Amines Release from Schiff Bases Polymers and Diffusion from Dosage Forms with Eudragit RL in Acidic Medium

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SYNOPSIS

Chloromethylstyrene **1** (mixture meta and para; 60/40) can be oxydized in corresponding aldehyde **2**. Vinylbenzaldehyde **2** reacts with primary amines such as aniline, benzylamine, 2-phenylethylamine, 3-phenylpropylamine, and 2-aminopyridin to give Schiff bases that are polymerized in bulk with a radical initiator. Poly(vinyl benzaldehyde) **6** prepared from corresponding monomer **2** also reacts with primary amines to give polymeric Schiff bases. Hydrolyses of these polymeric imines have been carried out either in heterogeneous acidic medium or basic heterogeneous medium; a suitable percentage of amines has been released after some hours. Finally, a study of hydrolysis and of diffusion of released amines in a dosage form (Eudragit RL) has been also carried out with some polymeric Schiff bases.

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 effect.[1,2] Drug delivery systems with macromolecules as carriers have been the object of much attention for the last few years, and synthetic macromolecules with functional groups of potential pharmacological activity have been developed.[3,4]

These therapeutic systems offer especially important advantages over traditional dosage forms in diseases requiring the most constant possible blood levels over prolonged durations of therapy. Especially interesting are investigations of pharmacologically active polymers that by themselves may be active as drugs or alternatively may be used as carriers for pharmaceutical agents largely used in medicine.[5]

Several mechanisms have been considered for this purpose, i.e., diffusion,[6] osmosis,[7] and polymer erosion,[1] and sometimes the release is controlled by various mechanisms. Another way for drug retardation has attracted considerable interest in the last 10 years: The drug is attached to a polymeric matrix or to an ethylenic monomer, then polymerized or copolymerized.

Whatever the technique employed, the problem is so complex that the proposed solutions depend largely on the chosen method for the drug transport: injection, implantation, or buccal absorption, since one of the main ideas on the use of pharmacologically active polymers is the depot effect that may be achieved with such drugs. However, this depot effect is not the only facet, and properties such as controlled polymer degradation or the release of active agents in the human body must be considered. The behavior of these polymer carriers in the gastric liquid is mainly affected by the nature of the functional groups of the pharmacological side group.

Various drugs have been attached to polymer carriers such as procaïne,[8] atropine,[9] aspirin,[10] and quinidine,[11] and the main polymers used were poly(ethylene glycol), poly(vinyl chloroformiate), or poly(vinyl alcohol). The attachment of a drug to a polymerizable monomer can be carried out directly or by means of a spacer group to favor the hydrolytic release of the drug moiety.[12]

In general, the drug is attached to the polymeric backbone through a degradable bond, which is quite stable until it is in contact with gastric liquid acidity or basicity, or by digestive intracellular enzymes.

In this sense five polymeric Schiff bases have been synthesized from corresponding monomers and pre-

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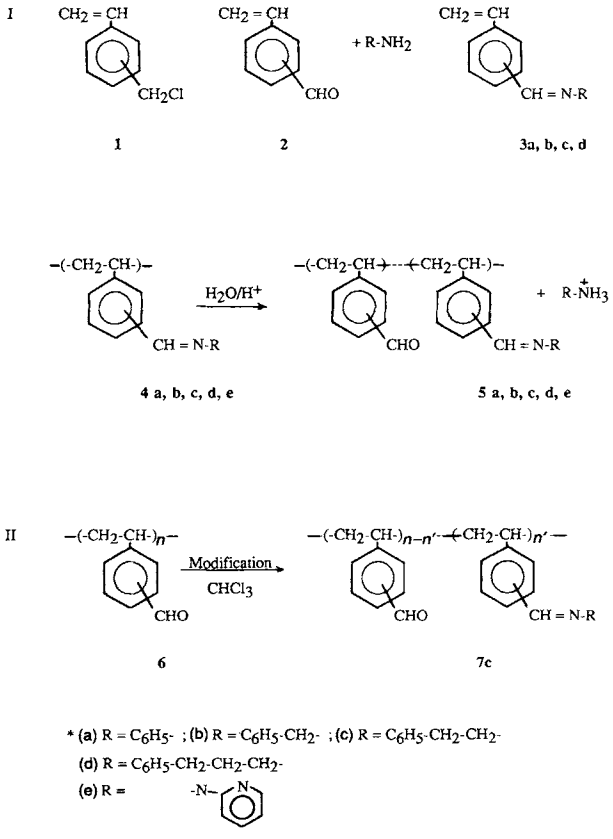
Journal of Applied Polymer Science, Vol. 43, 1837–1847 (1991)
 CCC 0021-8995/91/101837-11$04.00

pared by means of a radical polymerization (see scheme 1). Vinylbenzaldehyde **2** seems to be a valuable ethylenic monomer because it is constituted by an ethylenic chain, substituted by a phenyl group as a spacer with an aldehyde function to enable imine preparation to take place. This aldehyde **2** is prepared in one step from vinylbenzyl chloride **1** (commercially available, Dow Chemical; mixture meta/para: 3/2), by using the Sommelet reaction.[13]

Only some works have been devoted to the polymeric Schiff bases or imines: Anionic polymerization of the imine of cyclohexylamine with vinylbenzaldehyde[14] has been studied, and radical polymerizations of imines with heavy amines[15] have been described. We have also used a modification reaction of polymers: Vinylbenzaldehyde **2** has been polymerized in bulk with a radical initiator, and the corresponding polymer **6** reacts with 2-phenylethylamine, and hydrolysis has been carried out in the same acidic medium.

Finally, a sample of polymeric Schiff bases (**4c**, **4d**) has been dispersed in a polymeric matrix (Eudragit RL), and the kinetics of hydrolyses and diffusion of released amines have been studied.



Scheme 1 Preparation of monomers and polymers.

EXPERIMENTAL

Preparation of Schiff Bases 3

Schiff bases have been prepared by heating a mixture of aldehyde **2** (70 mmol), amine (aniline, benzylamine, 2-phenylethylamine, 3-phenylpropylamine, and 2-aminopyridin; 77 mmol), 2,6-di-*t*-butylcatechol (2 mg) and 50 mg of *p*-toluensulfonic acid as a catalyst in benzene (100 mL). After azeotropic removal of water (3–5 h), the solution has been cooled, neutralized with an aqueous sodium hydroxyde solution (1*N*), dried, and the solvent has been evaporated. The imine **3a** ($R = C_6H_5$) can be distilled under vacuum, but distillation with heavier radicals R produces polymers.

IR Spectra

IR spectra have been recorded with a Beckmann Acculab apparatus in $CHCl_3$ as a solvent. The main absorptions of monomers **3** are 1640 cm^{-1} (CH=N); 1600 cm^{-1} (Aromatic bonds); 990–900 cm^{-1} (CH_2=CH—).

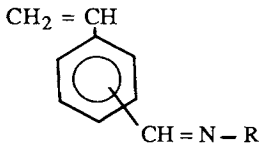
NMR Spectra

^{1}H-NMR spectra have been recorded with a Perkin-Elmer Hitachi 24A in a $CDCl_3$ solution with tetramethylsilane as a reference. Chemical shifts (in ppm) of monomers **3a**, **b**, **c**, **d**, **e** are given in Table I.

Preparations of Polymers 4

Syntheses of polymers **4** have been carried out in a sealed tube, in bulk, by using azobisisobutyronitrile (AIBN) as an initiator: A typical run is described for the preparation of polymer **4a**: a Schiff base **3a** (2 g, 9.66 mmol), and 4 mg of AIBN are heated at 70°C in a sealed tube under vacuum for 24 h. The resulting polymer is solubilized in a chloroform solution, then precipitated by hexane; two other precipitations have been carried out with the same mixture of solvents. The resulting polymer is dried under vacuum for several days. The experimental procedures are similar except for the polymerization of **3c** where transfer agent (dodecyl mercaptan: 1 mg) and a solvent (benzene 1 mL) were used. Molecular masses of polymers have been measured with a Knauer apparatus with Ultra-Styragel columns. Polystyrene standards have been used for the calibration. Elemental analyses of polymers have been realized at Service Central d'Analyse CNRS, Ver-

Table I Chemical Shifts in ^{1}H-NMR(δ ppm) of Monomer 3a, b, c, d, e[a]



	Monomer									
	3a		**3b**		**3c**		**3d**		**3e**	
	d (ppm)	*f*	*d* (ppm)	*f*	*d* (ppm)	*f*	*d* (ppm)	*f*	*d* (ppm)	*f*
$CH_2=C<$	4.95–5.66	2d	4.80–5.56	2d	4.76–5.48	2d	4.70–5.46	2d	4.80–5.50	2d
$CH=C<$	6.26–6.72	2d	6.13–6.52	2d	6.09–6.56	2d	6.08–6.56	2d	6.13–6.68	2d
Ar—	6.92–7.62	m	6.82–7.49	m	6.72–7.46	m	6.68–7.43	m	6.66–8.17	m
—CH=N—	8.00	s	7.85	s	7.60	s	7.78	s	8.83	s
—CH_2 Ar	—	—	4.49	s	2.63	t	2.40	t	—	—
$\underline{CH_2}$—N=CH	—	—	—	—	3.45	t	3.27	t	—	—
—CH_2—$\underline{CH_2}$—CH_2—	—	—	—	—	—	—	1.53–1.90	m	—	—
Ar–pyridil nucleus	—	—	—	—	—	—	—	—	6.66–8.17	m

[a] 2d = pair of doublets; s = singulet; t = triplet; m = multiplet; Ar = aromatic protons.

naison (France). These results and the molecular masses of products are given in Tables II and III.

Preparation of Poly(vinyl Benzaldehyde) 6

Polymerization of monomer **2** has been carried out in a sealed tube by heating **2** with 2% weight of AIBN during 20 h at 70°C. Then, the solid material is dissolved in chloroform and precipitated by petroleum ether. After two precipitations, the product is dried under vacuum for 2 days.

Modification of Poly(vinyl Benzaldehyde) 6

The polymeric Schiff base has been prepared by heating a mixture of polyaldehyde **6** (0.05*M*), 2-phenylethylamine (0.05*M*), and 50 mg of *p*-toluenesulfonic acid as a catalyst in a chloroform solution (100 mL). After removal of water for 8 h, the solution is cooled, then neutralized with 10 mL of NaOH (1*N*), dried with sodium sulfate, and the chloroform is evaporated. Elemental analysis of product **7c** (Table III) shows that 94% of polyaldehyde has reacted.

Table II Elemental Polymers (4a, b, c, d, e) and 7c Analyses

	C		H		N		O	
	Cal.	Exp.	Cal.	Exp.	Cal.	Exp.	Cal.	Exp.
4a	86.95	86.92	6.28	6.40	6.67	6.69	—	—
4b	86.80	85.94	7.23	7.43	5.95	6.40	—	0.23
4c	86.87	87.30	6.78	6.15	6.33	6.77	—	—
4d	86.70	86.02	5.67	5.56	7.60	7.71	—	0.71
4e	80.76	78.15	5.77	5.57	13.46	12.96	—	3.32
6[a]	81.80	81.21	6.06	5.95	—	—	12.12	12.09
7c[b]	86.87	85.55	6.78	7.15	6.33	5.82	—	1.11

[a] 6: 0.78% of Cl.
[b] **7c**: Modified polymer.

Table III Molecular Masses of Polymers 4a, b, c, d, e

Polymer	M_n	M_w	I
4a	26,000	105,000	4.04
4b	11,000	36,000	2.27
4c	7,500	14,000	1.86
4d	29,000	66,000	2.24
4e	14,000	26,000	1.85
6	37,000	89,000	2.40
7c	53,000	128,000	2.41

Hydrolyses of Polymeric Schiff Bases

The hydrolyses of polymeric Schiff bases have been achieved in acidic medium of pH = 1.2 prepared as follows: 80 mL of HCl 1*N* with 2 g of NaCl are dissolved in 1000 mL of distillated water. Hydrolyses of polymers in basic medium have been carried out in a solution of pH = 8 prepared from 50 mL of 0.025 *M* of borax with 20 mL of 0.1 *M* HCl. The rate of amine released from polymers has been followed by using a UV spectrophotometer (Hitachi U1100) calibrated at the λ_{max} of ammonium salt of studied amine. For the studies in acidic medium, the values of these λ_{max} and ϵ are given in Table IV with the λ_{max} values for amines in basic medium. The amine release is studied by soaking samples of polymers (50 mg) in the acidic or basic liquid at 37°C. The percentages of released amine from polymers are calculated with respect to initial masses of amines grafted, contained in hydrolyzed samples (50 mg).

Preparations of Dosage Forms

Eudragit RL (copolymer of dimethylaminoethylacrylate and ethylacrylate: M_n = 150,000 from Röhm Pharma) and polymeric Schiff bases **4c**, **4d** in powder form are 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 Eudragit RL matrix. Spherical beads are prepared from this paste and dried at room temperature for 4 or 5 days. Several dosage forms are prepared with various values of percentage of drug. All the beads have approximately the same weight, close to 380–400 mg, the beads with 50/50 w/wt. Eudragit/drug and 60/40 have been prepared and tested into synthetic gastric liquid.

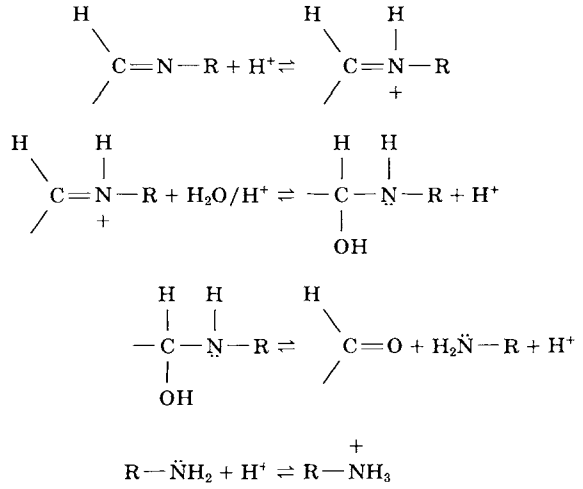
In Vitro Tests (Diffusion Study)

Experiments are carried out in a closed flask, kept at 37°C with a controlled rate of stirring. The beads (Eudragit RL and polymers **4c** and **4d**) (380–400 mg), inserted in a permeable fiberglass basket are soaked into simulated gastric liquid (100 mL) at pH = 1.2. Samples (1 mL) of simulated gastric liquid are taken at different intervals for analysis and the beads weighed.

RESULTS AND DISCUSSION

When the Schiff base polymer in powder form is soaked into simulated gastric liquid (pH = 1.2), a liberation of the drug (under ammonium ion form $R-NH_3$ is observed with typical kinetics as shown in Figure 1.

The hydrolysis of Schiff bases in the acidic medium is thought to proceed as follows:



These kinetics of drug delivery cannot be expressed by first- or second-order reactions since no linear line was obtained. These kinetics are probably partially controlled by diffusion as shown by the square root of time dependence of the amount of drug released, mainly, in short times of hydrolyses reactions. When a linear relationship is observed, the process can be controlled by diffusion.

From these experiments, some conclusions can be made about the process that can be described as follows:

1. The gastric liquid enters the random coil structure of the Schiff base polymer chains.
2. A chemical reaction between the active part of the polymer and the liquid takes place, provoking the dissolution of the drug in the liquid located in the polymer.
3. A transfer of the drug by diffusion out of the polymer through the liquid located in the polymer.

Table IV UV Characterizations of Ammonium Salts and Amines

	pH = 1.2		pH = 8	
Drug	λ_{max} (nm)	ϵ L mol^{-1} cm^{-1}	λ_{max} (nm)	ϵ L mol^{-1} cm^{-1}
Aniline	201	7480	—	—
Benzylamine	203	8800	204	8200
2-Phenylethylamine	204	7480	205	8750
3-Phenylpropylamine	205	7340	—	—
2-Aminopyridine	230	8730	228	7320

The whole process of drug delivery is thus controlled by diffusion through the Schiff base polymer itself, in spite of the fact that reactions between the active part of the Schiff base polymer and the liquid have to take place.

As seen, several parameters are considered, i.e., molecular polymer masses and nature of the released substrate. The percentage of released amine is high with the polymers **4e** (M_w = 26,000), **4c** (M_w = 14,000), **4b** (M_w = 36,000), and lower with **4a** (M_w = 105,000), and **4d** (M_w = 66,000). The rates of delivery depend on the molecular masses of polymers, since it is well known that the chemical reactions with polymers are more difficult and longer than with monomers or oligomers, with the following statement: The lower the molecular weight, the higher the rate of hydrolysis reaction. We have observed that the hydrolysis rate of imine depends on the nature of the ammonium ion resulting from hydrolysis. The anilinium cation $C_6H_5\overset{+}{N}H_3$ is probably the most stable comparatively to the cations $C_6H_5CH_2\overset{+}{N}H_3$, $C_6H_5CH_2CH_2\overset{+}{N}H_3$, and $C_6H_5CH_2CH_2CH_2\overset{+}{N}H_3$, but is the most difficult to form. Another parameter of interest is the pH of the medium with which the polymer is in contact. An attempt has been made with a liquid of pH = 8. The hydrolysis results of polymers **4b**, **4c** are given in Table V and Figure 2. The rates of hydrolysis are higher in pH = 1.2 than pH = 8 (see Table V and Fig. 1: hydrolysis results of **4a**, **4b**, **4c**, **4d**, **4e**, and **7c** in pH = 1.2).

Theoretical Approach with the Diffusion of the Matters

The following assumptions, which help the description of the process, have been obtained from experiments:

1. The dosage forms are homogeneous, the branched polymer being well dispersed in Eudragit.

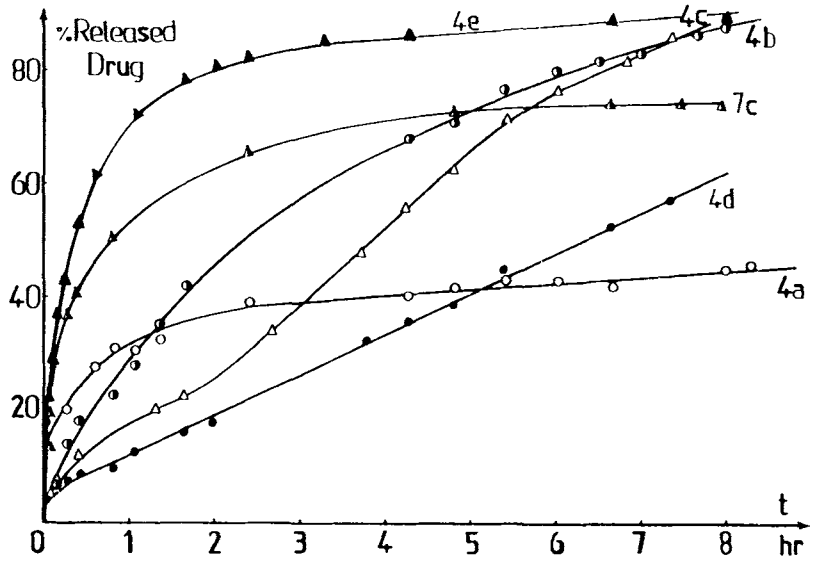


Figure 1 Percentage of drug released as a function of time for **4a**, **b**, **c**, **d**, **e**, and **7c** in pH = 1.2; T = 37°C.

Table V Percentage of Released Amine by Hydrolysis of Polymers 4a, b, c, d, e, and 7c in Acidic Medium (pH = 1.2) and 4b*, 4c* in Basic Medium (pH = 8)

Times (h)	0.5	1	2	3	4	5	6	8
4a	26	31	37	40	42	43	44	45
4b	19	29	46	57	66	73	79	88
4b*	04	06	08	10	11	12	13	14
4c	15	18	26	37	52	66	77	88
4c*	03	04	05	06	08	09	10	12
4d	10	13	20	27	34	42	49	60
4e	58	68	81	85	87	88	89	90
7c	43	53	62	69	71	73	74	75

2. Two matter transfers take place as previously shown. The former is concerned with the liquid that enters the polymer and reacts with the branched polymer; the latter is concerned with the drug dissolved in the liquid located in the polymer.[16–18]
3. Both these transfers are controlled by transient diffusion.
4. 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.[19]

As a result of these facts proved by our experiments, the process is more complex than in the case of the drug dispersed into a polymer. In the present case two matter transfers take place concerned with the liquid and the drug not only through the gastric liquid 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.[19]

The Fick equation describing the transient diffusion through the sphere is

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

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:

$$\frac{d(\text{drug})}{dt} = \frac{k(\text{drug})}{(\text{water})^n} \tag{2}$$

with a value of the order n for the water varying

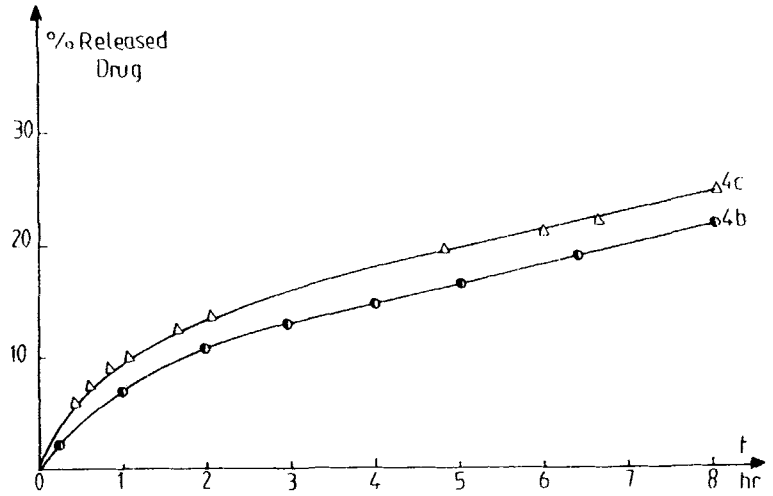


Figure 2 Percentage of drug released as a function of time for **4b**, **c** in pH = 8; T = 37°C.

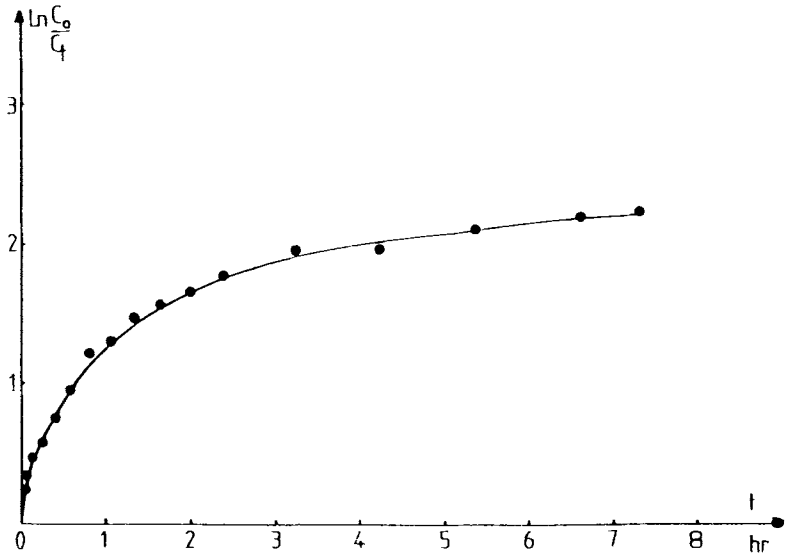


Figure 3 Kinetic of released drug from **4d** in pH = 1.2; T = 37°C. First-order reaction (n = 1).

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 equations. Only a numerical method, with finite differences taking into account all these facts, can be of interest to resolve this complicated problem.

Kinetic and Diffusion for the Dosage Forms

As this study is essentially concerned with the preparation of new dosage forms able to control the drug release in gastric liquid, the release of the drug is particularly studied in the case of the Schiff base polymer itself in contact with the liquid, and is enclosed in an Eudragit RL matrix and soaked into the same liquid.

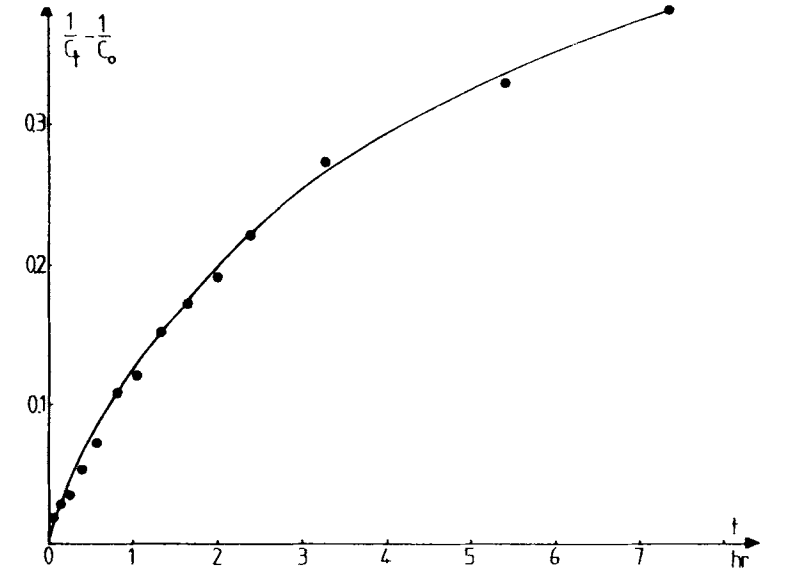


Figure 4 Kinetic of released drug from **4d** in pH = 1.2; T = 37°C. Second-order reaction (n = 2).

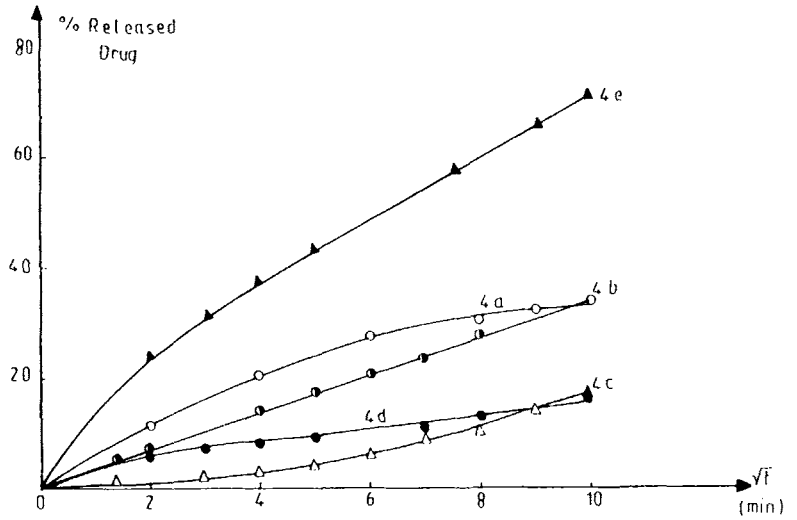


Figure 5 Percentage of drug released as a function of the square root of time for **4a**, **b**, **c**, **d**, **e** in pH = 1.2; T = 37°C.

Release of Drug from (Schiff Base) Polymer

As these polymers are dispersed into Eudragit, it is necessary to have a good knowledge on the reaction taking place between these polymers and the liquid. Some attempts are made to study this reaction between the polymers and the liquid. Several values of the order n are tested, but no answer can be given, the release of the drug being not described by a classical kinetic equation, especially for the short periods. (See Fig. 3 for the first-order reaction and Fig. 4 for the second-order reaction, i.e. **4d**.)

As proved by these experiments, it is impossible to follow the transfer of the liquid in the polymer. But an attempt has been made to test the validity of a diffusional process controlling the release of the drug, by plotting the amount of drug transferred as a function of the square root of time (Fig. 5).

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

1. The process of release is complicated for the polymers themselves because two matter transfers take place: the liquid entering the polymer and the drug diffusing out of the polymer.
2. No classical equation can describe the kinetics of the drug release.

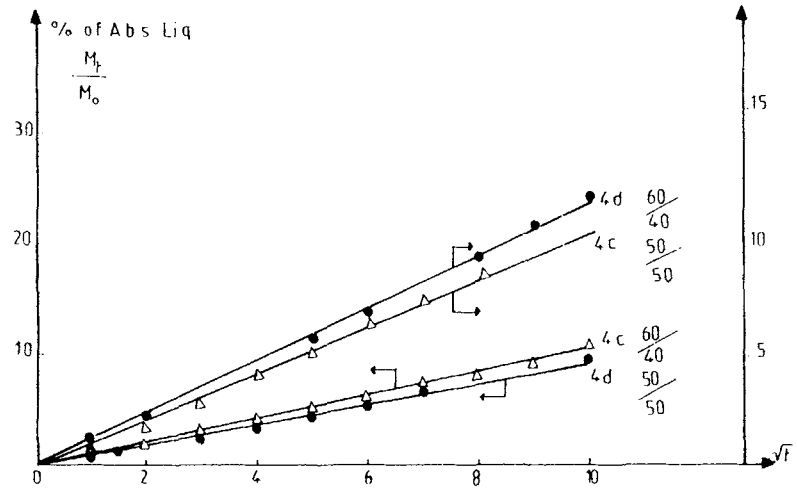


Figure 6 Percentage of absorbed liquid as a function of the square root of time for dosage forms 50/50, 60/40 with **4c**, **d** in pH = 1.2; T = 37°C.

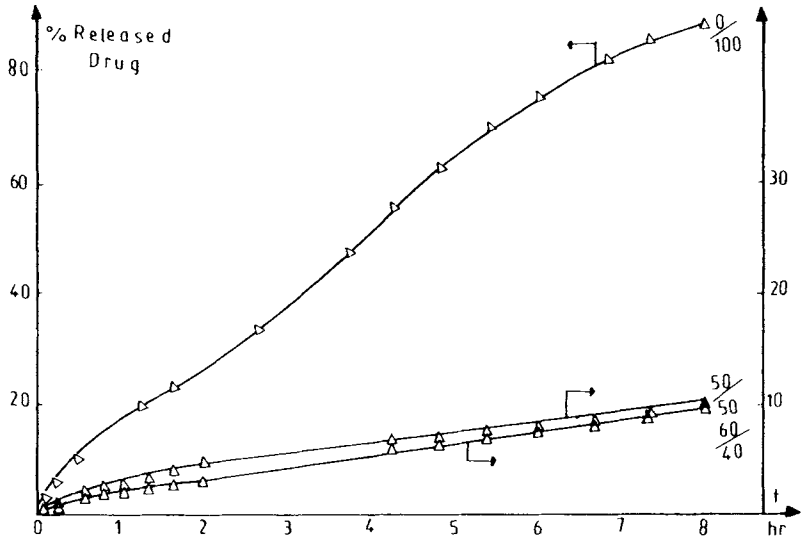


Figure 7 Percentage of drug released as a function of time for dosage forms 50/50, 60/40 with **4c** and polymer **4c**, in pH = 1.2; T = 37°C.

3. A diffusion process, playing the role of the limiting factor, could perhaps describe the whole process of release of the drug, as proved by the straight lines obtained by plotting the amount of drug released as a function of a square root of time.

Release of the Drug from the Dosage Forms

These galenic devices are made by dispersing the Schiff bases polymers in Eudragit RL, which plays the role of a polymer matrix. Two kinds of experiments are of interest: the kinetic of the liquid transfer and the kinetic of the release of the drug, when these galenic forms are in contact with the synthetic gastric liquid. In contrast with the polymers, it is easy to follow the kinetic of the transfer into the galenic forms by weighing these forms at intervals and measuring the amount of the drug released. As indicated in Figure 6, the liquid transfer is controlled by diffusion, as previously shown for Eudragit RL itself.[16]

The kinetics of the drug released (**4c**, **4d**) are drawn in Figures 7 and 8 in both cases: for the Schiff bases polymers themselves and for the dosage forms. The amount of the drug released (**4c**, **4d**) is also

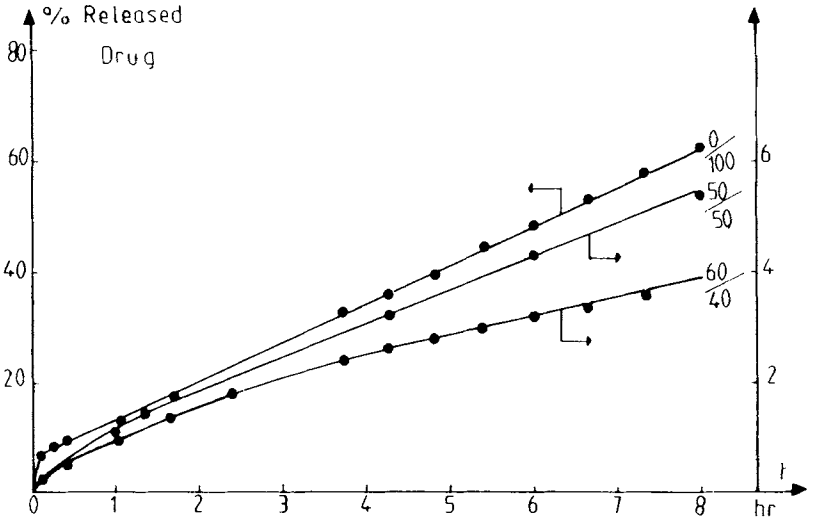


Figure 8 Percentage of drug released as a function of time for dosage forms 50/50, 60/40 with **4d** and polymer **4d** in pH = 1.2; T = 37°C.

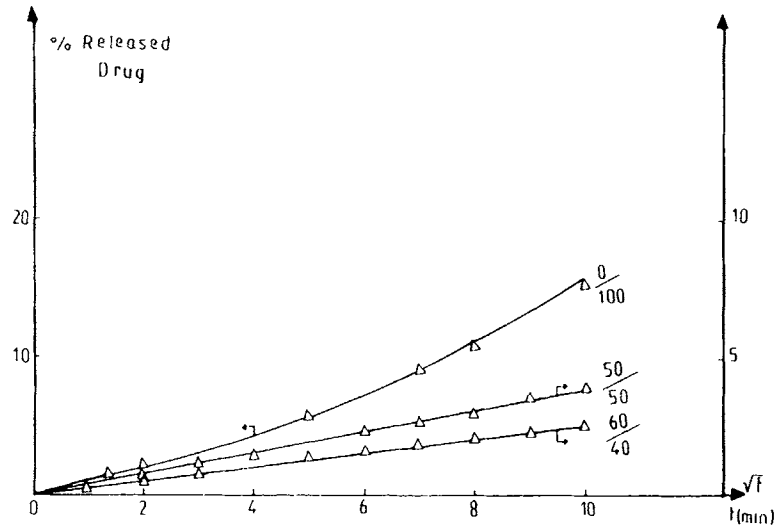


Figure 9 Percentage of drug released as a function of the square root of time for dosage forms 50/50, 60/40 with **4c** and polymer **4c** in pH = 1.2; T = 37°C.

plotted as a function of the square root of time in Figures 9 and 10, in order to appreciate the diffusion effect. From all these results, the following conclusions can be deduced:

1. The kinetics of the liquid transfer is higher than of the drug transfer.
2. The liquid transfer can be described by a diffusion process.
3. The rate of release of the drug is lower in case of the dosage forms than for the Schiff bases polymers because of the additional diffusion through the polymer matrix.

CONCLUSION

This study paves the way to a new technique for the preparation of various devices able to control the release of the drug in the stomach. In this case pharmacologically active polymers are prepared and then dispersed in a stable polymer matrix. The process of the drug release is very complicated because various matter transfers take place either through the dosage form and within the polymers themselves. 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.

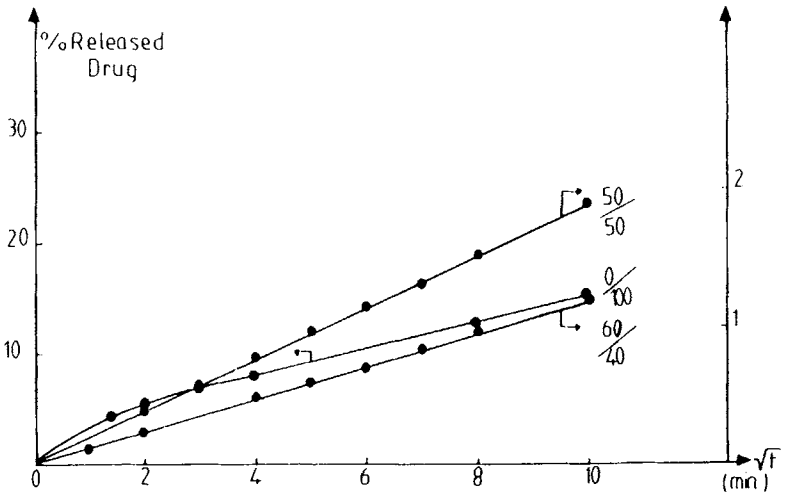


Figure 10 Percentage of drug released as a function of the square root of time for dosage forms 50/50, 60/40 with **4d** and polymer **4d** in pH = 1.2; T = 37°C.

The process of release is largely controlled by diffusion.

In case of dosage forms two matter transfers are also observed: The liquid enters the polymer matrix and the Schiff base polymer; after reaction, the drug is released out of the polymer and polymer matrix (Eudragit RL). In all cases the process is essentially controlled by diffusion of the liquid through the polymer. This kind of dosage form has some interest. It is stable because of the presence of the polymer matrix. Moreover, two limitations are able to control the drug release: One is concerned with the presence of Eudragit RL as polymer matrix; in case of accident the galenic form being crushed for instance, another way of controlling the drug release remains with the Schiff base polymer and its own kinetic of release.

A Schiff base polymer has been chosen in this study as it is a good potential drug carrier with easy hydrolysis in gastric liquid. It is possible to obtain similar Schiff bases polymers by modification of poly(vinyl benzaldehyde) having an adequate function able to react with the drug.

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Received March 28, 1990
Accepted January 14, 1991