ANTIPYRINE RELEASE FROM DOSAGE FORMS WITH AN EUDRAGIT-RL MATRIX

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ABSTRACT *:* New dosage forms able to control drug release in the stomach have been prepared and investigated in this paper. So as to follow and to control the release of Antipyrine (AP), medical agent (M.A), from spherical oral dosage forms in acidic and basic media, several kinetics of M.A release have been established at 37°C. Theoretical and experimental analysis of these kinetics were conducted for the case of contact with synthetic gastric fluids (pH=1.2 and pH=8.0), and the process was found to be controlled by transient diffusion of the liquid into and medical agent out of the dosage forms, with constant diffusivities. 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 medical agent.

KEYWORDS : Antipyrine, Diffusion, Fick's law, Ionisation, Modelisation.

RESUME : De nouvelles formes galéniques capables de contrôler la libération du médicament ont été établies et étudiées. Afin de suivre et de contrôler le relargage de l'Antypirine (AP), principe actif, à partir de formes galéniques sphériques dans des milieux acides et basiques, différentes cinétiques ont été établies à 37°C. L'étude théorique et expérimentale de ces cinétiques a montré l'influence du pH du milieux reconstitué (pH=1,2 et pH=8,0) sur celles-ci, et le processus de liberation est contrôlé par la diffusion du liquide à l'intérieur de la forme galénique et de l'agent actif vers l'extérieur, avec des coefficients de diffusion constants. Le traitement mathématique des équations de Fick a permis d'évaluer la quantité relarguée à chaque instant t. Cette étude montre la possibilité d'établir une expression de la vitesse de diffusion de cet agent actif.

MOTS CLES : Antipyrine, Diffusion, Loi de Fick, Ionisation, Modélisation

INTRODUCTION

The development of therapeutic systems that release a controlled amount of drug over a defined period of time represents a significant pathway for optimising drug effects through dosage forms [1]. These systems offer important advantages over traditional dosage forms in disease that require constant blood levels over prolonged duration of therapy. Such dosage forms can often deerease the total daily dosage of medical agent, and therefore decrease the number and frequeney of side-effects, and facilitate the treatment[2]. In tbis paper, we have focused our attention on the preparation of devices dispersing Antipyrine , a medical agent in a polymer matrix : Eudragit RL100 largely used in galenic industry[3]. Antipyrine (Phenazone) is strongly resorbed by the human blood by digestive way. It is an analgesic and both antipyretic and anti-inflammatory agent [4]. The knowledge of different chemical species to dose into the two mediums (pH=1.2 and pH=8.0) is necessary and the constant of ionisation pKa have been determined experimentally at 37°C, physiological temperature of the human body by referring to A.Albert and E.P. Serjeant's works [5].

This paper is devoted to the study of the transfer of matter obtained with several dosage forms and tested using synthetic gastric liquids (pH=1.2 and pH=8.0). These galenic forms were prepared with various values of medical agent percentage (w/w : matrix/drug : Eudragit RL/Antipyrine) and with different initial masses (100, 200, 300 and 400 mg), by using in vitro tests to determine the

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kinetics of transfers of the liquid entering the dosage form, as well as the release of the drug out of the dosage form. Another aim of this work is to investigate whether the mass transfer can be described by a transient diffusion process using some assumptions in order to clarify the problem : only Antipyrine and liquid take place, the diffusivity is constant, the concentration of Antipyrine on the surface of the dosage form is at equilibrium with the exterior medium (pH=1.2 and pH=8.0) as soon as the process starts. Under these conditions, an analytical solution for the kinetics of mass transfers as described by Cranck can be applied [6].

THEORETICAL PART

Assumptions

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

1/ The spherical dosage forms are homogeneous (the medicinal agent being well dispersed into the Eudragit matrix).

2/ Two matter transfers take place. 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.

Mathematical treatment

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

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

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

The initial and boundary conditions are :

Within the sample :	$t=0$	$0\leq r<R$	$C=C_{in}$	(2)
On the surface	$t>0$	$r=R$	$C=C_\infty$	(3)

where R is the radius of the dosage form, 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 (Cranck, 1975) can be obtained for equation1 with the above assumptions :

$$1-\frac{M_t}{M_\infty} = \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}.\exp\left[-\frac{n^2.\pi^2.D}{R^2}.t\right] \qquad (4)$$

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

For very short times [6], equation (4) can be reduced to the following equation:

$$\frac{M_t}{M_\infty} = \frac{6}{R}\left(\frac{Dt}{\pi}\right)^{1/2} \qquad (5)$$

For long times, another analytical solution is deduced from equation (4), which is also of interest for calculating the diffusivity.

$$\ln\left(1-\frac{M_t}{M_\infty}\right) = -\left(\frac{\pi^2}{R^2}\right).D.t + \ln\left(\frac{6}{\pi^2}\right) \qquad (6)$$

The values of diffusivities are obtained from the straight lines expressed either by equation (5) for short duration or equation (6) for long periods.

EXPERIMENTAL PART

Materials and Apparatus

Antipyrine (Phenazone) was chosen as a medical agent from Chemical company SIGMA.

The matrix used in the preparation of the different oral forms is the Eudragit RL100, copolymer of dimethylaminoethylacrylate and ethylmethacrylate with $\overline{Mn}$ = 150,000 g/mole from Röhm Pharma.

The buffered solutions , for kinetics :

pH= 1.2 is obtained with the classical composition (80 ml, 1N HCl and 2g NaCl to 1000 ml of aqueous solution) ;

pH=8.0 is obtained with 50 ml of Borax solution at 0.025M and 20.5 ml of HCl at 0.1N.

For determination of pKa :

pH = 0 - 1.5 : HCl 1N .

pH= 2 - 3 : $ClCH_2COOH$ / $ClCH_2COONa$; pKa = 2.87 à 25°C.

pH= 4 - 5 : CH_3COOH/ CH_3COONa ; pKa = 4.75 à 25°C.

pH= 6.3 - 8 : NaH_2PO_4/Na_2HPO_4 ; pKa = 7.21 à 25°C.

Preparation of the dosage forms

The medical agent (Phenazone) and Eudragit RL (above described), in powder form are well dispersed (using Perkin-Elmer vibror), and are intimately mixed in mortar and transformed into a thick paste with a small amount of absolute ethanol (2 or 3 pulverisations) 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 in desiccator. Several dosage forms are prepared with various values of percentage drug. All the beads have approximately the same weight for the same size.

In vitro tests

Experiments are carried out in closed flask, kept at 37°C with a controlled rate of stirring (500rpm). The beads, inserted in permeable fibber glass basket are soaked either into 80 ml of simulated gastric liquid (pH=1.2 or pH=8.0).

Samples (1 ml) of simulated gastric liquid are taken at different intervals for analysis and the beads weighed. For this, the dosage form is removed , properly dried, weighed, and replaced into the liquid.

For the drug release process, this sample (1 ml) is diluted with solution at pH=1.2 or pH=8.0, and the rate of Antipyrine released from the beads has been followed by using a double beam UV-Vis spectrophotometer Perkin-Elmer 550S calibrated at λ_{max} (202nm, ε=17,000 $l.cm^{-1}.mol^{-1}$, in pH=1.2, and at 204 nm, ε = 16,200 $l.cm^{-1}.mol^{-1}$ in pH=8.0).

RESULTS AND DISCUSSION

Determination of pKa of Antipyrine at 37°C

The constant of ionisation of Antipyrine was evaluated at 37°C, with different buffered solutions from pH=0 to pH=8 (Figure 1).

The value of pKa=1.54 ± 0.07 was determined by application of equation (7) (Table 1) or plotting O.D (optical density) as a function of pH obtained at λ=265 nm (Figure 2).

$$pK_a = pH + \log\left(\frac{A_{AP}^{\lambda,o} - A^{\lambda}}{A^{\lambda} - A_{APH^+}^{\lambda,o}}\right) \qquad (7)$$

With $A_{AP}^{\lambda,o} = \varepsilon_{AP}^{\lambda}.l.C_o$: absorbency of basic spice .

$A^{\lambda} = \varepsilon^{\lambda}.l.C_o$: absorbency at pH intermediary.

$A_{APH^+}^{\lambda,o} = \varepsilon_{APH^+}^{\lambda}.l.C_o$: absorbency of acid spice.

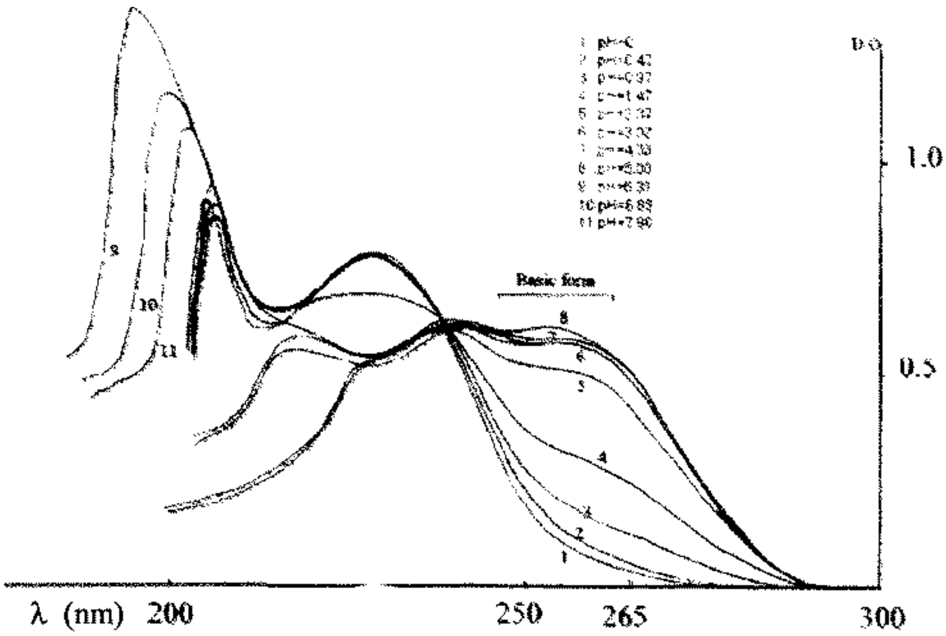


Figure 1: spectrographs of absorption of the Antipyrine in different buffered solutions from pH=0 to the pH=8

Table 1 : Determination of pKa values as a function of pH.

pH	D	$D_{AP}-D$	$D-D_{APH+}$	$\frac{D_{AP}-D}{D-D_{APH+}}$	$\log\left(\frac{D_{AP}-D}{D-D_{APH^+}}\right)$	pKa
0.97	0.138	0.365	0.103	3.543	0.549	1.519
1.21	0.195	0.308	0.160	1.925	0.284	1.494
1.47	0.251	0.252	0.216	1.166	0.066	1.536
1.63	0.294	0.209	0.259	0.807	-0.093	1.537
1.79	0.338	0.165	0.303	0.544	-0.264	1.526
2.03	0.384	0.119	0.349	0.341	-0.467	1.560
2.30	0.423	0.08	0.388	0.206	-0.685	1.610

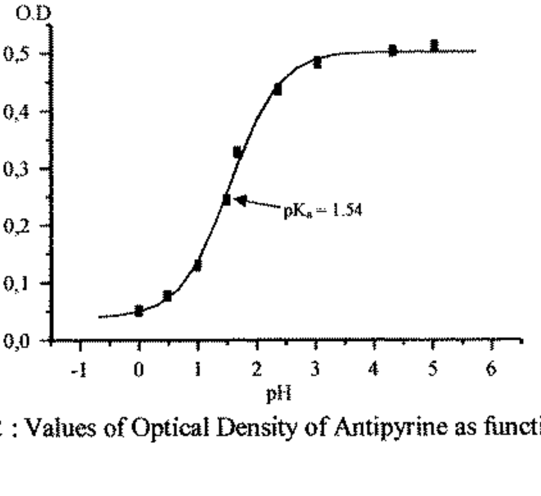
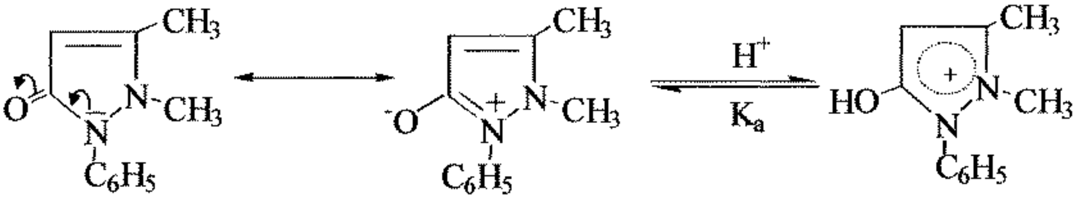


Figure 2 : Values of Optical Density of Antipyrine as function of pH

According to the value of the pKa found; Hendersen's equation gives us :

a/ In the acidic medium : $[APH^+] = 2.2\ [AP]$.

b/ In the basic medium : the protonic form $[APH^+]$ is neglected, and the neutral form [AP] is the most resorbed by the blood.



To control the effect of size of the dosage forms, we have chosen four different masses 100 mg, 200 mg , 300 mg and 400 mg with two compositions 80/20 noted a, b, c, d and 50/50, noted a*, b*, c*, d*.

Release of drug from the dosage forms

When the dosage forms were soaked in simulated gastric liquids (pH=1.2 or pH=8), liberation of the drug in the form of tbe ammonium salt was observed, with typical kinetics as shown in figure 3 and 4.

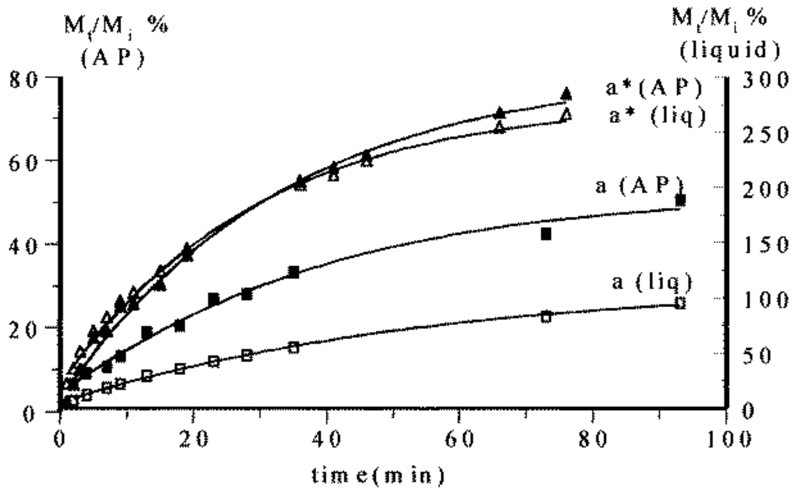


Figure 3 : % of liquid absorbed (pH=1.2) and of Antipyrine released from the oral forms "a" and "a*" as a function of time

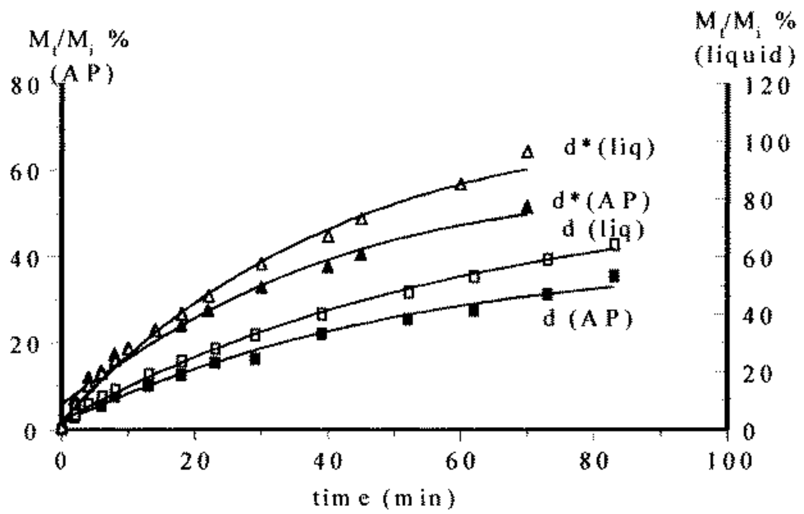


Figure 4 : % of liquid absorbed (pH=1.2) and of Antipyrine release from the oral forms "d" and "d*" as a function of time

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, as shown in figure 5 and figure 6.

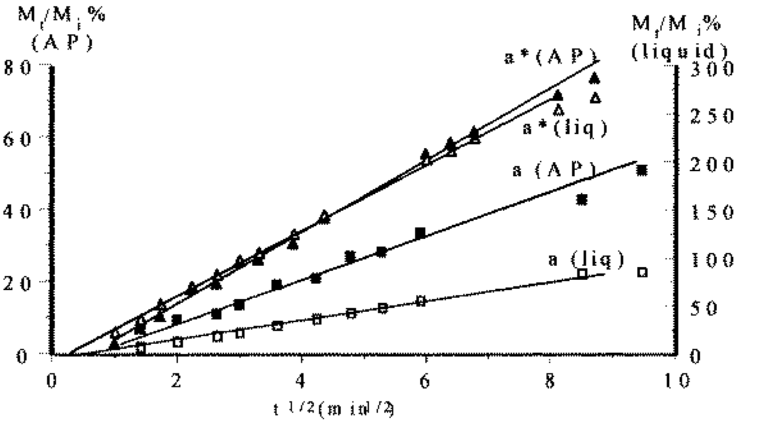


Figure 5 : % of liquid absorbed and of Antipyrine release from the oral forms "a" and "a*" as a function of square root of time

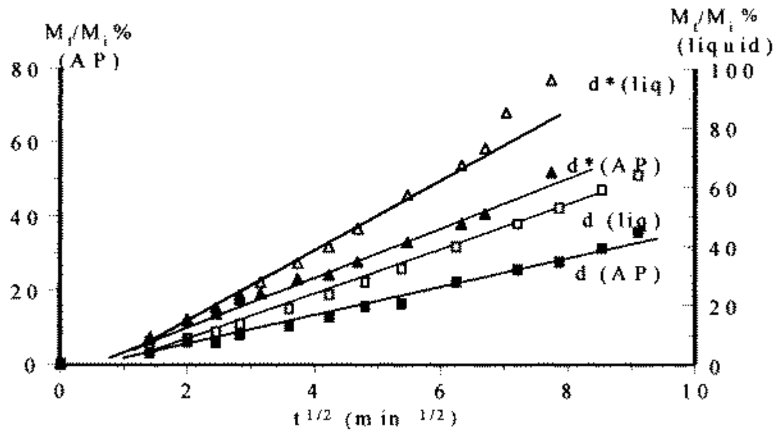


Figure 6 : % of liquid absorbed and of Antipyrine release from the oral forms "d" and "d*" as a function of square root of time

The effect of pH is shown in figure 7 for i.e. one dosage form (composition 80/20, weight 400 mg) in pH=1.2 and pH=8, the same aspect of curves was obtained (Figure 8 and 9).

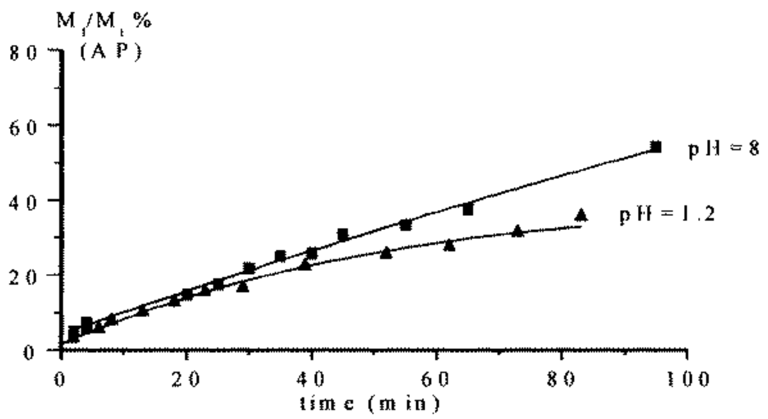


Figure 7 : % of Antipyrine released from the oral forms « 400mg and 80/20 » as a function of time and pH.

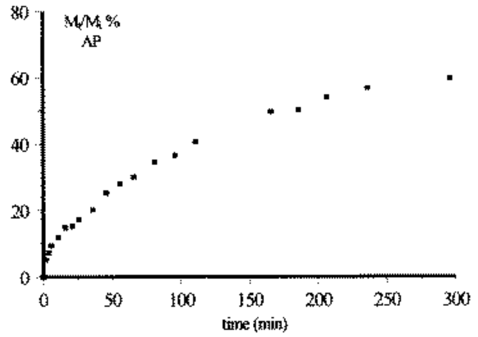


Figure 8 : % of Antipyrine released from the oral forms « 400mg and 80/20 » as a function of time

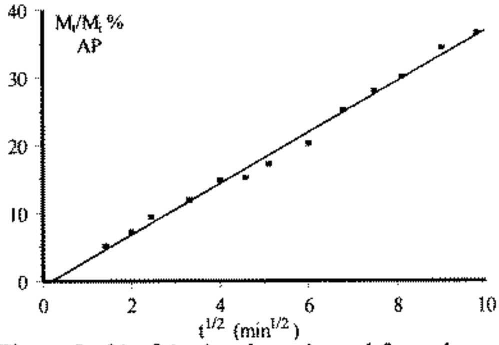


Figure 9 : % of Antipyrine released from the oral forms « 400mg and 80/20 » as a function of square root of time

DISCUSSION

From these experiments a number of conclusions can be drawn:

1- The process of matter transfer is not simple for the dosage form when it is in contact with synthetic gastric liquid : two matter transfers take place : the liquid enters the matrix-copolymer on the one hand, provoking on the other hand a dissolution of the drug which can then leave the dosage form and what ever this composition of bead may be (80/20, 50/50) we note that the rate of amine released at equilibrium depends on tbe initial masses of thc beads (Tahle II).

Table II : Values of percentage of masses at equilibrium

Oral form	**a**	**b**	**c**	**d**
$\%M_{AP\infty}$	96.95	93.65	91.60	74.56
Oral form	**a***	**b***	**c***	**d***
$\%M_{AP\infty}$	99.89	98.19	96.80	96.70

2- The results obtained on the rate of delivery show drug release at the beginning of the experiment and led to an increased percentage of drug release.

3- The total release of drug at the equilibrium takes place between 2 hours for a*(50/50) and 6 hours for d (80/20).

4- As shown in previous papers [7,8], 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

- Diffusion of the liquid entering the galenic form.
- Dissolution of the drug in the liquid.
-The drug thus dissolved is transferred by diffusion through the galenic form.

The diffusivities were calculated and evaluated (see the different results on table III and IV).

Table III: Values of diffusivities of the Antipyrine released in pH=1.2.
s,t : short time , l,t: long time

Oral forms	Composition	Diffusivities	
		$D.10^7$ ($cm^2.min^{-1}$) $D_{s,t}$	$D.10^9$ ($cm^2.min^{-1}$) $D_{l,t}$
a 100mg	80/20	1.73	3.90
b 200mg	80/20	1.81	5.40
c 300mg	80/20	2.70	7.20
d 400mg	80/20	2.30	6.00
a* 100mg	50/50	3.09	9.80
b* 200mg	50/50	3.80	10.98
c* 300mg	50/50	3.30	12.00
d* 400mg	50/50	4.89	11.04

Table IV : Values of diffusivities of the Antipyrine released as a function of a pH

Oral forms	Diffusivities	
	$D.10^7$ ($cm^2.min^{-1}$) $D_{s,t}$	$D.10^9$ ($cm^2.min^{-1}$) $D_{l,t}$
80/20 pH=8.0	2.76	5.73
80/20 pH=1.2	2.29	6.00

For these reasons, the matter transfer is studied either for the liquid or for the drug. It is often of interest to build a model even in a rough and simple model to describe the process, because mathematical simulations are then possible. In the case of the dosage forms containing the drug, the diffusional model with constant diffusivity expressed by equations (5) and (6) are successfully tested either for the transport of the drug and for that of the liquid.

CONCLUSION

This paper has paved the way to new oral galenic forms able to control the release of drug in stomach. The dispersion of medicinal agent was chosen to study this drug release in gastric medium by determining the kinetics of the liquid absorbed by the dosage forms and of 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 medical agent release from the dosage forms.

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