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Release of benzocaine, procaine, 2-aminothiazole and 4-amino-4H-1,2,4-triazole from polymer carriers

M. Kolli, J.P. Montheard and J.M. Vergnaud

Faculty of Sciences and Techniques, University of Saint-Etienne, 23, Rue Dr. Paul Michelon, 42023 Saint-Etienne Cedex 2 (France)

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Summary

The present paper describes the use of vinylbenzaldehyde as a monomer carrier of drugs such as benzocaine, procaine, and 2-aminothiazole, or of 4-amino-4H-1,2,4-triazole. The monomer carrier was polymerized, and the subsequent chemical reaction of drug release was investigated using a medium of synthetic gastric liquid. Benzocaine, followed by benzocaine linked to the polymer carrier was dispersed into a matrix composed of Eudragit RL. Analysis of the kinetics of controlled release of benzocaine was carried out on the basis of theoretical considerations and of experimental determination for the case where contact is made with the synthetic gastric liquid. The release of drug was found to be consistent with a process of transient diffusion of liquid. The data obtained on drug release provide the opportunity for the quantitative prediction of the rate of drug release from dosage forms or polymer carrier.

Introduction

Synthetic polymers used in biomedical applications are making a significant contribution to the progress currently being achieved in health care and in this regard the combination of pharmacologically active compounds with polymers via chemical reactions has been attracting an increasing degree of attention during recent years. The major objectives in such studies are aimed at prolonging the duration of drug activity by controlling the release of drug (Ringsdorf, 1975). The procedures employed to regulate the release of drug can be divided into three categories for the dispersion of the drug in a polymer according to whether the mechanism involves diffusion (Feijen, 1984), osmosis (Brossard et al., 1983), or polymer erosion (Heilmann, 1984). Another technique which may be used in achieving this goal is the synthesis either of macromolecular drug derivatives by means of chemical modification of a polymer carrier or of an ethylenic monomer linked to the drug which is then subjected to polymerization or copolymerization.

Irrespective of the method used, this problem is of such complexity that the solutions proposed are largely dependent on the procedure chosen

Correspondence: J.M. Vergnaud, Faculty of Sciences and Techniques, University of Saint-Etienne, 23, Rue Dr. Paul Michelon, 42023 Saint-Etienne Cedex 2, France.

for drug transport: injection, implantation or buccal absorption. One of the main ideas in motivating the use of pharmacologically active polymers is the depot effect that may be produced with the drugs. However, this is not the only factor of importance since properties such as the controlled degradation of polymer or the release of the active agent into the human body must be taken into account.

Since our attention has been focused upon the preparation of drug release devices by means of carrying out the bonding of a drug to a polymer, and in the case of one of the products, subsequently dispersing the bound polymer in another polymer, a survey of the available literature on this method was also conducted. Linking of chloramphenicol to a methacrylate derivative via an acetal function, followed by copolymerization with 2-hydroxyethylmethacrylate has been reported (Meslard et al., 1986). The use of methacrylate derivatives as a carrier monomer has also been proposed for salicylic acid, chlorambucil and antivitamin K (Pinazzi et al., 1977; Brosse and Soutif, 1986).

Polyethylene glycol (PEG) has been used as a Polymer carrier, since it is known to be non-toxic and soluble in water, as well as being available in high or low molecular mass forms.

Procaine (Weiner and Zilkha, 1973), atropine (Weiner et al., 1976) and substituted salicylates (Weiner et al., 1974) have been linked to PEG. Other examples of molecules that have been attached to PEG are penicillin, aspirin, amphetamines, quinidine and enzymes (Davis et al., 1976; Zalipsky et al., 1983). Benzocaine has been attached to vinyl chloroformate and then polymerized (Brosse et al., 1985). In order to favour enzymatic and hydrolytic release of a drug moiety, Ringsdorf (1975) has proposed the fixation of drug to a polymerizable group, attached to an organic molecule which is considered as a spacer.

It would therefore appear that the ethylenic monomer, vinylbenzaldehyde (**2**), should be a valuable tool for use in theoretical studies since it is constituted of an ethylenic chain with a substituent phenyl group as a spacer containing an aldehyde function which would allow the preparation of an imine or a Schiff base. This aldehyde (**2**) is obtained via a single-step procedure from chloromethylstyrene (**1**; available commercially as a 3:2 mixture of the *meta* and *para* isomers) by means of the Sommelet reaction (Kamogawa et al., 1975). The present paper describes the preparation of controlled release formulations of a number of drugs or organic species, such as benzocaine, procaine, 2-aminothiazole and 4-amino-4H-1,2,4-triazole, attached to **2** followed by polymerization, dispersion of one of the polymers in Eudragit RL and analysis of the process of chemical release.

Theoretical

Assumptions

Several reactions must be considered in the cases of hydrolysis of polymer carrier, drug dispersion into Eudragit RL, or dispersion of polymer carrier into the same matrix.

A number of processes should also be taken into account, namely: diffusion of synthetic gastric liquid into the polymer followed by hydrolysis of the imine group; diffusion of the liquid through the Eudragit RL matrix and through the polymer also followed by hydrolysis of the imine; and diffusion of the drug.

In order to simplify the problem, the assumptions listed below are necessary:

(1) The spherical dosage forms are homogeneous, the drug and medicinal agent, as well as the polymer carriers being thoroughly dispersed within the Eudragit matrix. (2) Two processes of matter transfer take place: liquid entering the polymer carrier or Eudragit matrix and drug leaving the dosage form. These processes are studied successively but not simultaneously. (3) Both forms of matter transfer are governed by transient diffusion throughout the galenic form in addition to drug transfer within the polymer. (4) The rate of reaction between the liquid and polymer carrier is not taken into consideration since it does not regulate the process and since its determination is a difficult task.

Mathematical treatment

Transient radial diffusion for the case of a sphere is expressed as:

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

with constant diffusivity.

An analytical solution exists in this case when: (i) the initial concentration of matter transferred is uniform throughout the sphere at the beginning of the process; (ii) the concentration of matter transferred on the surface attains its equilibrium value as soon as the process has been initiated.

The solution is expressed as a function of time by the following exponential series:

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \sum_0^\infty \frac{1}{n^2} \exp\frac{(-n^2\pi^2 D \cdot t)}{R^2} \quad (2)$$

For the case of short periods of time, where $M_t/M_\infty < 0.2$

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

Materials and Methods

Materials

Benzocaine and procaine (Janssen Chimica) were used as local anesthetics. 2-Aminothiazole (Janssen Chimica) was employed in anti-ulcer tablets.

The ammonium salts of the above compounds and of 4-amino-4H-1,2,4-triazole are soluble in acidic water (pH 1.2) and show strong UV absorption bands as listed in Table 1.

Apparatus

The IR spectra of both the monomers and polymers were measured using a Beckman Acculab Spectrometer. ^{1}H-NMR spectra were recorded with a Perkin-Elmer Hitachi R-24 (60 MHz) instrument. Samples of monomer were dissolved in $CDCl_3$. Elemental analyses (conducted by Service Central d'Analyse de Vernaison, France) of the synthesized monomers and polymers were consistent with the calculated values.

TABLE 1

UV absorptions and ϵ of ammonium salts of drugs in acidic medium at pH 1.2

Drugs	λ_{max} (nm)	ϵ
Benzocaïne	227	12500
Procaïne	229	13200
2-Aminothiazole	225	9200
4-Amino-4H-1,2,4-triazole	200	1750

Determination of the amount of drug released was carried out on a Hitachi 1100 UV Spectrophotometer calibrated at the corresponding λ_{max} of the ammonium salt of the drug.

Molecular masses of the polymers were evaluated with the aid of a Knauer apparatus and Ultra-Styragel columns (10^3–10^5 Da) using polystyrene standards.

Drug release from polymer carriers or dosage forms was determined by soaking samples of the products (50 mg polymer) or beads (average weight 350–400 mg) in synthetic gastric liquid (100 ml) of pH 1.2 at 37°C.

Experimental

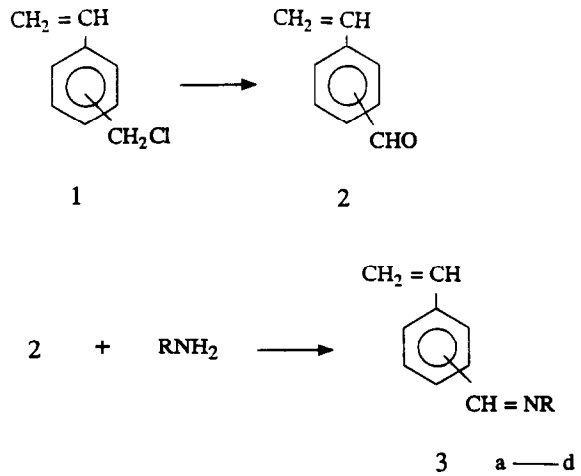
The present work concerned the three objectives listed below:

(1) The synthesis of a polymer carrier with the capability of releasing the drug over a relatively prolonged period of time.

(2) Comparison of the behaviour of a given dosage form obtained by dispersion of the drug into a matrix composed of Eudragit RL.

(3) Evaluation of the release of drug linked to a polymer and dispersed into a Eudragit RL matrix.

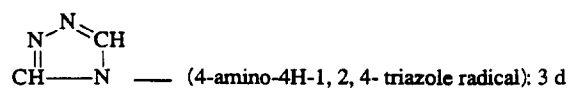
These dosage forms are of interest, since they have a wide range of possible applications: various parameters can help in controlling the rate of delivery of a drug, for example, the molecular mass of the polymer, diameter and composition of the beads, pH of the medium and stirring rate. The procedure employed in this investigation for

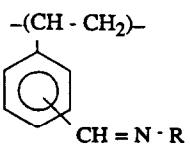


R = $CH_3CH_2OCO\varphi$ -(Benzocaine radical): 3 a

$(C_2H_5)_2NCH_2CH_2OCO\varphi$ - (Procaine radical): 3 b


(2 -amino thiazole radical): 3 c


(4-amino-4H-1, 2, 4- triazole radical): 3 d



4 a —— d

Scheme 1. Preparation of **4a–4d** (**1**, chloromethylstyrene; **2**, vinylbenzaldehyde; **3a**, R = CH_3CH_2OCOPh-benzocaine radical; **3b**, R = $(C_2H_5)_2NCH_2CH_2OCOPh$-procaine radical; **3c**, R = 2-aminothiazole radical; **3d**, R = 4-amino-4H-1,2,4-triazole radical).

the synthesis of organic polymer carriers was based on the reactions as represented in Scheme 1.

*Preparation of monomers **3a–3d***

Schiff bases were prepared by heating a mixture of the aldehyde, **2** (70 mmol), amine (benzocaine, procaine, 2-aminothiazole and 4-amino-4H-1,2,4-triazole, 77 mmol), 2,6-di(*t*-butyl)catechol (2 mg) as an antioxidant and *p*-toluenesulfonic acid (50 mg) as a catalyst in benzene (100 ml). Following the azeotropic removal of water (3–8 h), the solution was cooled, neutralized using an aqueous solution of NaOH (1 N), dried and the solvent removed by evaporation. The Schiff bases **3a–3d** cannot be distilled in vacuo.

Monomers were characterized as described below and the following data were obtained.

^{1}H-NMR. ^{1}H-NMR spectra ($CDCl_3$ as solvent; chemical shifts in ppm): (**3a**) $\underline{CH_3}-CH_2-$, 1 (t); $CH_3-\underline{CH_2}-OCO-$, 4.1 (q); $\underline{CH_2}=\overline{CH_2}$, 4.9–5.3 (2d); $-\underline{CH}=\overline{CH_2}$, 6.1 (2d); aromatic protons and $-\overline{CH}=\overline{N}-$, 6.1–8 (m). (**3b**) $\underline{CH_3}-CH_2-$, 1 (t); $CH_3-\underline{CH_2}-N<$ and $-OCH_2-\underline{CH_2}-N<$, 2.5 (m); $-\overline{COO}-\underline{CH_2}-$, 4.15 (t); $\underline{CH_2}=CH-$, 5–5.6 (2d); $CH_2=\underline{CH}-$, 6.2 (2d); aromatic protons and $-\overline{CH}=\overline{N}-$, 7–8.2 (m). (**3c**) $\underline{CH_2}=CH-$, 5.1–5.8 (2d); $-\underline{CH}=CH_2$, 6.5–6.8 (2d); aromatic protons, triazole nucleus and $-CH=N-$, 7–9 (m). (**3d**) $\underline{CH_2}=CH-$, 5.1–5.8 (2d); $-\underline{CH}=CH_2$, 6.5–6.8 (2d); aromatic protons, triazole nucleus and $-CH=N-$, 6.9–8 (m).

IR. IR spectra: main absorption of monomers (**3**), 1630–1640 cm^{-1} ($-CH=N-$), 1600 cm^{-1} (aromatic bonds), 990–900 cm^{-1} ($CH_2=CH-$). Main absorption of polymers (**4**), 1630–1640 cm^{-1} ($-CH=N-$), 1600 cm^{-1} (aromatic bonds).

*Preparation of polymers, **4a–4d***

Syntheses of **4a–4c** were carried out in bulk, using azobisisobutyronitrile as an initiator: Schiff bases, **4a–4c** (3 g) and 30 mg of azobisisobutyronitrile (1% by wt) were heated under vacuum for 24 h at 70°C in a sealed tube. The resulting polymer was solubilized in $CHCl_3$, then precipitated with hexane. The yields obtained were close to 50%. Polymer **4d** was prepared via heating a mixture of **3d** (3 g), azobisisobutyronitrile (30 mg) and benzene as solvent (3 ml). After 24 h of heating, an insoluble polymer was obtained (yield 50%). Polymers **4a–4d** were characterized according to elemental analyses and **4a–4c** addi-

TABLE 2

Molecular masses of polymers

Polymers	M_n	M_w	M_w/M_n
4a	4500	7800	1.71
4b	2000	3500	1.77
4c	6700	8000	1.18

4d is insoluble in all organic solvents.

tionally on the basis of molecular mass (Table 2).

Preparation of dosage forms

Eudragit RL (copolymer of dimethylaminoethylacrylate and ethyl methacrylate; $M_n = 150000$; from Röhm Pharma) and drug in powder form were intimately mixed in a mortar, and transformed into a thick paste by adding a small amount of ethanol (two or three pulverization steps), which acts as a solvent for both drug and polymer matrix. Spherical beads were prepared from the paste and dried at room temperature for 4 or 5 days.

All beads were of approximately equal weight, close to 350–400 mg.

Beads with a 50:50 (w/w%) Eudragit/drug ratio (Eudragit/benzocaine diameter, 0.86 cm [oral form no. 1] and Eudragit/polymer support diameter, 0.85 cm [oral form no. 2]) were prepared and tested using synthetic gastric liquid.

Conditions for in vitro test

Experiments were conducted in a closed flask, maintained at 37°C, with stirring at a controlled rate. The beads (350–400 mg), placed in a permeable fiberglass basket, were soaked in simulated gastric liquid (100 ml) at pH 1.2, and having the classical composition of 80 ml HCl (1 N) and 2 g NaCl to 1000 ml of aqueous solution. 1-ml samples of the simulated gastric liquid were removed at various intervals for analysis and the beads weighed.

Identical experiments were also performed with the polymer carriers (50 mg of sample in 100 ml of pH 1.2), by soaking them in synthetic gastric liquid under the same conditions (pH 1.2 and equal rate of stirring).

Results and Discussion

Release of drug from polymer carriers

When the polymer carriers (**4a–4d**) in powder form were soaked in synthetic gastric liquid (pH 1.2), drug was observed to be liberated in the form of the ammonium salt.

The percentages of amines released were determined by UV. Several reactions occur during the hydrolysis of polymeric Schiff bases. Firstly, the hydrolysis of imines in acidic medium takes place according to the following scheme:

$$-CH{=}N{-}R + H^+ \rightarrow -CH{=}\overset{+}{N}H{-}R$$

$$-CH{=}\overset{+}{N}H{-}R + H_2O \rightarrow -CHOH{-}NH{-}R + H^+$$

$$-CHOH{-}NHR \rightarrow -CHO + R\ddot{N}H_2$$

$$-R\ddot{N}H_2 + H^+ \rightarrow -R\overset{+}{N}H_3$$

The relatively high percentages for drug release after a number of hours can be explained on the basis of the low molecular masses of the polymers, since in this case the chemical modification of the polymers can readily be carried out.

Typical plots illustrating the kinetics of drug delivery are depicted in Figs 1 and 2 for various drugs (**4a–4d**). As demonstrated by the linear relationship between the amount of drug released and the square root of time, the entire process is controlled by transient diffusion (Droin et al., 1985; Vergnaud, 1990) rather than being governed by the hydrolysis reaction. This expression is clearly useful in the case of small amounts of drug released, as indicated by Eqn 3.

TABLE 3

Diffusivities and amounts at equilibrium

Oral form	D (cm^2 s^{-1})		Mass (%)	
	Liquid	Drug	Liquid	Drug
4a″: 50:50 no. 1	15.6×10^{-8}	10×10^{-8}	105	100
4a′: 50:50 no. 2	15.2×10^{-8}	7.5×10^{-8}	70	52

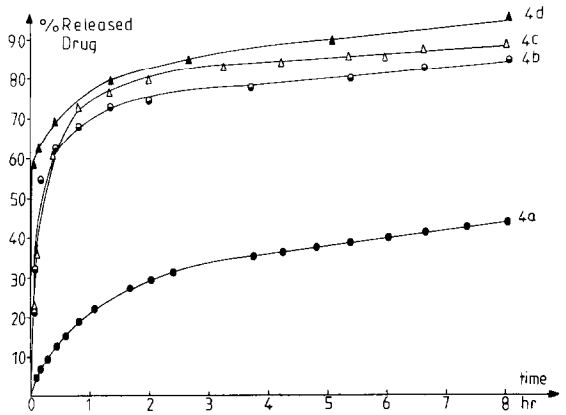


Fig. 1. Percentage of drug released as a function of time for **4a–4d** at pH 1.2 and 37°C.

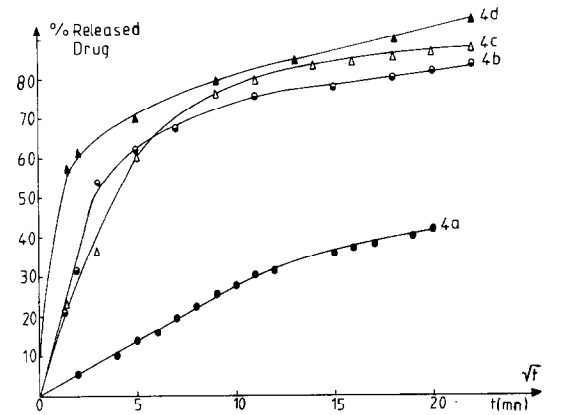


Fig. 2. Percentage of drug released as a function of square root of time for **4a–4d** at pH 1.2 and 37°C.

The process is in fact rather complex, since the following stages must be taken into account:
(1) diffusion of the liquid into the grains of polymer carrier, initially inducing swelling and finally the formation of a gel;
(2) the hydrolysis reaction with the liquid contained in the polymer carrier, the order of reaction being to some extent on the concentration of the liquid, a high value leading to degeneracy of the reaction order;
(3) diffusion of the drug dissolved in the liquid present in the polymer carrier.

Under these conditions, determination of the diffusivities of the drug and liquid is a difficult task, on the basis of at least three reasons, namely:
(1) the grains of the polymer carriers are not of uniform dimensions;
(2) the polymer undergoes a considerable degree of swelling;
(3) the behaviour of the polymer is different when in the solid state as compared to that when it is gelatinous.

Drug release from dosage forms with Eudragit as matrix

Two types of dosage form were prepared by dispersing benzocaine either (**4a″**) in Eudragit (50:50%, w/w) or fixed to the polymer carrier (**4a′**). The kinetics of drug delivery for both dosage forms were determined in synthetic gastric liquid and compared with those measured on benzo-

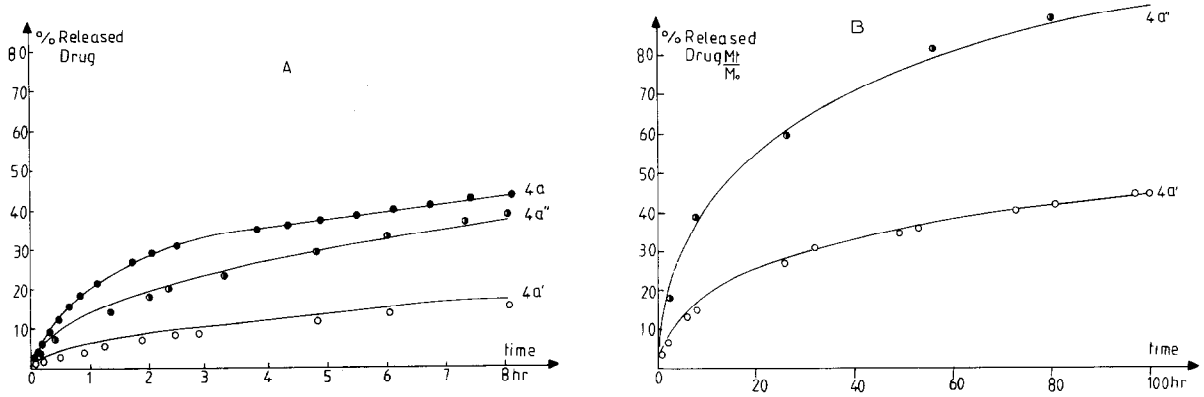


Fig. 3. Percentage of drug released as a function of time (A, short time periods; B, long time periods) for **4a** and for dosage forms 50:50 (**4a′**) and 50:50 (**4a″**) at pH 1.2 and 37°C. (———) Theoretical; (○) experimental (**4a′**); (◑) experimental (**4a″**).

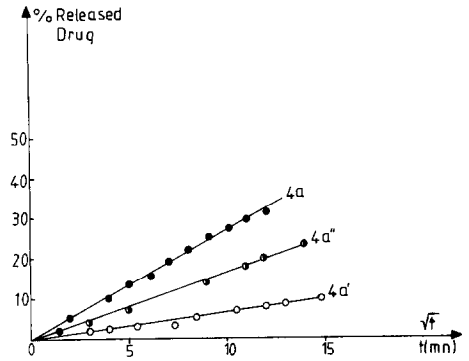


Fig. 4. Percentage of drug released as a function of square root of time for **4a** and for dosage forms 50:50 (**4a'**) and 50:50 (**4a''**) at pH 1.2 and 37°C.

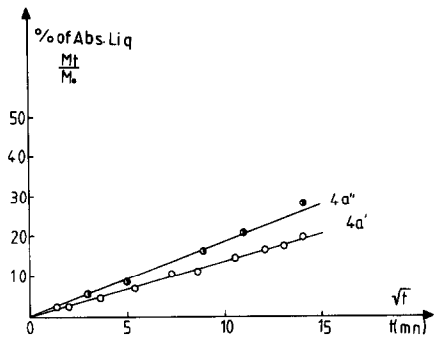


Fig. 6. Percentage of liquid absorbed as a function of square root of time for dosage forms 50:50 (**4a'**) and 50:50 (**4a''**) at pH 1.2 and 37°C.

caine-polymer carrier alone. As shown in Fig. 3, a faster rate of drug delivery was observed in the latter case. The effect of Eudragit as polymer matrix on the rate of drug transfer is particularly marked for the benzocaine-polymer carrier. For each of the above three dosage forms, drug delivery is a diffusion-controlled process, as indicated by the $t^{1/2}$ dependence of the amount of drug released (Fig. 4). The diffusivity can be readily evaluated from the corresponding linear plots (Table 3).

The kinetics of absorption of synthetic gastric liquid by the two dosage forms prepared with Eudragit as polymer matrix were also determined experimentally (Fig. 5). The process of absorption of liquid is also governed by transient diffusion,

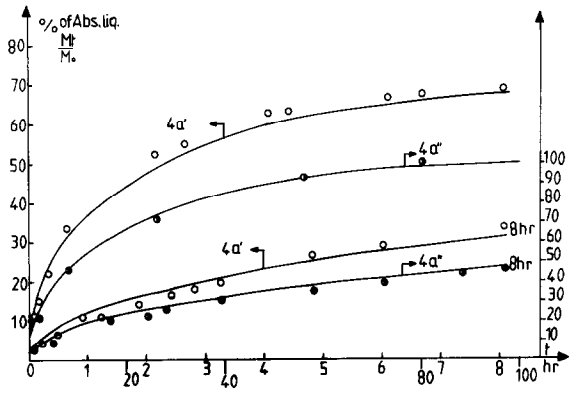


Fig. 5. Percentage of liquid absorbed as a function of time for dosage forms 50:50 (**4a'**) and 50:50 (**4a''**) at pH 1.2 and 37°C. (———) Theoretical; (○) experimental (**4a'**); (◑) experimental (**4a''**).

as demonstrated by the linearity of the plots obtained for the amount of liquid absorbed as a function of $t^{1/2}$ (Fig. 6) (Eqn 3). The kinetics calculated theoretically on the basis of the exponential series given in Eqn 2 and the diffusivities evaluated from the curves shown in Fig. 6 are consistent with the experimentally determined kinetics, as indicated by the superimposition of the traces in Fig. 5.

Conclusion

A number of the present results with benzocaine as the drug are worthy of note. The attachment of benzocaine to a polymer, referred to as a polymer carrier, via a chemical bond has been found to be possible. The polymer carrier exhibits controlled delivery of drug in synthetic gastric liquid. The main drawbacks of this polymer carrier are that it is in powder form and that it becomes gelatinous when immersed in synthetic gastric liquid.

The polymer carrier was dispersed in Eudragit as a polymer matrix. Such a dosage form is readily shaped, possesses reliable mechanical properties due to Eudragit and releases drug over a long period of time. In this case, the mass transfer process is as follows: the liquid enters the polymer, reacts with the chemical bond in the polymer carrier, and allows diffusion of the drug out of the dosage form through the liquid present in the dosage form. The process of drug delivery is

under the control of transient diffusion with a constant diffusivity. Therefore, prediction of the bead dimensions for any given purpose concerning the time of drug delivery is readily achieved by means of calculation.

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