A new approach of 7-hexahydro-aza-indolerelease study from dosage forms in heterogeneous media and calcul of diffusivities

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Abstract
Several alkaloids have proved to be either too toxic or not enough biologically available to be used directly as treatments for diseases. Nevertheless they remain a source of inspiration for the design of new drugs mediators and can lead after chemical modifications to new interesting therapeutic candidates. In order to evaluate the biological interest of a product miming a natural product, 7-hexahydro-aza-indole as medical agent was synthesized and characterized recently. A spherical dosage forms composed from Eudragit RL100 and the medical agent were prepared and tested to control the drug release, these formulations was followed in heterogeneous media at different pH simulating the human digestive rout at 37°C. The release mechanism of the medical active agent is investigated according to Fick’s laws. So, the diffusivities were calculated and the results demonstrated that the drug release can be modified using these formulations. The data on drug release provide the opportunity for predicting quantitatively the rate of medical agent release from dosage forms, directly into the organism and the gradual transfer of active molecules is well-known in the pharmaceutical field.

Key words: 7-hexahydro-aza-indoles, Alkaloids, drug release, galenic form.

1. Introduction
The interest of the current study, it permits to control a drug release over a defined period of time and represents a significant pathway for optimizing drug effects through dosage forms. Several techniques have been developed in this way and different formulations based on polymers were conceived [1]. The 7-hexahydro-aza-indole as medical active agent, which could be considered as bioisosteres of indoles, occupy a central position in modern heterocyclic chemistry due to their physicochemical and therapeutic properties; it’s a very interesting class of pharmaceuticals and investigational drugs. In this context, these derivatives have been reported to possess a range of biological activities and have the potential to act as kinases inhibitors, cardio-vascular components, antitumor agents and agonists or antagonists of other various pathologies [2; 3]. The release of the drug after oral absorption, involves hydrolysis of the organic group connecting the drug to the support. This hydrolysis may be associated with diffusion of the physiological gastric and intestinal liquid through the polymeric support. Whatever method it is chosen to legate the drug, the proposed solutions are mainly related to the way to introduce the drug, injection or oral absorption [4]. Actually, it is necessary that the drug is free from the support after few hours, the time corresponding to the stay of the drug-support system in the body. In the particular case of a drug grafted onto a polymer, the organic group must be easily hydrolyzed and the kinetic must be independent of the initial concentration, moreover, it is very important to have non-toxic macromolecular systems [5]. The obtained medical active agent (M.A) was synthesized and characterized by FTIR, NMR (1H, 13C, 2D). In the second part, spherical dosage forms composed from the medical active agent synthesized and Eudragit RL were elaborated in order to modify the drug release. Eudragit matrixes were largely used in galenic industry prepare controlled release formulations (%/%, Eudragit RL/7-hexahydro-aza-indole). In the other of the hand, the drug release was followed using UV-Vis spectrophotometer in gastro intestinal media at different pH (pH=1.2, 6.0 and 8.0) at 37°C with various initial masses (100, 200, and 300mg). In this case, the results demonstrated that the drug release is governed by Fick’s law [6-12]. The drug release data showed that the system can provide drug release for a long time. Also, the device behavior is fully
predictable, according to our theoretical model of structure design, and gives many opportunities for model investigations of drug release and its kinetics.

2. Materials and methods

2.1. Synthesis of products

All the reactions were carried out under atmosphere of argon excepted for those carried out in aqueous solution. Thin layer chromatographies were carried out onplatesilicagelMerck-Kieselgel60F254. Theseplates were observedinlightUVandwere revealedbyKMinO. The spectra of NMR 1H and NMR 13C were recorded respectively to 200 MHz and 50 MHz on a device BRUKER AC 200 MHz in the deuterated chloroform (CDCl3) unless otherwise specified. The THF and the ethyl ether were distilled on sodium in the presence of benzenophenone, the methylene chloride and the acetonitrile were distilled on the calcium hydride. The chromatographies flashes were carried out on silica gel(230-400mesh) with eluants mixtures in variable quantity of acetate of ethyl(ACOEt) and cyclohexane(CH).The melting points were taken in capillary tubes on a device at melting point Stuart SMP10. Infra-redspectrometry was carried out on spectrometer Perkin.The solid compounds were put in the form of pastilles KBr (1mg of composed for 50 Mg of KBr) and the principal absorption bands are given of many waves (cm⁻¹). Classifications of the molecules for attributions NMR do not follow the nomenclature.

2.1.1. Procedure of synthesis of polysubstituted imides (±) - a

Acryloyl chloride (500 μl, 6.0 mmol) was added at 0 °C to a solution of the (±)-2-Amino-1-benzyl-5-oxo-4,5-dihydro1H-pyrrol-3-carbonitrile (4.0 mmol) in CH2Cl2 (40 mL). After 12 h attr, the reaction mixture was cooled to 0 °C and quenched carefully by addition of an aqueous saturated solution of NaHCO3 (50 mL). The aqueous layer was extracted with CH2Cl2 (3×30 mL) and the organic layers were combined, dried over MgSO4 and evaporated. The residue was then purified by chromatography on silica gel to furnish (±)-2-AcOEt/cyclohexane).C13H13N2O3 Mp = 163-165 °C; Yield=60% (AcOEt/cyclohexane, 30/70). This product was isolated as a pink solid.

2.1.2. Procedure of synthesis (the 7-hexahydro-aza-indole(±) - c

In a balloon of 20ml, we put 1 eq of (a) more 5ml of CH2Cl2 under argon, to let well agitate during 30min. By follows to add drop by drop in the balloon 2eq of BF3.OEt2, to let the reaction react under agitation during 12h. Under agitation to wash with 5ml of NaHCO3 solution, to extract the organic phase with 3×5ml from CH2Cl2, to dry under MgSO4, to filter and recrystallize the product obtained with Et2O ether. We could obtain the final product(c) by using an acid of Bronsted (CF3CO2H) instead of the Lewis acid (BF3.OEt2). The strategy is simple to realize with identical outputs. The analytical sample was obtained by recrystallisation from dry ethanol and the product was isolated as a white solid: C15H16N2O3 Mp = 163-165 °C; Yield=65% (AcOEt/cyclohexane, 20/80).

2.2. The buffered solutions for kinetics

The buffered solutions were prepared according to the acid/base couples proposed by Michaelis and Mizutani (pH=1.2: HCl solution, pH=6: CH3COOH/CH3COO-, pH=8: CH3COOH/CH3COO- and pH=8: NH4Cl/NH3).  

2.3. Drug release kinetics from dosage forms

Various compositions and sizes have been prepared and the release of the drug in synthetic liquids was determined in vitro tests by using the galenic forms described above. The experiments were carried out in closed flask, kept at 37°C with a controlled rate of stirring (500 rpm). The bead, inserted in permeable fiber glass basket was soaked into 100 ml of simulated gastro intestinal liquid (pH=1.2) for a period of 3 hours, then the bead was replaced successively in another buffered solutions: at pH=6.0 for 1h 30 min and finally for 3hours in buffered solution at pH=8.0, in order to simulate the in vivo rout of the dosage form. Samples (1 ml) of liquid were taken at different intervals for analysis after appropriate dilutions using UV-Vis-2401PC-SHIMADZU spectrophotometer at the corresponding λ max of 7-hexahydro-aza-indol (pH=1.2: λ max= 251.2 nm and ε = 17.600 L.cm⁻¹.mol⁻¹; in pH= 6.0: λ max = 251 nm and ε = 16.500 L.cm⁻¹.mol⁻¹ and in pH=8: λ max = 253 nm and ε = 17.700 L.cm⁻¹.mol⁻¹). The release media are composed from: HCl and NaCl for pH=1.2, CH3COOH/CH3COO- and NaOH for pH=6.0, HCl and Borax for pH=8.0, in accordance with US pharmacopoea.

3. Results and discussion

3.1. Characterization results

The imides (±)-asee (Scheme1) was prepared particularly by examining their behaviour by using N-acyliminim chemistry [13-16], thereduction of the amide-imidepolysubstituted(±)-apvideeasily the obtained of the corresponding-lactamshydroxy(±)-b,its interest since the transformation could target the racemates 7-hexahydro-aza-indole product (±)-c(Azindoled poly unsaturated), The structural assignments of the new compounds were based on their elemental analysis and spectral (IR, 1H NMR, 13C NMR and 2D NMR) data. The preparation data of all the new compounds is presented in experimental part.

3.1.1. Characterization of the (±)-3-(1-Benzyl-3-cyano-2, 5-dioxopyrrolidin-3-yl) propanamide (±)-a:

In the IR (KBr) spectra of this compoundshows the important absorption bands in the range of 2247 cm⁻¹, which are attributed to the CN group and the most important bands were observed are: 3525, 3015, 2400, 1396 cm⁻¹.
The structure of the compound is confirmed by $^1$H NMR (300 MHz, CDCl$_3$), the spectrum gives the following proton signals $\delta$(ppm): 7.36 (s, 5H), 5.65 (bs, 2H), 4.70 (s, 2H), 3.20 (d, $J$ = 18.2 Hz, 1H), 2.94 (d, $J$ = 18.2 Hz, 1H), 2.60-2.48 (m, 1H), 2.46-2.19 (m, 3H).

In the $^{13}$C NMR (300 MHz, CDCl$_3$) we not practically in the spectrum the following proton signals $\delta$(ppm): 172.8, 172, 171.7, 134.6, 129.3, 128.5, 117.3, 43.6, 42.4, 39.4, 32, 30.7.

The NMR 2D (cosy) of ($\pm$)-3-(1-Benzyl-3-cyano-2, 5-dioxopyrrolidin-3-yl) propanamide($\pm$)-a is presented in Fig.1.

3.1.2. Regioselectivity of the reduction of the imide.

The Hydride H-must attack carbonyl according to an angle 109° with carbonyl, it is what one calls the angle of Burgi-Dunits. Thus if there are substituent’s in $\alpha$ of the imide there are a constraint due to the steric obstruction what disadvantages this attack. This explains why one of the approaches is less under privileged (Scheme2). The expected obtains an equimolaire mixture of both hydroxylactames ($\pm$)-b that does not pose a problem because the center stereogenic created at the time of this stage will be lost in the following stage by consequent we could obtain the finished product ($\pm$)-c.

3.1.3. Characterization of the ($\pm$)-1-Benzyl-7a-ethoxy-2, 6-dioxooctahydro-1H-pyrrolo [2, 3-b] pyridine-3a-carbonitrile ($\pm$)-c:

In the IR (KBr) spectra of this compound, the CN group was observed at value absorption band in the range of 2241cm$^{-1}$ and the most important bands are: 3192, 3098, 2939, 2241, 1314,1207, 1064cm$^{-1}$. The structure of
this compound is confirmed by \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}), the spectrum gives the following proton signals \(\delta\) (ppm): 8.33 (s, 1H), 7.27 (s, 5H), 4.62 (d, \(J = 15.5\) Hz, 1H), 4.31 (d, \(J = 15.5\) Hz, 1H), 3.42-3.55 (m, 2H), 3.19 (d, \(J = 17.0\) Hz, 1H), 2.66 (td, \(J = 18.0\) and 5.0 Hz, 1H), 2.64 (d, \(J = 17.0\) Hz, 1H), 2.40 (dt, \(J = 18.0\) and 3.8 Hz, 1H), 2.19 (dt, \(J = 13.5\) and 3.8 Hz, 1H), 1.96 (td, \(J = 13.5\) and 4.4 Hz, 1H), 1.10 (t, \(J = 6.9\) Hz, 3H). In the \textsuperscript{13}C NMR (300 MHz, CDCl\textsubscript{3}) we not practically in the spectrum the following proton signals \(\delta\) (ppm): 170.3, 168.7, 136.4, 128.7, 128.0, 127.8, 117.9, 99.7, 60.9, 42.6, 40.6, 40.2, 30.5, 28.0, 14.8.

The Analysis calculated for C\textsubscript{17}H\textsubscript{19}N\textsubscript{3}O\textsubscript{3}: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.02; H, 5.98; N, 13.31.

The NMR 2D (cosy) of the (±)-1-Benzyl-7a-ethoxy-2, 6-dioxooctahydro-1H-pyrrolo [2, 3-b] pyridine-3a-carbonitrile (±)-c is shown in Fig. 2.

![Figure 2](image_url)

**Figure 2.** Spectrum NMR 2D (cosy) of the (±)-1-Benzyl-7a-ethoxy-2, 6-dioxooctahydro-1H-pyrrolo [2, 3-b] pyridine-3a-carbonitrile (±)-c.

### 3.2. Kinetics results

#### 3.2.1. Mechanism of hydrolysis

We have recently explored detailed (scheme 3) one of the mechanism of hydrolysis. However, the formation was proved by isolating an ethoxy equivalent (±)-c when the reaction was quenched with ethanol. The latter after acidic hydrolysis led to polysubstituted imides (±)-a.

![Scheme 3](image_url)

**Scheme 3.** Transfer of the Bi cyclic product (closed) to the cyclic product (open).

The succinimide framework results from the second \(N\)-acyliminium ion after departure of HCl. The migration of grouping NH\textsubscript{2} with this position showed that one obtained the product bicycle well, the bicycle (Scheme 3) was unstable in acid medium because it was hydrolyzed to give the opened product, the mechanism of hydrolysis at summer tested with a treatment with water in acid medium with some drops of THF (tetrahydrofurane). The cascade process can be explained by a sequence tandem ring closure/ring opening of the γ-lactam skeleton. This produces unexpected nitrogen atom transfer by the way of the \(N\)-acyliminium ion hydrolyzed to lead to the hydroxyl bislactam (Scheme 4).

#### 3.2.2. Preparation of oral forms

The 7-hexahydro-aza-indole was chosen as a medical agent (M.A) and the matrix used in the preparation of the different oral forms was the Eudragit RL100, copolymer of dimethylaminoethylacrylate and ethylmethacrylate with Mn = 150.000 g/mole from Allemande RöhmPharma.

The medical agent (M.A) and Eudragit RL, in powder form were well dispersed (using Perkin-Elmer vibrator), and were 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 drug and Eudragit RL matrix. Spherical beads were prepared.
from this paste and dried at room temperature for 5 or 7 days. Several dosage forms were prepared with various values of drug percentage [17-21]. All the dosage forms have approximately the same weight close to 100 - 300 mg for the same size. beads with 50% / 50% (W / W, Eudragit RL / M.A), diameter close to 0.301-0.305cm), indexed a*,b*,c* and beads with 80% / 20% (W/W, Eudragit RL / M.A, diameter close to 0.297-0.301cm, indexed a, b, c) were prepared and tested using synthetic liquids of pH= 1.2, pH=6.0 and pH= 8. When the dosage forms were soaked into simulated gastro intestinal liquid, liberation of the M.A was observed with typical kinetics.

Scheme 4. Transfer mechanism of hydrolysis of the (±) 1-Benzyl-7a-ethoxy-2, 6-dioxooctahydro-1H-pyrrolo [2, 3-b] pyridine-3a-carbonitrile.

3.2.3. Drug release study

The drug release and the absorption of the liquid by the dosage forms were studied from spherical dosage forms a, b, c and a*, b*, c* in three media at different pH: 1.2, 6.0 and 8.0. The kinetic results demonstrate that the hydrolysis rate of the drug release is inferior to that the absorption of the liquid by the corresponding dosage forms in all pH. In fact, the hydrolysis of the drug release includes a preliminary stage which is the penetration of ionic solution (H3O+ or OH-) through the tangled structure of macromolecule. Both, the hydrolysis rate from the drug release and the absorption of liquid by the dosage forms increases under the acidic (HCl/H2O) hydrolysis. An example of the drug release and the absorption of the liquid were studied from spherical dosage form ‘a*’ with a composition (50/50 (Eud/M.A), weight 100 mg) consecutively at pH=1.2, pH=6.0 and pH=8.0. The results show (Fig.3) that the drug release is slower than the absorption of the liquid by the dosage form. In fact, after two hours (the time corresponding to the drug stay in human stomach from the dosage form), the percentages of drug released and the absorption of liquid by dosage form are respectively 53% and 59%. At the end of 6 hours, 100% of drug released from 50/50 dosage form is reached. This is confirmed by the experimental results for the water levels absorbed by the dosage form after 36 h.

Figure 3. Profiles of absorbed liquid and drug released from the dosage form ‘a*’ (100 mg) as a function of time, in pH= 1.2, pH=6.0 and pH=8.0.
In addition, the drug release and the absorption of the liquid were studied consecutively in tree media at different pH from spherical dosage forms at a composition of 80/20 and 50/50 (w/w): Eud/M.A. An example of the drug release and the absorption of the liquid were studied from spherical dosage forms from c and c* with a composition (80/20 and 50/50, weight 200 mg) at a pH= 6.0. The profiles are illustrated in fig.4.

We have observed (fig.4), that the absorption of the liquid by the dosage forms 50 / 50 and 80/20 was more significant than drug release from dosage forms corresponding, as well the absorption of the liquid by the dosage form 50/50 is more important than form 80/20 and this in spite of the existence of a strong rate in Eudragit thus in hydrophilic, it is due to the molecular composition of the medium of study. Consequently a larger molecule will diffuse less.

**Figure4.** Profiles of absorbed liquid and drug released from the dosage form 'c' and 'c*' (200 mg) as a function of time, in pH=6.0.

The process is not simple; two matter transfers take place when the form is in contact with liquid: the liquid enters the matrix-copolymer and initiates the drug dissolution.

At this stage, the drug can be released from the dosage form, a larger volume of liquid which facilitates drug dissolution and diffusion through the matrix structure. We have noted that the fractional release of 7-hexahydro-aza-indole is proportional to the square root of time during the short time as shown in Fig.5, a linear relationship being observed for mainly short periods as in the case of a process controlled by diffusion. An example of the drug release and the absorption of the liquid were studied from spherical dosage forms from b and b* with a composition (80/20 and 50/50, weight 300 mg) at a pH= 8.0.

So, in line to draw a release model, we have tested the approached analytical solution derived from Fick’s law for diffusion in a sphere. The following assumptions are thus made in order to simplify the problem: (i) The spherical dosage forms are homogeneous (the medicinal agent or copolymer being well dispersed into the Eudragit matrix), (ii) 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, (iii) Both these transfers are controlled by transient diffusion throughout the galenic form. If we suppose that drug diffuse through dosage form with radius R and constant diffusivity and taking into account the following initial and boundary conditions:

Within the sample  
\[ t=0 \quad 0 \leq r < R \quad C=C_m \]

\[ t>0 \quad 0 \leq r < R \quad C=f(t, r) \]

On the surface  
\[ t>0 \quad r=R \quad C=C_\infty \]

\[ C_\infty= \text{Concentration at equilibrium.}\]

In the earlier stages of the process [22], the following analytical solution is given by:

\[ \frac{C - C_\infty}{C_m - C_\infty} = R \sum_{n=1}^{\infty} \left\{ \frac{erfc \left( \frac{(2n+1)R - r}{2\sqrt{Dt}} \right) - erfc \left( \frac{(2n+1)R + r}{2\sqrt{Dt}} \right)}{2n^2} \right\} \] (1)

This equation is written as a function of the amount of diffusing substance at time t (Mt):

\[ 1 - \frac{M_t}{M_\infty} = \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp \left[ - \frac{n^2 \pi^2 D}{R^2} t \right] \] (2)
Where \( M_\infty \) is the amount of diffusing substance at infinite time (equilibrium) and \( n \) is an integer.

For the very short times, the (Eq. (2)) is more simplified and the diffusivity can be calculated by applying the following equation

\[
\frac{M_t}{M_\infty} = \frac{6}{R} \left( \frac{D t}{\pi} \right) ^{\frac{1}{2}}
\]  

(3)

For long times, another analytical solution is deduced from (Eq. (2)), which is also of interest for calculating the diffusivity for long periods.

\[
\ln(1 - \frac{M_t}{M_\infty}) = -\frac{\pi^2 \cdot D t}{R^2} + \ln \frac{6}{\pi^2}
\]  

(4)

The table 1 and 2 gives the results of the diffusion coefficient \( D_{s,t} \) in short periods and \( D_{l,t} \) in long periods consecutively in tree media at different pH: 1.2, 6.0 and 8.0. The diffusivities of 7-hexahydro-aza-indole are in the range of \( 10^{-7} \) cm\(^2\) sec\(^{-1} \) in Eud/M.A dosage forms. Of these different values from "D" we can say that in the heterogeneous media; the release mechanism includes the hydrolysis reaction of amide-imide function and the diffusion phenomenon which is the determinant. Consequently, we can choose the appropriate medium as a function of the desired medicinal application and pharmacokinetic.

When equilibrium is attained, the increase of the process is visible, it reaches approximately the 90.12% for the dosage forms a, b, c and about 94.52% for the dosage forms a*, b*, c* at pH=1.2. We noted that the mass at equilibrium are function of the characteristics of the dosage forms and the medium of study influencing the coefficients of diffusion (see Table 2: mass % liquid/drug).

### Table 1: Values of diffusivities of the M.A released at pH=1.2, 6.0 and 8.0. (s,t : short time, l,t : long time).

<table>
<thead>
<tr>
<th>Composition</th>
<th>80/20</th>
<th>80/20</th>
<th>80/20</th>
<th>50/50</th>
<th>50/50</th>
<th>50/50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indexation</td>
<td>a</td>
<td>b</td>
<td>c</td>
<td>a*</td>
<td>b*</td>
<td>c*</td>
</tr>
<tr>
<td>Initial mass of dosage form (mg)</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>100</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>( D_{s,t} (cm^2 min^{-1}) \times 10^7 )</td>
<td>2.35</td>
<td>1.49</td>
<td>1.62</td>
<td>1.83</td>
<td>1.80</td>
<td>1.38</td>
</tr>
<tr>
<td>( D_{l,t} (cm^2 min^{-1}) \times 10^9 )</td>
<td>0.34</td>
<td>0.47</td>
<td>0.50</td>
<td>0.31</td>
<td>0.52</td>
<td>0.68</td>
</tr>
<tr>
<td>( D_{s,t} (cm^2 min^{-1}) \times 10^7 )</td>
<td>0.70</td>
<td>1.24</td>
<td>1.17</td>
<td>0.78</td>
<td>0.60</td>
<td>0.71</td>
</tr>
<tr>
<td>( D_{l,t} (cm^2 min^{-1}) \times 10^9 )</td>
<td>0.56</td>
<td>0.52</td>
<td>0.50</td>
<td>0.52</td>
<td>0.61</td>
<td>0.50</td>
</tr>
<tr>
<td>( D_{s,t} (cm^2 min^{-1}) \times 10^7 )</td>
<td>2.45</td>
<td>2.36</td>
<td>2.16</td>
<td>2.38</td>
<td>2.34</td>
<td>2.26</td>
</tr>
<tr>
<td>( D_{l,t} (cm^2 min^{-1}) \times 10^9 )</td>
<td>0.45</td>
<td>0.50</td>
<td>0.52</td>
<td>0.61</td>
<td>0.70</td>
<td>0.71</td>
</tr>
</tbody>
</table>

### Table 2: Values of percentage of masses at equilibrium at pH=1.2, 6.0 and 8.0.

<table>
<thead>
<tr>
<th>Oral forms</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>a*</th>
<th>b*</th>
<th>c*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% M(<em>{M.A})(</em>\infty) pH=1.2</td>
<td>98.67</td>
<td>91.23</td>
<td>80.47</td>
<td>98.60</td>
<td>92.55</td>
<td>92.35</td>
</tr>
<tr>
<td>% M(<em>{M.A})(</em>\infty) pH=6.0</td>
<td>93.54</td>
<td>91.56</td>
<td>90.12</td>
<td>95.69</td>
<td>69.15</td>
<td>70.10</td>
</tr>
<tr>
<td>% M(<em>{M.A})(</em>\infty) pH=8.0</td>
<td>98.12</td>
<td>97.54</td>
<td>96.58</td>
<td>99.89</td>
<td>98.17</td>
<td>96.84</td>
</tr>
</tbody>
</table>

Such hydrolyses were not able to be described by traditional kinetic equations, the equilibrium masses obtained is a function of characteristics of the dosage forms and of the nature of the medium and the amount of drug released at the end of the process. Finally it is very important to know the plasmatic concentration of medicinal agent which will determine the optimal quantity to obtain in therapeutic zone, in order to avoid all the harmful side-effects [23-26].
Conclusion
This study paves the way to a new technique of develop controlled release formulations (copolymer, dosage form) based on 7-hexahydrop-aza-indole as a medical agent using physicochemical methods. In homogeneous media, the kinetic constants depend strongly on the type of support (polymer /copolymer) and also on the pH medium. The synthesis of this kind of molecules miming natural products allows opening new ways for the pharmacology with various significant biological potentialities to in vivo treatment. The study and the comprehension of the complex biophysical systems, such phenomena will intraextracellular, is a scientific real challenging which passes ineluctably by the experimentation.

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