tests by using either the polymer carrier itself or the galenic forms described above.

Theoretical

Assumptions

The whole process is rather complicated, due to the several successive and simultaneous steps: diffusion of the liquid into the galenic matrix made of Eudragit RL, and into the polymer carrier; reaction between the liquid and the polymer carrier (amide function in our case); diffusion of the dissolved drug obtained from the reaction, into the polymer carrier and polymer matrix.

The following assumptions are thus made in order to simplify the problem:

(1) The spherical dosage forms are homogeneous (the medicinal agent, and the polymer carriers being well dispersed into the Eudragit matrix).

(2) Two matter transfers take place as shown previously: the liquid entering the dosage form, and the drug leaving the galenic form. They are studied successively, but not simultaneously.

(3) Both these transfers are controlled by transient diffusion throughout the galenic form, as

well as the transfer of the drug within the polymer carrier.

(4) The rate of the reaction between the liquid and polymer carrier is not considered, because it does not control the process, and is difficult to determine.

Mathematical treatment

The transient diffusion for the liquid and the medicinal agent can be described by Fick's law for spherical samples:

$$\partial C/\partial t = 1/r^2 \cdot \partial/\partial r(D \cdot r^2 \cdot \partial C/\partial r) \qquad (1)$$

where D is diffusivity, r is the radial abscissa in the sphere, and C the concentration at position r in a spherical bead at time t.

The initial and boundary conditions are:
(within the sample)

$$t = 0 \quad 0 \leq r < R \quad C = C_{\text{in}} \qquad (2)$$

(on the surface)

$$t > 0 \quad r = R \quad C = C_\infty \qquad (3)$$

where R is the radius of the bead, and C_{in} and C_∞ are the initial concentration of diffusing material and the concentration at infinite time when equilibrium is reached, respectively. The well-known analytical solution (Crank, 1975) can be obtained for Eqn 1 with the above assumptions:

$$[M_\infty - M_t]/M_\infty = 6/\pi^2 \cdot \sum 1/n^2 \cdot \exp[-n^2\pi^2 Dt/R^2] \qquad (4)$$

where M_t and M_∞ are the amount of diffusing material at time t and on achieving equilibrium (infinite time), respectively, when the process is complete, and n is an integer.

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

$$M_t/M_\infty = 6/R \cdot [Dt/\pi]^{0.5} \qquad (5)$$

For long times, another analytical solution is deduced from Eqn 4, which is also of interest for calculating the diffusivity:

$$\ln[(M_\infty - M_t)/M_\infty] = -(\pi^2/R^2)Dt + \ln(6/\pi^2) \qquad (6)$$

The values of diffusivities are obtained from the straight lines expressed either by Eqn 5 for short durations or Eqn 6 for long periods.

Materials and Methods

Materials

2-Aminothiazole (Aldrich) and derivatives used formerly as antithyroid agents are now employed in anti-ulcer tablets or as gastric antisecretory agent in medicine (Crossley, 1977, 1979; Beattie et al., 1979). These compounds have a significant solubility in hot water and are freely soluble in dilute HCl (experiments carried out at pH 1.2); and have high UV absorption at $\lambda_{\max} = 252$ nm with an ϵ of the ammonium salt equal to 9250 l mol^{-1} cm^{-1}.

Apparatus

IR spectra of monomers and polymers were measured with a Beckman Acculab Spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Perkin-Elmer Hitachi R-24 (60 MHz) and a Bruker (75 MHz) apparatus, respectively. Samples of monomers were dissolved in $CDCl_3$ (5 and 15% w/v) for ^{1}H and ^{13}C. The elemental analyses (from Service Central d'Analyse de Vernaison, France) of synthesized compounds are in good agreement with the calculated values. The amount of released drug was determined by using a Hitachi UV 1100 UV Spectrophotometer calibrated at $\lambda_{\max}$ 252 nm. The drug release from polymer carriers or from galenic forms was examined by soaking samples of product (50 mg polymer) or the beads (average weight 380–400 mg), in synthetic gastric liquid (100 ml) of pH = 1.2 at 37 °C.

Experimental

Three main purposes are considered in this paper:

(1) Firstly, to synthesize and investigate a polymer carrier able to deliver the medicinal agent (MA).

(2) Secondly, to study the behavior of galenic forms obtained by dispersing the MA into a matrix of Eudragit RL.

(3) Finally, to synthesize an organic product (modification of the initial structure) which has the same function able to deliver the drug (MA), and also to disperse this organic product into a Eudragit RL matrix.

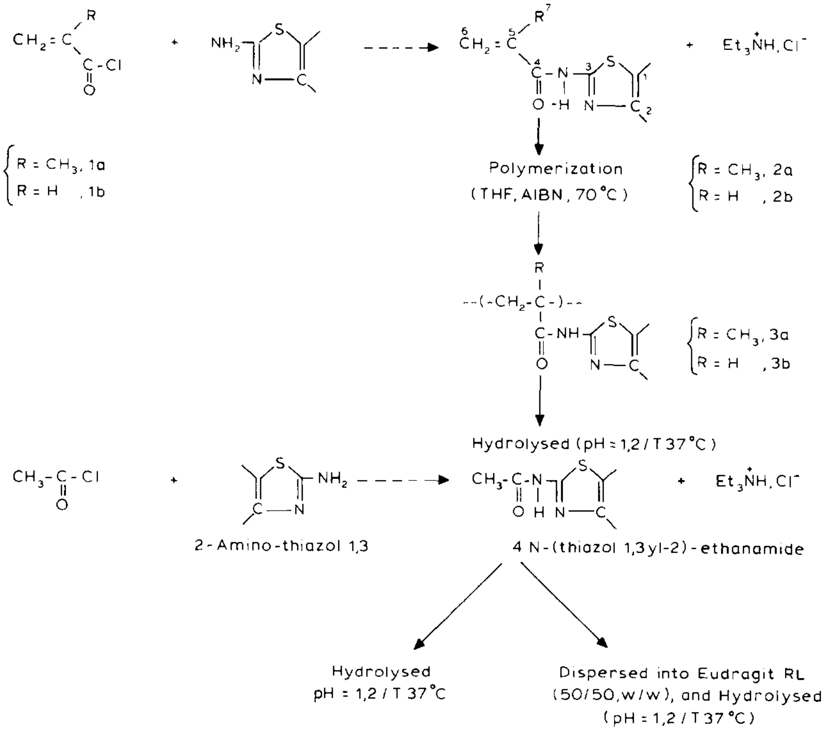
These galenic forms are of interest because of their wide possibilities: various parameters are of help in controlling the rate of drug delivery, i.e., the diameter and composition (percentage of drug) of the beads, pH of medium, and the rate of stirring. All the organic products and polymer carriers were synthesized according to the reactions presented in Scheme 1.

*Preparation of monomers **2a**, **2b**, polymers **3a**, **3b**, and **4***

These products have been synthesized according to the procedures described by Monthéard et al. (1988).

N-(Thiazol-1,3-yl-2)ethanamide (**4**) is obtained by acetylation of 2-aminothiazole.

The characteristics of **2a**, **2b** and **4** are as follows: IR spectra (**2a**, **2b**): 3300, 1670 and 1540 cm^{-1}: amide function; 1630 cm^{-1}: double bond. IR spectrum (**4**): 3450 and 1720 cm^{-1}: amide function. ^1H-NMR spectra: ($CDCl_3$ as solvent, chemical shifts in ppm). **2a**: $\underline{CH_3}$-C=C: 2.12 (s); -N$\underline{H}$CO-: 7.08 (s); $\underline{CH_2}$=C: 5.66–5.93 (2d); -C$\underline{H}$=CH-: 7.02–7.45 (2d) (thiazole nucleus). **2b**: N$\underline{H}$CO-: 7.06 (s); $\underline{CH_2}$=C: 5.66 (2d); -C$\underline{H}$=C: 6.43 (2d); -CH=C$\underline{H}$-: 7.00–7.62 (2d) (thiazole nucleus). **4**: $\underline{CH_3}$CO: 2.15 (s); -N$\underline{H}$CO-: 7.10 (s); -C$\underline{H}$=CH-: 7.15–7.41 (2d) (thiazole nucleus). δ (ppm) ^{13}C-NMR: **2a**: C_1: 113.35; C_2: 137.08; C_3: 160.14; C_4: 166.97; C_5: 121.93; C_6: 139.25; C_7: 18.60. **2b**: C_1: 114.05; C_2: 136.32; C_3: 160.30; C_4:



Scheme 1. Preparation of **2a**, **2b**, **3a**, **3b** and **4**.

163.32; C_5: 128.94; C_6: 130.11.

The characteristics of **3a, 3b** are as follows: IR spectra: 1680 and 1540 cm^{-1}: amide function (pellet with KBr). The measurements of molecular masses and the recording of NMR spectra were not possible because of the insolubilities of polymers **3a, 3b** in all organic solvents.

Preparation of dosage forms *

Eudragit RL (copolymer of dimethylaminoethylacrylate and ethyl methacrylate: $\overline{M}_n$ = 150000 from Röhm Pharma) and drug in powder form were intimately mixed in a mortar, and transformed into a thick paste with a small amount of ethanol (2 or 3 pulverizations), which is a solvent of the drug and polymer matrix. Spherical beads were prepared from this paste and dried at room temperature for 4 or 5 days. Several dosage forms were prepared with various values of drug percentage. All the beads have approximately the same weight, close to 380–400 mg. The beads with 50%/50% (w/w Eudragit/drug) (Eudragit/2-aminothiazole diameter: 0.80 cm: oral form no. 1) and (Eudragit/*N*-(thiazol-1,3-yl-2)ethanamide, diameter: 0.83 cm: oral form no. 2) were prepared and tested using synthetic gastric liquid.

Conditions of the test in vitro

Experiments were carried out in a closed flask, kept at 37 ° C, at a controlled rate of stirring. The beads (380–400 mg), inserted in a permeable fiber-glass basket, were soaked in simulated gastric liquid (100 ml) at pH 1.2 of the classical composition (80 ml 1 N HCl and 2 g NaCl to 1000 ml of aqueous solution). Samples (1 ml) of simulated gastric liquid were taken at different intervals for analysis and the beads weighed.

The same experiments were also performed with the carrier polymers (samples of 50 mg in 100 ml of pH 1.2), by soaking them in synthetic gastric liquid under the same conditions (pH = 1.2, 37 ° C, and the same rate of stirring).

Results and Discussion

Hydrolysis of acetylated drug

Hydrolysis of acetylated drug (*N*-thiazol-1,3-yl-2)ethanamide (**4**) shows a good rate of release (i.e. 54% is delivered in 1 h) (Fig. 1); however, a slight variation in pH of the gastric liquid, most certainly due to the formation of acetic acid during the reaction, was observed. The kinetics of drug release cannot be described by a simple equation.

Release of drug from the polymers carriers

When the polymer carrier (**3a, 3b**), in powder form was soaked in simulated gastric liquid (pH = 1.2) liberation of the drug, in the form of the ammonium salt, was observed, with typical kinetics as shown in Fig. 1. These kinetics of drug delivery cannot be expressed by simple classical equations. The diffusional nature of this delivery was demonstrated when the amount of drug release was plotted as a function of the square root of time, a linear relationship being observed for short periods as in the case of a process controlled by diffusion. It is difficult to determine the amount of liquid which enters the polymer, due to the very small size of the polymer grains. Moreover, we noted that this polymer carrier became gelatinous during the process, resulting from a transfer of liquid into the grains of polymer carrier.

From these experiments a number of conclusions can be drawn:

(1) The process of matter transfer is not simple for the polymer carrier when it is in contact with synthetic gastric liquid. Two matter transfers take place: the liquid enters the polymer, on the one hand provoking considerable gelling, and on the other, a dissolution of the drug which can then leave the polymer.

(2) The results obtained on the rate of delivery show a very slow hydrolysis of the amide function in synthetic gastric liquid. Hydrolysis led to an increased percentage of drug release at the beginning of the experiment, up to 240 min, but then fell after a few hours. As shown in previous papers (Droin et al., 1985; Armand et al., 1987; Malley et al., 1987), the whole process of release of drug from the dosage forms (where the drug is dispersed in polymeric matrix) can be divided into three steps:

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* Elemental analyses were in good agreement with the calculated structures.

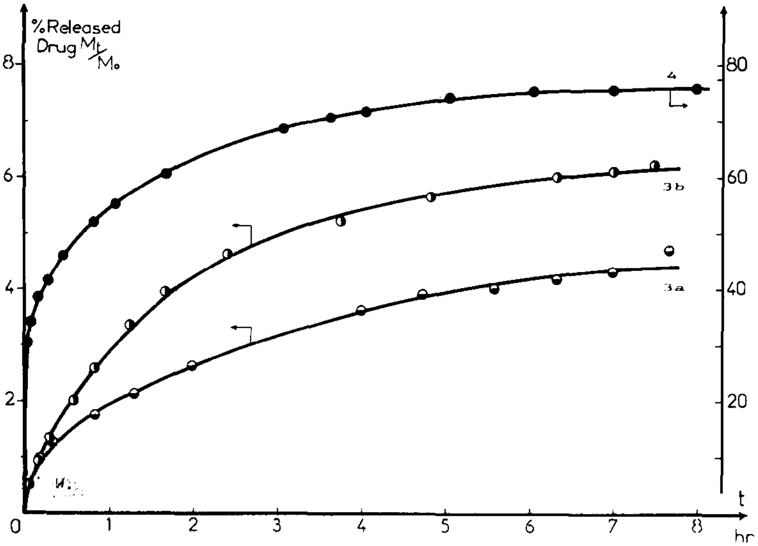

Fig. 1. Percent released drug as a function of time for **4**, **3a** and **3b** at pH 1.2 (*T* 37 °C). **4**, *N*-(thiazol-1,3-yl-2)ethanamide; **3a**, poly(2-methyl-*N*-2-thiazolyl-2-propenamide); **3b**, poly(*N*-2-thiazolyl-2-propenamide).

Diffusion of the liquid entering the galenic form.

Dissolution of the drug in the liquid. In the case of polymer carrier or acetylated drug, the reaction takes place, and the resulting drug is dissolved.

The drug thus dissolved is transferred by diffusion through the galenic form. For these reasons,

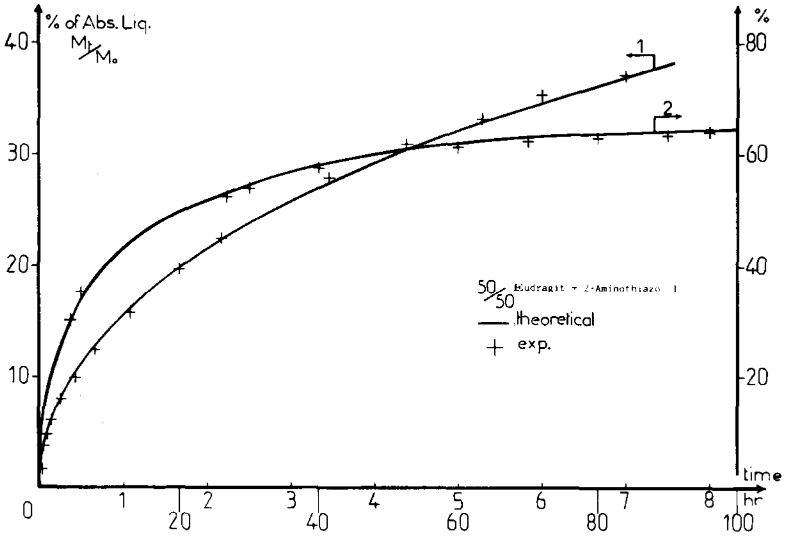

Fig. 2. Percent absorbed liquid as a function of time for dosage form 50 : 50 with 2-aminothiazole (———, theoretical; +, experimental). **1**, scale for 8 h (short periods); **2**, scale for 100 h (long periods).

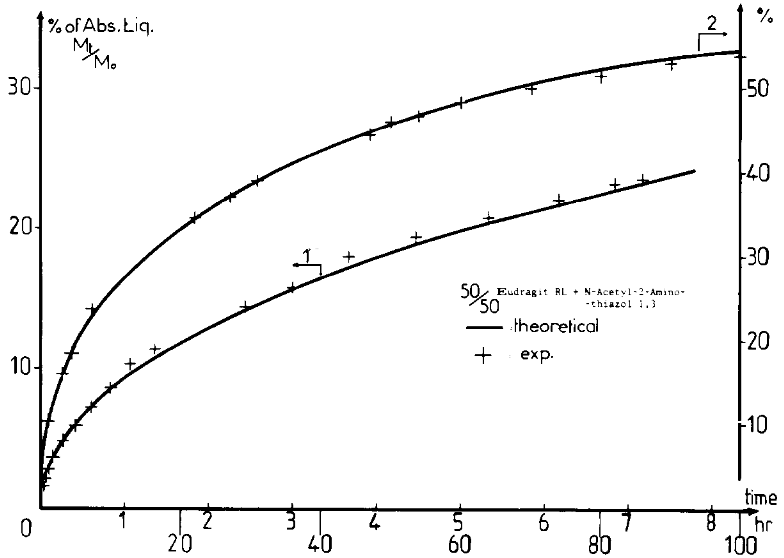

Fig. 3. Percent absorbed liquid as a function of time for dosage form 50 : 50 with *N*-(thiazol-1,3-yl-2)ethanamide (———, theoretical; +, experimental). **1**, scale for 8 h (short periods); **2**, scale for 100 h (long periods).

the matter transfer is studied either for the liquid or for the drug.

Transfer of the liquid into the dosage forms

The kinetics of the absorption of liquid were determined by using oral forms with the same composition (50 : 50). These dosage forms were soaked in synthetic gastric liquid of pH = 1.2 under the conditions described above. The curves obtained are drawn in Figs 2 and 3. The amount of liquid transferred into galenic forms 1 and 2 were also plotted as a function of square of time

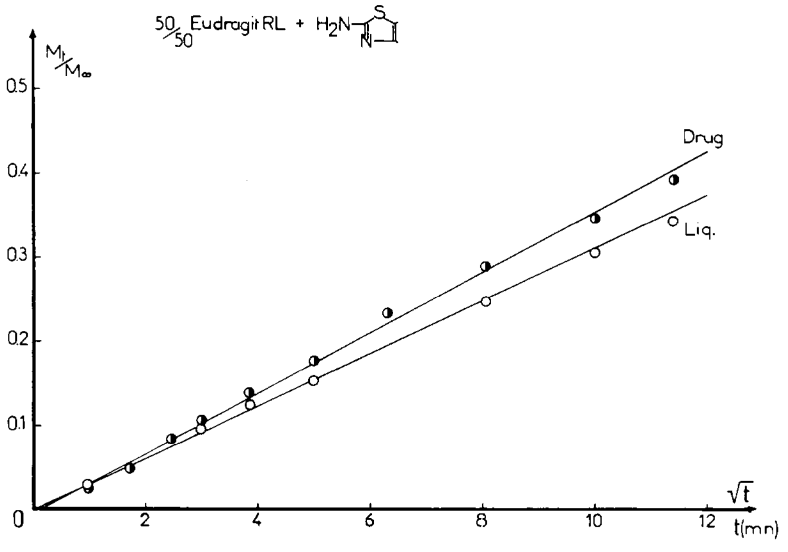

Fig. 4. M_t/M_∞ of drug released and of absorbed liquid as a function of square root of time for the dosage form 50 : 50, with 2-aminothiazole.

TABLE 1

Diffusivities and amounts at equilibrium

	Oral form	D (cm^2 s^{-1})		Mass (%)	
		Liquid	Drug	Liquid	Drug
Short times	1	2.70×10^{-7}	4.30×10^{-7}	64.90	88.70
	2	1.10×10^{-7}	2.30×10^{-7}	60.65	38.00
Long times	1	2.10×10^{-7}	3.70×10^{-7}		
	2	0.90×10^{-7}	2.10×10^{-7}		

(Figs 4 and 5). The diffusivities of the liquid were determined for short and long times for the two oral forms (see Table 1).

The following conclusions are worth pointing out from these results:

The process of liquid transfer can be considered as being controlled by diffusion, since straight lines are obtained by plotting the amount of absorbed liquid vs the square root of time.

The diffusivity varies slightly, and can be considered as remaining constant during the entire process.

The amount of liquid at equilibrium is around 65% for the two dosage forms.

The validity of the simple mathematical model can be appreciated by comparing the experimental kinetic with the theoretical results obtained by using Eqn 4, with the two dosage forms (Figs 2 and 3).

Drug delivery in synthetic gastric liquid from the galenic forms

The amount of drug in the liquid is readily evaluated and the kinetics of release of drug may be determined for the dosage forms.

The following conclusions can be drawn from these experiments:

The amount of drug released at the end of the process, when equilibrium is attained, is less than that initially present (about 90% for dosage form no. 1 and about 40% for the dosage form no. 2) (see Table 1).

The drug delivery is also controlled by diffusion. By plotting the amount of released drug as a function of the square root of time, straight lines were obtained for the two beads (Figs 4 and 5). Constant diffusivity is also observed. The kinetics can be described by the well-known series as shown by the good agreement exhibited between the theoretical value (full line) and experimental value (+)(o) (Fig. 6).

The rate of transfer as well as the amount of

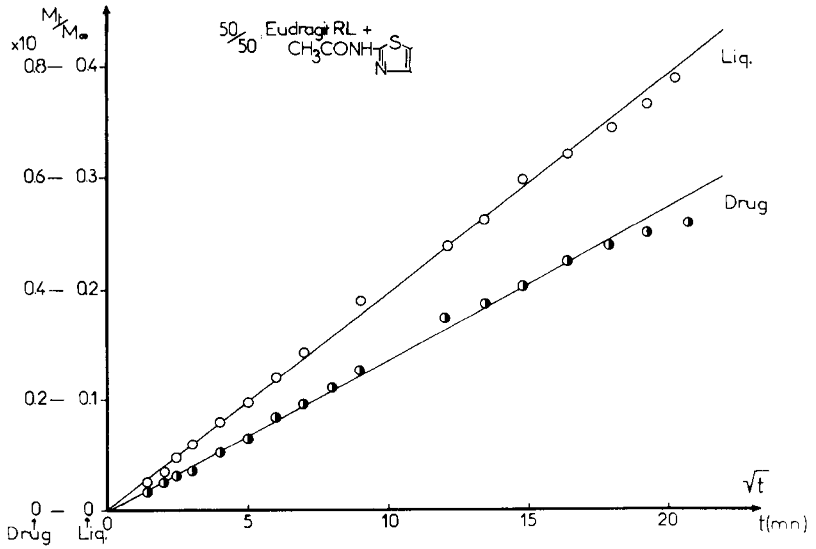

Fig. 5. M_t/M_∞ of drug released and of absorbed liquid as a function of square root of time for the dosage form 50 : 50, containing N-(thiazol-1,3-yl-2)ethanamide.

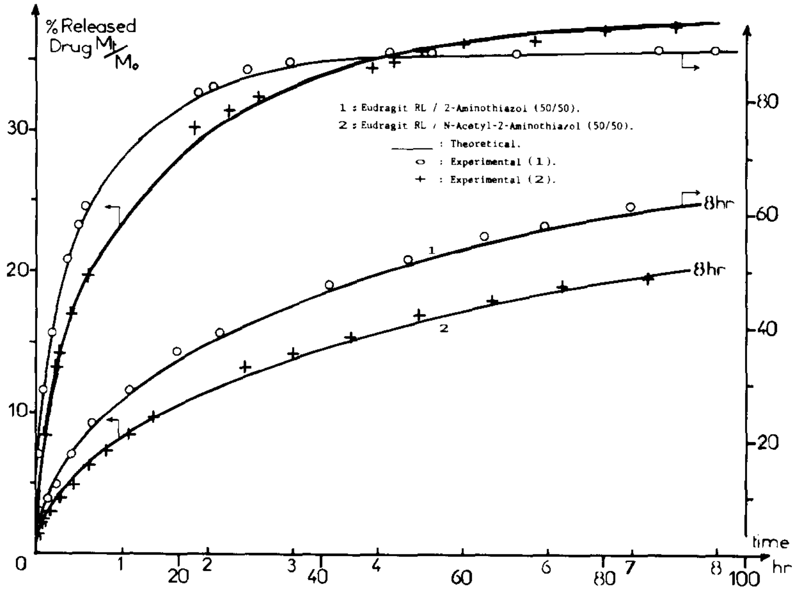

Fig. 6. Percent released drug as a function of time for dosage form 50 : 50 (**1**) containing 2-aminothiazole and dosage form 50 : 50 (**2**) with *N*-(thiazol-1,3-yl-2)-ethanamide at pH 1.2 (*T* 37 ° C). (———) Theoretical; (○) experimental (**1**); (+) experimental (**2**).

matter transferred at equilibrium is higher for the liquid than for the drug.

The rate of release of the drug is higher for the dosage forms than for the polymer carriers.

The rate of drug released and the rate of liquid absorbed are higher for the dosage form with 2-aminothiazole than for *N*-(thiazol-1,3-yl-2)ethanamide.

The dosage forms maintain good physical properties during the entire course of drug delivery, while the polymer carrier alone exhibits the disadvantage of turning into a microgel at the end of the process, when soaked in the simulated gastric liquid.

Conclusion

This paper has paved the way to new oral galenic forms able to control the release of drug in stomach. Three different types of bonding of medicinal agent (MA) were chosen to study this drug release in gastric medium by determining the kinetics of the liquid absorbed by the dosage forms and of the release of the drug. Both these matter transfers are controlled by transient diffusion with constant diffusivity, and can be described by a simple mathematical model. These drug release results help in the quantitative prediction of the rate of MA release from the polymer carrier or from the dosage forms.

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