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# Evaluation of anilines models release kinetics from dosage forms using Eudragit-RL as matrix

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## Abstract
The galenic forms able to control drug release have been prepared and investigated in this paper. In order to follow and to control the release of anilines model $(MA)_{1-4}$, from spherical oral galenic forms in acidic medium, several kinetics of $(MA)_{1-4}$ release have been carried out at 37°C. Theoretical and experimental analysis of these kinetics were conducted in synthetic gastric fluid medium (pH=1.2), and the process was found to be controlled by transient diffusion, with constant diffusivities, for the liquid into and medical agent (MA) out of the galenic forms. According to Fick's law, a mathematical treatment led to evaluate the amount of matter transferred at time (t). The present study demonstrates that it is possible to derive a direct expression for rate diffusion's of medical agent (MA).

*Key words:* Monomers; Copolymers; Imine; Drug Release; Diffusion; Hydrolysis.

## 1. Introduction
Diffusional release of active molecules from polymeric systems is an important method and commonly used in achieving controlled release. Several literature reviews discus drug delivery systems from different matrices. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance as Eudragit RS 100[1], Hydroxypropyl methylcellulose [2], and Ethyl cellulose [3]. Drug release from hydrophilic matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanisms.

Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from dosage form is controlled by the hydration of the polymer used, which forms the gel barrier through which the drug diffuses.

Several mathematical models have been published, to elucidate the water and drug transport processes and to predict the resulting drug release kinetics [2-3]. The mathematical description of the entire drug release process is rather difficult, because of the number of physical characteristics that must be taken into account. These include the diffusion of water into the polymeric matrix, polymer swelling, drug diffusion out of the device, polymer dissolution, concentration dependent diffusivities of the species, moving boundaries, and changing matrix dimensions, porosity and composition. Each model makes certain assumptions and due to these hypotheses, the applicability of the respective models is restricted to certain drug-polymer systems.

This paper is devoted to the study of the transfer of matter obtained with several galenic forms and tested in synthetic gastric liquid (pH=1.2). These galenic forms were prepared from initial masses (~200 mg), and various $(CP)_{1-4}$ percentage [w/w: (Eudragit RL)/ $(CP)_{1-4}$] to determine in vitro tests, the kinetics of transfers of the liquid entering the galenic form, and release of the drug $(MA)_{1-4}$ out of the galenic form. Under these conditions, an analytical solution for the kinetics of mass transfers is described by Fick's law [4].

## 2. Materials et Methods

*2.1. Theoretical part:*

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

- The spherical dosage forms are homogeneous (the copolymers $(CP)_{1\text{-}4}$ bearing model anilines being well dispersed into the Eudragit RL matrix).
- Two matter transfers take place. The liquid entering the galenic form, and the drug leaving the galenic form. They are studied successively but not simultaneously.
- Both these transfers are controlled by transient diffusion throughout the galenic form.

*2.2. Mathematical treatment:*

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

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

Were 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: $t = 0$ $\quad o \leq r < R$ $\quad C = C_{in}$ **(2)**

On the surface: $t > 0$ $\quad r = R$ $\quad C = C_{\infty}$ **(3)**

Where R is the radius of the dosage form, and $C_{in}$ and $C_{\infty}$ 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 equation (1) with the above assumptions:

$$\frac{m_{\infty} - m_t}{m_{\infty}} = \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left( - \frac{D.n^2.\pi^2.t}{R^2} \right) \qquad \textbf{(4)}$$

Where $m_t$ and $m_{\infty}$ 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, equation (4) can be reduced to the following equation:

$$\frac{m_t}{m_{\infty}} = 6 . \left( \frac{D.t}{R^2} \right)^{1/2} \cdot \frac{1}{\pi^{1/2}} \qquad \textbf{(5)}$$

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

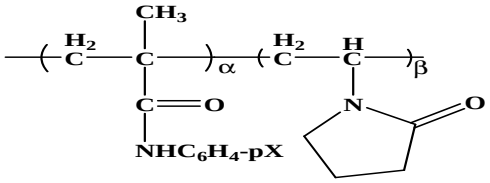
$$Ln\left( 1 - \frac{m_t}{m_{\infty}} \right) = - \frac{D \pi^2 t}{R^2} + Ln \frac{6}{\pi^2} \qquad \textbf{(6)}$$

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

*2.3. Experimental part:*

**2.3.1. Synthesis of the monomers $(MS)_{1\text{-}4}$ and copolymers supports $(CP)_{1\text{-}4}$:**

Four secondary amides $(MS)_{1\text{-}4}$ have been prepared by the Schotten-Baumann reaction [5-6] between model anilines [$(MA)_{1\text{-}4}$: p-$XC_6H_4NH_2$: $X_1$: H; $X_2$:$CH_3$; $X_3$:$COCH_3$; $X_4$: CN] and methacryloyl chloride using aqueous THF/NaOH mixture at 0°C (scheme a). $(MS)_1$, $(MS)_2$ and $(MS)_4$ represent liquid monomers, whereas $(MS)_3$ is a solid monomer. Mass radical copolymerization of the different monomers $(MS)_{1\text{-}4}$ with N-vinyl-2-pyrrolidone (VP) yields to the corresponding four copolymers $(CP)_{1\text{-}4}$. All the monomers have been characterized by IR, $^1H$ and $^{13}C$ NMR. The $(CP)_{1\text{-}4}$ have been characterized by IR spectra, microanalysis, DSC and viscosimetric masses Mv [7].



**$X_1$: H; $X_2$:$CH_3$; $X_3$:$COCH_3$; $X_4$: CN**

**Scheme a:** Structure of $(CP)_{1-4}$

### 2.3.2. Preparation of buffer solution:

The buffered solution pH=1.2 is obtained with the classical composition:

HCl : 1N, 60 mL
NaCl : 2 g
Aqueous solution : 1000 mL

The medium is prepared to the standards described by American Pharmacopeia U.S.P [8].

### 2.3.3. Preparation of the dosage forms:

The copolymers $(CP)_{1-4}$ and Eudragit RL, in powder form are well dispersed, and are intimately mixed in mortar and transformed into a thick paste with a small amount of absolute 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 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.

Example:

A galenic form [Eud/$(CP)_1$ :( 70/30)] with initial masses 192.3 mg has the following composition:

70% its mass corresponds to 134.6 mg of l'Eudragit RL.

30% its mass corresponds to 57.7 mg of the bearing copolymer $(CP)_1$.

According to the percentage of incorporation of $(CP)_1$ : -$(MS_1)_{0.13}$— $(VP)_{0.87}$-, the initial mass calculated of $(MA)_1$ incorporate in $(CP)_1$ is 5.9 mg.

### 2.3.4. 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 fiber glass basket are soaked into 100 mL of simulated gastric liquid (pH=1.2).

Samples (1 mL) of simulated gastric liquid are taken at different intervals for analysis and the beads are weighed. In this case, 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, and the rate of $[(MA)_{1-4}H^+]$ released from the beads has been followed by using the double beam UV-Vis spectrophotometer SHIMADZU UV-2401 PC calibrated at $\lambda_{max}$ of the $[(MA)_{1-4}H^+]$**.**

## 3. Results and discussion:

According to Henderson's equation (7), and pK of amines in pH=1.2, the protonic form is favored according to the sequence as shows in table1:

$$[(MA)_2\,H^+] > [(MA)_1\,H^+] > [(MA)_3\,H^+] > [(MA)_4\,H^+]$$

$$pH = pK + \log \frac{[MA]}{[MAH^+]} \qquad \textbf{(7)}$$

$pK(MA)_1 = 4.62$; $pK(MA)_3 = 2.19$ [9].

$pK(MA)_2 = 5.1$ ; $pK(MA)_4 = 1.74$ [10].

We can consider that the protonic forms of p-toluidine and aniline are widely majority at pH = 1.2, whereas for p- cyanoaniline and p-aminoacetophenone, we have a quantitative mixture of acid and base forms. The standard calibration curves have been established by UV for each amine at pH = 1.2 and T = 37 ° C. The example in Figure 1 shows the UV spectra of aniline at different concentrations. The spectra rise two bands (E) and (B) of anilinium cation originate from $\pi \rightarrow \pi^*$ transitions in the highly symmetrical benzene chromophore: the intense band (E) at 203 nm result from an allowed transition and the weaker band (B) at 253.6 nm result from forbidden transitions. These bands are placed in the same wavelengths as these of benzene [11].

The (B) band appears with a significant fine structure due to the near-absence of $n \rightarrow \pi^*$ interaction of amine function entirely protonated as usually observed for benzene. The standard curve was drawn up of the B band centered at $\lambda_{max}$ =253.6 nm and $\varepsilon_{max}$ =1754 l.mole$^{-1}$.cm$^{-1}$ of anilinium cation [$(MA)_1H^+$] (Figures 1 and 2).

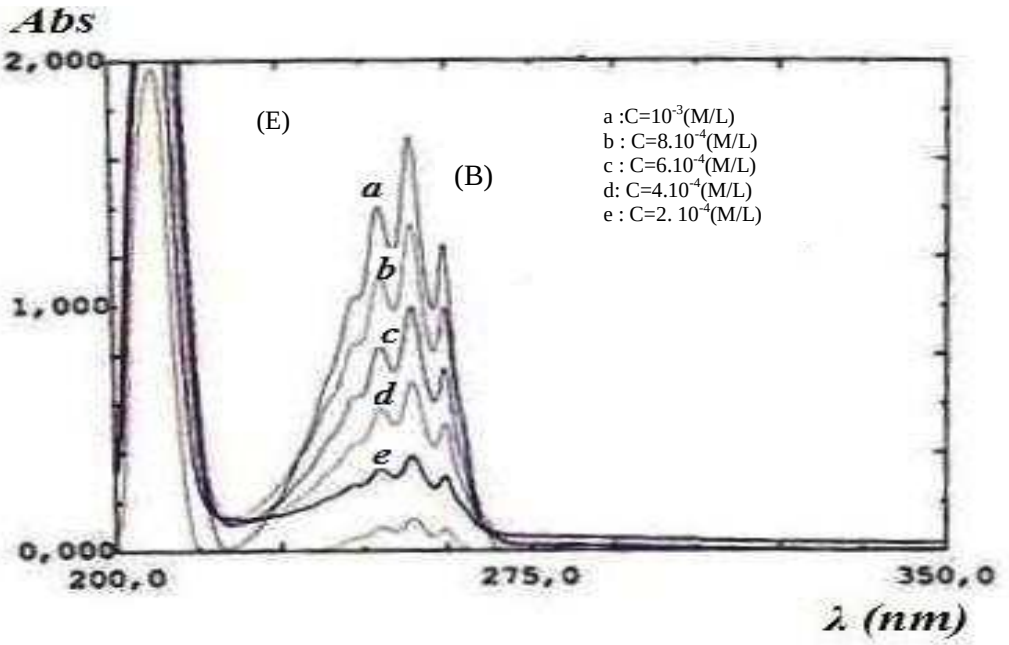



**Figure1:** Spectra UV of the anilinium [$(MA)_1H^+$] in the pH =1.2 with various concentrations

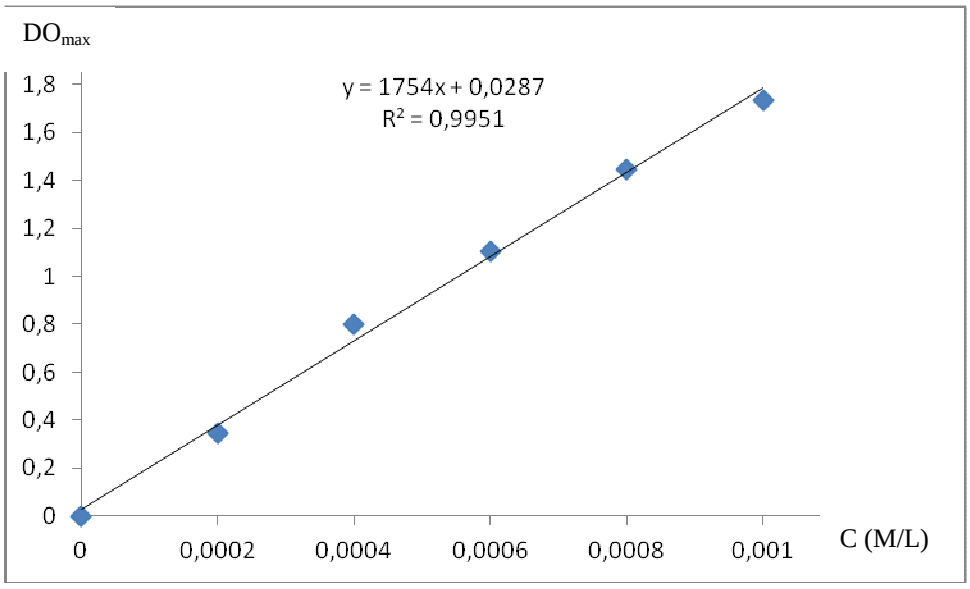



**Figure2:** Standard curve of the aniline [$(MA)_1H^+$]in the pH=1.2 medium at $\lambda_{max}$ =253.6 nm

**Table 1:** Reports [Aniliniums [$(MAH^+)_{1-4}$]/ Anilines $(MA)_{1-4}$] at pH=1.2.

| $(MA)_{1-4} : X_{1-4}$ | pK $(MA)_{1-4}$ | $[(MA)H^+] /[MA]$ |
|---|---|---|
| $(MA)_1 : X_1 : H$ | 4.62 | 2630 |
| $(MA)_2 : X_2 : CH_3$ | 5.10 | 7943 |
| $(MA)_3 : X_3 : COCH_3$ | 2.18 | 9.8 |
| $(MA)_4 : X_4 : CN$ | 1.74 | 3.5 |

When the dosage forms were soaked in simulated gastric liquids (pH=1.2), liberation of the drug and the absorbed liquid was observed, with typical kinetic as shown in figure3 and figure4.

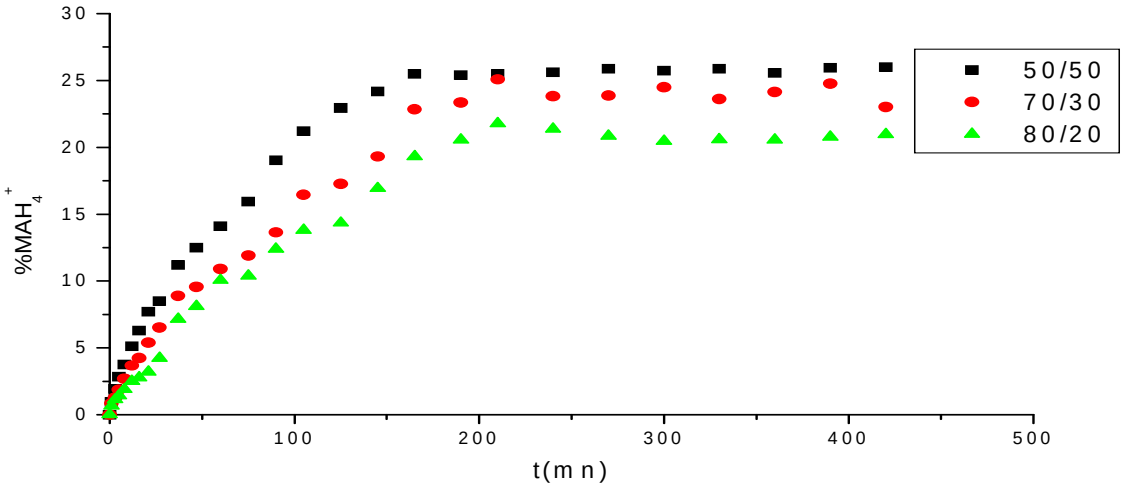



**Figure 3:** Cumulated percentage of $[(MA)_4H^+]$ released from the galenic forms $[Eud/(CP)_4]$ in pH=1.2 at T=37°C.

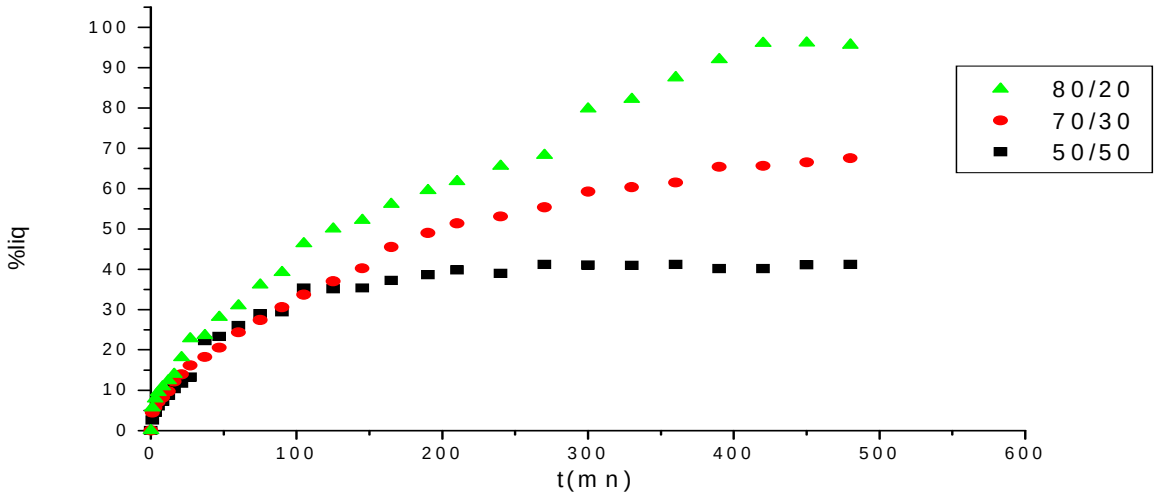



**Figure 4:** Swelling percentage of the galenic forms $[Eud/(CP)_4]$in the pH=1.2 at T=37°C.

The comparison in figure 3 and 4 shows an inversion of the curves according to the percentage in Eudragit RL of the galenic forms. The galenic form 80/20 richest in matrix copolymer absorbent Eudragit RL is that which absorbs the most aqueous solution of pH=1.2 and it is in the same time that which releases less protonic aniline [$(MA)_4H^+$], the same phenomenon is observed for the release of the other three model anilines [$(MA)_{1\text{-}3}H^+$] starting from the galenic forms of the same composition. The phenomenon of gelation being a function of the absorptive quantities of water, with swelling of the galenic form, will be a barrier preventing the salting out of the active ingredient: of this barrier would be the principal cause of the inversion of the curves observed.

Thus the cumulated percentages of [$(MA)_4H^+$] released and those of percentage of absorptive liquid, the absorptive aqueous solution follow the following sequences opposite:

**Table 2:** Percentages of transferred matters at t= 100 mn and 400 mn by the galenic forms [(Eudragit RL)/ $(CP)_4$]

| *the galenic forms* | *80/20* | | *70/30* | | *50/50* | |
|---|---|---|---|---|---|---|
| *Time (t) (min)* | *100* | *400* | *100* | *400* | *100* | *400* |
| *The rate of [$(MA)_4H^+$] released* | *13.12* | *20.65* | *15.26* | *23.13* | *20.62* | *25.63* |
| *The rate of liquid absorbed* | *30.90* | *89.08* | *34.35* | *63.63* | *41.81* | *38.18* |

These kinetics of drug delivery cannot be expressed by simple classical equations giving orders 0, 1 and 2. The diffusionnel 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.

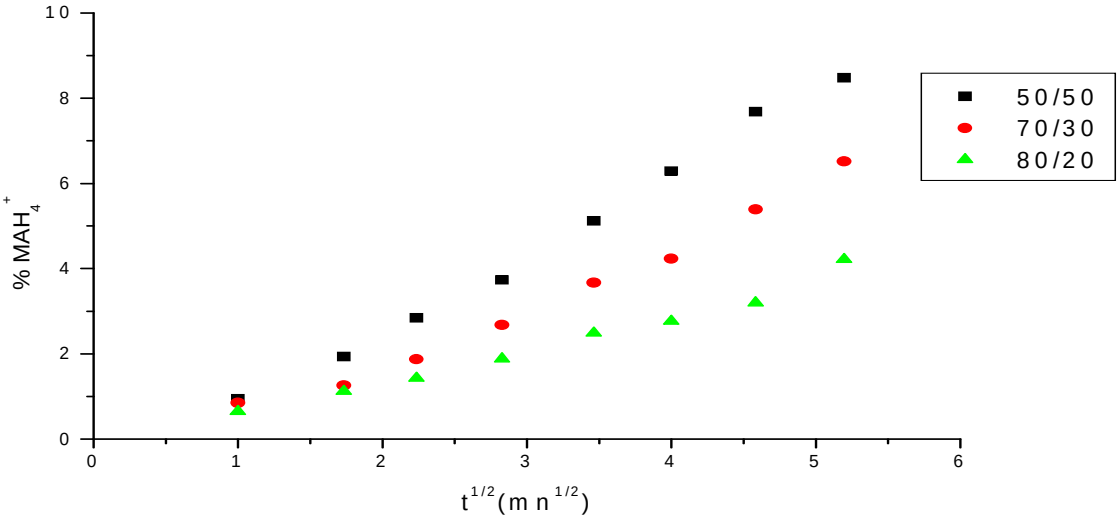


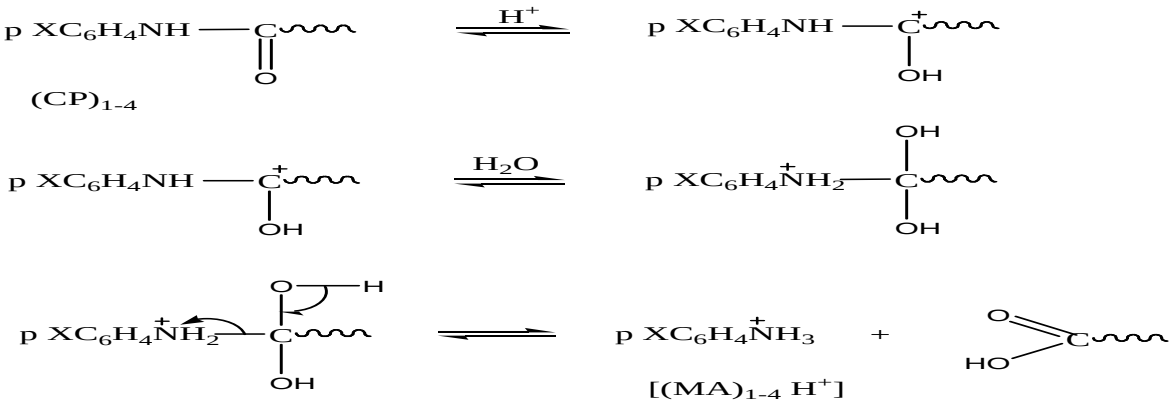

**Figure 5:** Cumulated percentage of [$(MA)_4H^+$] released from oral form as a function of square root of time.

From these experiments a number of conclusions can be drawn:

1-The process of matter transfer is not simple for the galenic form when it is in contact with synthetic gastric liquid. Two matter transfer take place: the liquid enters into the matrix-copolymer, provoking on the other hand a dissolution of the drug [$(MA)_4H^+$] released by acid hydrolysis of the secondary amide function (scheme b), which can then leave the galenic form and whatever the composition of these bead (50/50, 70/30, 80/20) we note that the rate of anilinium ion [$(MA)_4H^+$] released at equilibrium depends on the initial masses of the beads (table3).

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 quantity of the drug released is not total compared to the initial mass for example the galenic form 50/50 of $(CP)_1$ is 45.24% and for the galenic form 80/20 of $(CP)_2$ is 56.53%.




**Scheme b:** Mechanism of hydrolysis of amide function in $(CP)_{1-4}$

4-As shown in previous papers [12, 13], 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 after hydrolysis from the polymer chain.
- The drug thus dissolved is transferred by diffusion through the galenic form.

The diffusivities were calculated and evaluated (table 4)

**Table 3:** The infinite masses $m_\infty$ of $(MA)_{1-4}$ of galenic forms in the pH = 1.2

| ***Eudragit RL /(CP)$_{1-4}$*** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ***Composition of oral forms*** | ***(50/50)*** | | | ***(70/30)*** | | | ***(80/20)*** | | |
| ***Masses (mg)*** | **$m_i$ fg** | **$m_i$ MA** | **$m_\infty$ MA** | **$m_i$ fg** | **$m_i$ MA** | **$m_\infty$ MA** | **$m_i$ fg** | **$m_i$ MA** | **$m_\infty$ MA** |
| ***$(MA)_1$*** | **196,1** | **9,97** | **4,51** | **192,3** | **5,86** | **2,66** | **185,5** | **3,77** | **1,74** |
| ***$(MA)_2$*** | **173,7** | **8,73** | **4,73** | **187,9** | **5,67** | **3,83** | **175,3** | **3,52** | **1,99** |
| ***$(MA)_3$*** | **192** | **17,38** | **9,96** | **185,6** | **10,08** | **1,74** | **190,8** | **6,91** | **1,22** |
| ***$(MA)_4$*** | **185,5** | **9,37** | **4,45** | **196,8** | **5,96** | **2,55** | **194** | **3,91** | **2,61** |

For these reasons, the matter transfer is studied either for the liquid or 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 **(5)** and **(6)** are successfully tested either for the transport of the drug and for that of the liquid.

**Table 4:** Evaluation of diffusivities D at short time (Ds,t) and long time (Dl,t) of $[(MA_4)H^+]$ in the pH = 1.2

| **Eudragit RL / $(CP)_{1-4}$** | | | | | | |
|---|---|---|---|---|---|---|
| ***Composition of oral forms*** | **(50/50)** | | **(70/30)** | | **(80/20)** | |
| ***D ($cm^2.s^{-1}$)*** | ***Ds,t. $10^7$*** | ***Dl,t. $10^7$*** | ***Ds,t. $10^7$*** | ***Dl,t. $10^7$*** | ***Ds,t. $10^7$*** | ***Dl,t. $10^7$*** |
| ***$(MA)_1H^+$*** | **0.39** | **0.10** | **1.60** | **1.38** | **0.70** | **0.09** |
| ***$(MA)_2H^+$*** | **0.46** | **0.48** | **0.33** | **0.19** | **0.31** | **0,37** |
| ***$(MA)_3H^+$*** | **1.06** | **0.16** | **0.05** | **0.14** | **8.40** | **0.11** |
| ***$(MA)_4H^+$*** | **0.29** | **0.34** | **0.03** | **0.43** | **0,90** | **0,59** |

## Conclusion

Oral galenic forms able to control the release of drug in stomach was prepared successfully using Eudragit RL as polymer to delayed release and achieve required dissolution profile. The dispersion of medical agent was chosen to study this drug release in gastric medium by determining the kinetics of the liquid absorbed by the dosage forms and 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. Drug release kinetics of this formulation corresponds better to Fick's model.

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